Is methicillin-resistant *Staphylococcus aureus* an emerging community pathogen? A review of the literature

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OBJECTIVES: To discuss the historical epidemiology of methicillin-resistant *Staphylococcus aureus* (MRSA) and review the literature suggesting that MRSA has become a community pathogen.
DATA SOURCES: A search of the MEDLINE database was performed, encompassing all English or French language citations from 1966 to 1999 and containing the subjects and/or text words: '*Staphylococcus aureus*', 'methicillin resistance', 'endocarditis', 'cellulites', 'pneumonia' and 'community-acquired'. Articles published in other languages that provided English or French abstracts were included. All relevant references cited in articles obtained from the MEDLINE database and book chapters were also included.
DATA EXTRACTION: All articles obtained from the above sources were examined and were included in the review if a laboratory or epidemiological study of community-acquired MRSA was presented.
DATA SYNTHESIS AND CONCLUSIONS: MRSA has emerged over the past 30 years to become a worldwide nosocomial pathogen and has recently been reported as a cause of community-acquired infections. The changing epidemiology of MRSA is likely because of two mechanisms: the movement of nosocomial MRSA strains into the community and the de novo appearance of community strains resulting from the transfer of genetic material from methicillin-resistant Gram-positive organisms to sensitive *S aureus* strains. The emergence of MRSA as a community pathogen has occurred at a slower rate than it did for penicillin-resistant *S aureus* (PRSA) in the 1950s and 1960s, possibly because the mechanism of methicillin resistance does not exhibit the same ease of transferability as that of penicillin resistance. Four case reports, seven case series, 10 case-control studies and two cohort studies on community-acquired MRSA were analyzed. Determining whether these reports involve new community-acquired strains rather than previously acquired nosocomial strains can be problematic. It appears, however, that MRSA strains of both nosocomial and community origin are now endemic in certain communities in different parts of the world. Few surveillance studies of nonhospitalized patient populations have been performed to date; thus, the true prevalence of MRSA in the community at large is essentially unknown, although it appears to be low. At present, the empirical treatment of community-acquired *S aureus* infections with a beta-lactamase-stable beta-lactam antibiotic is appropriate for most populations. However, empirical vancomycin therapy for serious *S aureus* infections should be strongly considered for patients with significant risk factors for previously-acquired nosocomial MRSA or for patients belonging to outpatient populations with a proven high prevalence of MRSA. Increasing vancomycin use will likely have a significant impact on the development of resistance in Gram-positive organisms.

Key Words: *Community-acquired disease; Drug resistance; Methicillin-resistant* Staphyloccus aureus

Pour le résumé, voir page suivante

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Staphylococcus aureus résistant à la méthicilline est-il un pathogène émergent ? Une revue de la littérature

OBJECTIFS : Discuter de l'épidémiologie historique de *Staphylococcus aureus* résistant à la méthicilline (SARM) et passer en revue la littérature qui semble indiquer que SARM est devenu un pathogène de la communauté.
SOURCES DES DONNÉES : On a procédé à une recherche dans la base de données Medline incluant toutes les citations en français et en anglais de 1966 à 1999 et contenant les sujets et/ou les mots : « *Staphylococcus aureus* », « *methicillin-resistant* » ou résistant à la méthicilline, « *endocarditis* » ou endocardite, « *cellulites* » ou cellulites, « *pneumonia* » ou pneumonie et « *community-acquired* » ou extrahospitalier. On a inclus les articles publiés dans d'autres langues qui s'accompagnaient de résumés traduits en anglais ou en français, de même que toutes les références pertinentes citées dans les articles obtenus par Medline, ainsi que les chapitres des livres.
EXTRACTION DES DONNÉES : On a examiné et inclus dans la revue de littérature tous les articles provenant des sources mentionnées ci-dessus s'ils s'accompagnaient d'une étude épidémiologique ou de laboratoire sur les infections extrahospitalières à SARM.
SYNTHÈSE DES DONNÉES ET CONCLUSIONS : SARM a émergé au cours des 30 dernières années pour devenir un pathogène impliqué dans les infections nosocomiales dans le monde entier. Récemment, il a été rapporté comme une cause d'infections extrahospitalières. L'épidémiologie changeante de SARM est probablement due à deux mécanismes : le mouvement des souches de SARM de l'hôpital vers la communauté et l'apparition *de novo* des souches extrahospitalières résultant d'un transfert de matériel génétique de germes Gram positif résistants à la méthicilline aux souches sensibles de *S. aureus*. L'émergence de SARM comme pathogène extrahospitalier a été plus lente que celle de *S. aureus* résistant à la pénicilline (SARP) qui s'est produite dans les années 50 et 60, peut-être parce que le mécanisme de résistance à la méthicilline ne déploie pas la même facilité de transférabilité que celui de la résistance à la pénicilline. Quatre rapports de cas, sept séries de cas, 10 études comparatives et deux études de cohortes sur SARM extrahospitalier ont été analysés. Déterminer si ces rapports impliquent des nouvelles souches extrahospitalières plutôt que des souches d'origine hospilalière peut poser problème. Cependant, il semble que les souches de SARM à la fois d'origine hospitalière et extrahospitalière soient maintenant endémiques dans certaines communautés dans différentes parties du monde. Jusqu'à maintenant, peu d'études de surveillance ont été menées dans les populations de patients non hospitalisés ; par conséquent, la prévalence véritable de SARM dans l'ensemble de la communauté est en grande partie méconnue, bien qu'elle semble être faible. Actuellement, le traitement empirique des infections extrahospitalières attribuables à *S. aureus* avec des antibiotiques de la classe des bêtalactamines résistantes aux bêtalactamases est approprié pour la plupart des populations. Toutefois, un traitement empirique avec de la vancomycine en cas d'infections graves à *S. aureus* devrait être sérieusement envisagé pour les patients qui possèdent des facteurs de risque significatifs pour une infection à SARM d'origine hospitalière ou chez des groupes de patients traités en externe dans lesquels une forte prévalence de SARM a été confirmée. Un usage accru de la vancomycine aura vraisemblablement un impact significatif sur le développement d'une résistance chez les germes Gram positif.

Staphylococcus aureus has historically been a major human pathogen and continues to be one of the most commonly implicated bacteria causing human disease throughout the world. Before the widespread use of penicillin in the late 1940s and 1950s, staphylococcal septicemia was associated with an extremely high mortality rate (1). Penicillin dramatically improved the prognosis of this infection; however, penicillin-resistant strains were discovered by several investigators shortly after their detection (2-4). Penicillin-resistant *S aureus* (PRSA) rose to prominence in the hospital setting in the 1950s and 1960s. PRSA strains were discovered in the community shortly after they were found in hospitals, making hospital control of PRSA essentially meaningless within two decades of the strains' appearance (5). Within the past 20 years, over 90% of North American community and hospital isolates of *S aureus* have been found to be penicillin resistant (6).

The development of beta-lactamase-resistant penicillins such as methicillin and oxacillin in the early 1960s once again revolutionized the treatment of staphylococcal infections. Within a year of their release, however, resistant *S aureus* strains were reported (7,8) and outbreaks of MRSA infections were described on several continents within several years (9). Over the next 30 years, MRSA emerged as a near ubiquitous nosocomial pathogen. The prevalence of *S aureus* infections being caused by MRSA as reported by the National Nosocomial Infection Surveillance system in the United States has been steadily increasing, from 2.4% in 1974, 5% in 1981, 29% in 1991 to 43% in 1997 (10-12). Furthermore, the percentage of hospitals treating patients with MRSA infections is also increasing. In a survey of Society for Healthcare Epidemiology of America members in 1990, 97% reported having managed patients with MRSA in their hospitals. While the prevalence of MRSA is increasing, it is increasing at a slower rate than did PRSA in the 1950s and 1960s.

It is tempting to predict that MRSA will follow a course similar to that of PRSA, namely that rapid and widespread colonization of people outside of the hospital milieu will result in MRSA becoming the predominant phenotype causing human disease. Such an outcome would obviously have a profound effect on hospital infection control practice and on the empirical use of vancomycin therapy for community-acquired staphylococcal infections. The resulting increased use of vancomycin would in turn have grave implications for the selection of other multidrug-resistant organisms such as vancomycin-resistant enterococci and vancomycin-intermediate *S aureus*, both of which are selected for by vancomycin use (13,14). Before making such grave predictions, however, it is important to question whether the epidemiology of PRSA and MRSA are truly comparable and examine critically the evidence suggesting that MRSA may be becoming a pathogen in the community.

MECHANISMS OF RESISTANCE AND HISTORICAL EPIDEMIOLOGY OF PRSA AND MRSA

Beta-lactam antibiotics achieve bacterial killing by binding to penicillin-binding proteins (PBP), thus inhibiting the cross-linking of the bacterial cell wall. The mechanism of penicillin resistance in staphylococci is well known and involves the production of beta-lactamase(s), which hydrolyzes the cyclic amide bond of the beta-lactam ring. It is clear that beta-lactamase-producing strains of *S aureus* existed before the discovery of penicillin. Parker and Lapage (15) reported that the majority of isolates responsible for outbreaks of staphylococcal food poisoning before 1940 were, in retrospect, found to be penicillin resistant. The ultimate origin of staphylococcal beta-lactamase is unclear; however, it is believed that it may have an as yet unknown role in cell wall synthesis.

The production of beta-lactamase in most strains is inducible by the presence of beta-lactam antibiotics; however, rare strains that constitutively produce beta-lactamase have been reported (16). The staphylococcal beta-lactamase is encoded by the *blaZ* gene, which is controlled by both a repressor gene (*blaI*) and an antirepressor gene (*blaR1*) (17,18). These regulatory elements allow for the inducible expression of beta-lactamase should a beta-lactam antibiotic be present in the environment. In most *S aureus* strains, the beta-lactamase gene and regulatory elements are located on an easily transferable plasmid (19). Weber and Goering (20) have reported a beta-lactamase transposable element, *Tn4201*, which is capable of movement between plasmid and chromosomal sites, and is equally well expressed in either insertion orientation. The percentage of *S aureus* strains that produce beta-lactamase by this mechanism is not known.

The mechanism of staphylococcal resistance to methicillin and other beta-lactamase-resistant, beta-lactam antibiotics is considerably different. MRSA strains produce a unique penicillin-binding protein, PBP2a, which has a much lower affinity for beta-lactam antibiotics (21). The gene encoding for PBP2a has been named *mecA* and is incorporated into the chromosome of MRSA strains as part of a conserved 30 kb region termed *mec*. The origin and evolution of the *mec* locus is a subject of considerable controversy. Kreiswirth et al (22) constructed an evolutionary tree using DNA fingerprinting with variable gene probes directed against the *mecA* region and Tn*554* (a transposon present in more than 90% of MRSA strains) of 450 MRSA strains isolated over 30 years from around the world. These researchers showed that all of the studied isolates could be linked to a single parent strain, indicating that essentially all of the studied MRSA strains arose from a single clone. They concluded that the horizontal transfer of the *mecA* gene between staphylococcal species is likely an extremely rare event (22). Mussuer and Kapur (23) used multilocus enzyme electrophoresis of 15 metabolic enzymes to construct a similar evolutionary hierarchy of MRSA isolates but found quite different results. While they concluded that European and northern African isolates were likely derived from a single clone, isolates from North America exhibited considerable diversity, more in keeping with ongoing horizontal acquisition of the *mec* locus by *S aureus* (23). Archer et al (24) analyzed 105 MRSA isolates obtained worldwide over a 30-year span by probing for DNA sequences 5 to the *mecA* gene. This group found that MRSA isolates dating from the 1960s had identical sequences, suggesting that they may have arisen from the same clone. Those isolates from the 1970s onwards, however, contained additional DNA sequences and were more heterogeneous, suggesting that they arose independent of the 1960s clone and that horizontal transfer of the *mecA* gene was likely occurring (24). Finally, a recent study by Hiramatsu et al (25) has again found somewhat different results. By cloning and sequencing *mec* genes from MRSA isolates gathered worldwide, these investigators were able to group MRSA isolates into three distinct categories: those isolates prevalent in Britain; those prevalent in Japan and the United States; and finally, those prevalent in Britain, Europe, and former British colonies in the Middle East and South East Asia. Hiramatsu et al (25) concluded that these different categories of MRSA strains appear to have developed independently, thus arguing against a single clonal origin for MRSA. Furthermore, considerable genetic diversity was found within each category supporting the findings of Mussuer and Kapur (23) and Archer et al (24), again suggesting that the sharing of genetic material between organisms is a common occurrence.

The origin of the *mecA* gene and *mec* DNA has also been the subject of intense investigation. It has been suggested that MRSA arose as a result of horizontal transfer of *mec*-encoding DNA between *S aureus* and coagulase-negative staphylococci at some point(s) in the past (23,24). Other potential sources of the *mec* locus have recently been discovered: The MRSA PBP2a has a high degree of homology with PBP molecules produced by *Staphylococcus sciuri* (26,27) and *Enterococcus hiriae* (28).

In summary, it appears likely that the *mecA* gene found in MRSA originated from similar genes found in other Gram-positive organisms. Worldwide MRSA isolates are not derived from a single clone, but rather from several clones that may have arisen independently. Furthermore, the genetic diversity of MRSA isolates within a particular category strongly suggests that there is some degree of horizontal transfer occurring between *S aureus* species. The discrepancy in the degree of MRSA genetic diversity observed in the different studies outlined above is likely because of several factors including the discriminatory power of the laboratory technique used, the genetic sequences that were examined and the MRSA isolates studied.

Thus, the mechanism of the spread of genes coding for penicillin and methicillin resistance in staphylococci is considerably different. PRSA have likely become the predominant staphylococcal phenotype because the plasmid-encoded genes responsible for penicillin resistance are readily transferable between staphylococcal species by both horizontal and vertical routes. Bacteria harbouring the resistance plasmid enjoyed a substantial selective advantage over sensitive strains during the 1950s and 1960s because of the widespread and indiscriminant use of penicillin. By the 1960s, plasmid-carrying strains essentially replaced penicillin-sensitive strains as 'normal' human flora. Given the absence of sophisticated molecular epidemiol-

ogical techniques 40 years ago, it is impossible to determine the origin of community-based PRSA strains, ie, whether they first arose in hospitals and then spread into the community or whether community strains arose independently of nosocomial strains because of the horizontal transfer of resistance genes.

By contrast, the genes responsible for methicillin resistance do not appear to be as easily transferred between staphylococci via the horizontal route. This is not surprising given the fact that the transfer of chromosomally based DNA is typically less frequent than the transfer of plasmid-based DNA. The dissemination of MRSA strains likely relies largely upon vertical transfer of genetic material during bacterial replication, although some horizontal transfer of the *mec* gene locus undoubtedly occurs. These differences may in part explain why, despite the fact that PRSA and MRSA appeared within a year of the introduction of penicillin and methicillin, respectively, PRSA rapidly rose to prominence within two decades, whereas MRSA has not been disseminated to the same degree over almost four decades.

MRSA IN THE HOSPITAL SETTING

Risk factors for the hospital acquisition of MRSA include prolonged hospitalization, stay in an intensive care unit, chronic diseases such as chronic renal failure and malignancy, prior exposure to antibiotics, surgery and contact with a patient known to be colonized or infected with MRSA (29). MRSA infection is typically preceded by colonization of the anterior nares and skin. Other sites of potential colonization include the urine of patients with indwelling urinary catheters, the implantation sites of invasive devices and postoperative wounds.

Once acquired, MRSA carriage, such as that of wild type *S aureus*, is typically difficult to eradicate and carriage is often long term. One study involving patients associated with a tertiary care teaching hospital in the United States documented a median duration of MRSA colonization of more than 3.5 years after acquisition (30).

It is a common practice to discharge MRSA colonized patients who were isolated while hospitalized to their homes or long care facilities where contact precautions may not be practised. Transmission of MRSA to close contacts when colonized patients are discharged home has been well documented but has rarely been associated with invasive disease (31-33). Similar transmission has been reported to occur in nursing homes (34,35). The extent to which nosocomial strains of MRSA are then further transmitted into the community is essentially unknown.

MRSA IN THE COMMUNITY SETTING

Defining true cases of community-acquired MRSA can be problematic because of the ambiguity associated with the definition of community-acquired infections. A community-acquired infection has been traditionally defined as one that occurs within 48 to 72 h of hospitalization, unless it is clear that it was acquired during a previous hospitalization (36). This definition has been used by hospital epidemiologists to classify and study patients with nosocomial infections (ie, those who acquired their infection at least 72 h after hospitalization) rather than to study community-acquired disease. There are several problems with this definition. Diseases such as HIV, hepatitis C and hepatitis B, which have long incubation periods, may not be taken into account and thus may be misclassified. In addition, the use of this definition to classify community-acquired MRSA cases is complicated by the fact that MRSA carriage can continue for years after acquisition. A widely used, yet arbitrary, definition for prior hospitalization refers to hospitalization within six months to one year of the current admission. This may misclassify a substantial proportion of true nosocomial MRSA patients who have been colonized with MRSA for a prolonged period after a previous remote hospitalization. Thus, even remote hospitalization is an important variable that must be taken into account. Finally, many institutions classify MRSA colonization acquired in a nursing home or long term care facility as community acquired, which is misleading because such institutions and their patients are not representative of the general population. Defining a case as community acquired can be greatly aided by molecular epidemiological techniques such as ribotyping and pulsed field gel electrophoresis (PFGE). Should an MRSA isolate yield a restriction pattern distinct from known nosocomial isolates, this argues against nosocomial acquisition.

With the above discussion in mind, there have been multiple reports of community-acquired MRSA infections from several countries published over the past two decades. These studies have been summarized in Table 1. Most of the earlier studies did not adequately control for prior hospitalization as a risk factor for MRSA colonization, hence 'community-acquired' strains may in fact be misclassified nosocomial strains. The following is a chronological review of this growing body of literature grouped by reporting country.

THE UNITED STATES

The first report of community-acquired MRSA in the United States was published in 1982. Saravolatz et al (37) reported a case-control study of community-acquired MRSA infections in 24 intravenous drug abusers from Detroit who had been self-administering cephalosporins as prophylaxis against skin infections. There was no difference between the case and control groups with respect to prior hospitalization, which was defined as hospitalization within the prior four months, and an unspecified number of patients had no history of prior hospitalization. The community-acquired MRSA isolates were shown to be the same phage type and have similar antimicrobial sensitivity patterns as the known predominant nosocomial isolate, suggesting the outbreak was caused by a nosocomial strain.

In the same year, another Detroit hospital reported 24 cases of MRSA endocarditis in intravenous drug abusers (38). Unfortunately, although the cases were defined as community-acquired, no definition for community-acquired disease was provided, nor was information presented pertaining to prior hospitalization of the patients. All of the isolates were of the same phage type (and were similar to the phage type reported by Saravolatz et al [37]), but no comparison was

TABLE 1
Summary of the community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) reported in the literature

Authors	Year	Setting	Study type	Probable source of MRSA isolate(s)	Population studied	Molecular typing analysis performed
United States						
Saravolatz et al (37)	1982	Detroit	CCS	Nosocomial	24 IV drug users with infection (soft tissue, endocarditis/bacteremia, respiratory, osteomyelitis)	Phage typing; susceptibility patterns
Levine et al (38)	1982	Detroit	CCS	Nosocomial	24 IV drug users with endocarditis	None given
Craven et al (39)	1986	Boston	CS	Nosocomial	7 IV drug users with bacteremia	Phage typing; susceptibility patterns
Berman et al (70)	1993	New York City	CR	Community	1 adult with endocarditis	DNA hybridization
Moreno et al (40)	1995	Texas	CCS	Nosocomial	99 adults with infection or colonization (wound, respiratory, urine, blood)	PFGE
Pate et al (71)	1995	Missouri	CR	Community	1 child with osteomyelitis	PFGE
Layton et al (42)	1995	Connecticut	PCS	Nosocomial and community	36 adults with infection or colonization (respiratory, wound, blood, urine)	PFGE
Steinberg et al (43)	1996	Georgia	CCS	Nosocomial	35 adults with bacteremia	None given
Herold et al (44)	1998	Chicago	CCS	Community and Nosocomial	35 children with infection (soft tissue, respiratory, blood)	PFGE on a minority of isolates
Akram and Glatt et al (45)	1998	New York	CCS	Nosocomial	16 adults with bacteremia	None given
Lindenmayer et al (46)	1998	Vermont	CS, RCS	Unknown	7 members of wrestling team (6 skin infections, 1 colonized)	PFGE; susceptibility patterns
Adcock et al (47)	1998	Texas	CS	Unknown	12 children at day care centres (1 respiratory infection, 11 colonized)	PFGE
Groom et al (49)	1999	New Mexico	CCS	Community	48 American Indian outpatients with MRSA infection	PFGE
Centers for Disease Control and Prevention (50)	1999	North Dakota, Minnesota	CS	Community	4 children with fatal MRSA infection	PFGE
Canada						
Taylor et al (51)	1990	Alberta	CCS	Nosocomial	24 members of a native community with colonization	Phage typing; susceptibility patterns
Embil et al (52)	1994	Canadian Prairies	CCS	Nosocomial	85 adults with colonization or infection (wounds, respiratory, urine, joints, blood)	PFGE
Berlet et al (53)	1997	Ontario	CR	Nosocomial	1 adult with wound infection	None given
Gardam et al (54)	1998	Ontario	CR	Community	1 adult with endocarditis	PFGE
Australia and New Zealand						
Udo et al (58)	1993	Western Australia	CCS	Community	25 adults from Northern Australia 18 infected (sites not specified), 7 colonized	Plasmid analysis; PFGE
Collignon et al (61)	1998	Australia	CS	Community	74 outpatients with infection (soft tissue, blood, respiratory, bone)	Susceptibility patterns; phage typing
O'Brien et al (63)	1999	Australia	CS	Community	MRSA-colonized inhabitants of remote northern Australian communities	Susceptibility patterns; phage typing; plasmid analysis; PFGE; RFLP
Europe						
May et al (64)	1993	France	CS	Nosocomial	6 adults with invasive infection	None given
Simpson et al (65)	1995	England	CS	Nosocomial	2 adults with endocarditis (acquired from family member)	Phage typing; susceptibility patterns

CCS Case-control study; CS Case series; CR Case report; IV Intravenous; PFGE Pulsed field gel electrophoresis; PCS Prospective cohort study; RCS Retrospective cohort study; RFLP Restriction fragment length polymorphism

made with known nosocomial strains at the reporting institution. Again, self-administration of antibiotics and, in particular, cephalosporins was found to be an independent risk factor for the acquisition of MRSA.

In 1986, another outbreak of MRSA infections in intravenous drug abusers was reported, this time in Boston (39). Seven patients were described as having community-acquired disease, but this was neither defined specifically nor was information provided regarding past hospitalizations. However, all seven patients developed invasive staphy-

lococcal infections with a strain of MRSA of a different phage type and antimicrobial sensitivity pattern than known nosocomial strains, suggesting that this may have been caused by a new community-based strain. The authors hypothesized that a local 'shooting gallery' frequented by the majority of the cases was the source of the MRSA.

Multiple reports of community-acquired MRSA colonization with or without infection have been reported from the United States within the past five years. Moreno et al (40) reported that 58% of MRSA strains isolated from patients in Texas over a 21-month period were from the community, defined as MRSA isolated within 48 h of admission (40). A case-control study failed to reveal significant risk factors for the community acquisition of MRSA compared with methicillin-sensitive *S aureus*. It has been suggested, however, that the small sample size may have limited the power of the study to detect differences in the two populations (41). Two-thirds of the community isolates were of distinct types on PFGE, but were not compared directly with nosocomial strains. However, the majority of the community-acquired MRSA patients had at least some hospital contact within the preceding six months, suggesting prior colonization with nosocomial strains.

A prospective study of the epidemiology of MRSA at a large tertiary care northeastern American hospital revealed that 41% of MRSA clinical isolates obtained over 14 months were community acquired (42). MRSA infections in patients who had not been hospitalized for at least one month were defined as community acquired, which likely included a large number of previously unknown nosocomial cases. However, 22% of patients had no known risk factors for the acquisition of MRSA, including previous hospital admission, intravenous drug abuse and residence in a nursing home. A minority of the community isolates were identical to nosocomial strains on PFGE, but 60% had unique PFGE patterns, suggesting a heterogeneous population of community-based MRSA strains.

In a study of nosocomial and community-acquired *S aureus* bacteremias, Steinberg et al (43) reported in 1996 that the rate of community-acquired MRSA bacteremia at their institution had increased approximately threefold over a 10-year period. Approximately two-thirds of the community-acquired patients had been hospitalized within the previous year and 22% of were associated with the use of outpatient intravascular devices. No PFGE analysis was performed on the isolates, but it is likely that the majority of community-acquired bacteremias were caused by known nosocomial strains, given the high rate of previous hospitalization.

A retrospective review of hospitalized children with positive cultures for *S aureus* showed that the number of community-acquired MRSA infections in children increased fourfold over a 10-year period at a Chicago paediatric hospital (44). More important, community-acquired infections in children without known risk factors for the acquisition of MRSA increased 26-fold. Risk factors were defined as any of the following: previous hospitalization or antimicrobial therapy within six months of the date of MRSA isolation, history of endotracheal intubation, underlying chronic disorder, presence of an indwelling venous or urinary catheter, a history of any surgical procedure or notation in the medical record of a household contact with an identified risk factor. Restriction pattern analysis was not available for the majority of community-acquired strains; however, those isolates that were analyzed were distinct from nosocomial strains. In addition, the antibiograms of community-acquired strains isolated from children without risk factors differed substantially from those isolated from children with risk factors and from nosocomially acquired strains. The former strains tended to remain sensitive to clindamycin and gentamicin, whereas the 'risk factor' and nosocomial strains were largely resistant to these antibiotics. While some of the patients with community-acquired strains may have actually acquired their MRSA during remote hospital admissions, the epidemiological and molecular evidence strongly suggests that the majority of children were infected with novel community-based MRSA strains.

A retrospective review of 360 MRSA blood isolates from a New York state hospital collected over 18 months found that 16 patients (4%) had 'true' community-acquired MRSA bacteremias (45). The authors considered a patient to have a 'true' community-acquired MRSA bacteremia if the infection was present within 48 h of admission, the patient had not been hospitalized for four weeks and the patient was admitted from home. Although this definition would likely capture patients who acquired MRSA during a recent hospital admission, 10 of the 16 patients had no history of hospitalization. It was not stated whether these 10 patients were close contacts of hospitalized patients. No molecular subtyping for the isolates was reported.

Lindenmayer et al (46) described an outbreak of MRSA in a high school wrestling team. The index patient had undergone three emergency procedures at a local hospital, and surveillance cultures had been negative for MRSA on his last admission. Screening of the wrestling team and the local community revealed additional cases colonized with the same strain by PFGE. No comparison was made between the outbreak strain and nosocomial isolates, hence the origin of the MRSA outbreak strain is unclear. However, this outbreak clearly reveals that MRSA can quickly spread among otherwise healthy members of a community.

Another community outbreak, this time involving two child care centres in Texas, was described by Adcock et al (47). Surveillance cultures were taken from children attending two different child care centres after two toddlers were diagnosed with MRSA infections. One centre found an MRSA colonization rate of 24% with the outbreak strain and a second, unrelated strain on PFGE. The other centre had a colonization rate with the outbreak strain of 3%. Of note, both of the index cases were previously healthy and had no histories of hospitalization. No comparison was made between the outbreak strains and nosocomial strains. The authors speculated that child care centres may be becoming community foci for MRSA based on the above observations and prior observations that such centres are reservoirs for other antibiotic resistant bacteria (48).

Groom et al (49) have reported on the emergence of MRSA in a rural American Indian community in New Mexico.

Seventy-five per cent of MRSA clinical isolates collected over one year were from patients who did not have risk factors for the acquisition of nosocomial strains. Most of the isolates were found to be susceptible to antibiotics other than beta-lactams, and most were found to be closely related on PFGE, suggesting the emergence of one or more community-based strain(s) in that population.

Recently, four fatal cases of paediatric community-acquired MRSA infection in children were reported from Minnesota and North Dakota (50). In all cases, neither the children nor their family members had had contact with health care settings. The patients originated from both urban and rural settings, and were from different ethnic backgrounds. Three of the four cases had been given empirical therapy with a beta-lactam antibiotic, the fourth was treated empirically with vancomycin. All the isolates were sensitive to all antimicrobial agents tested with the exception of beta-lactam antibiotics. Two of the isolates were indistinguishable by PFGE, while the other two isolates were closely related. All isolates were found to be distinct by PFGE from nosocomial isolates obtained from the same geographic area. The geographic (urban and rural) and ethnic diversity of the four cases suggest that community colonization with MRSA may be widespread in this area of the United States.

CANADA

Community-acquired MRSA was first reported in Canada in 1990. Taylor et al (51) reported a multistrain cluster of MRSA from a native community in Alberta. All admissions from the native community were screened upon admission to the hospital over two year and 5% of those screened were found to be positive for MRSA. However, 91% of positive patients had been hospitalized within the preceding 12 months. Although no comparison was made between the community and nosocomial isolates using molecular typing, the cluster of cases was likely because of the spread of a nosocomial strain within the community. The authors suggested that the relatively poor and overcrowded conditions of the community likely contributed to the dissemination of MRSA.

Embil et al (52) retrospectively studied all known cases of MRSA reported by five tertiary care teaching hospitals located on the Canadian prairies between the years 1990 and 1992. They noted that 85 (62%) of the isolates were found on admission screening and were classified as community-acquired using the traditional definition. Fourteen of the isolates were obtained from patients who had been transferred from other hospitals; however, it was not stated how many of the remaining 69 cases had had prior hospital exposure. Interestingly, community-acquired MRSA was statistically associated with rural residence, younger patient age and native ancestry, which is supportive of the findings of Taylor et al (51). These two studies taken together strongly suggest that MRSA of nosocomial origin is endemic in certain native communities of western Canada.

Two case reports of community-acquired MRSA infection have been published in the Canadian literature. The first case involved an MRSA infection of the hand (53). The patient had been hospitalized a week before admission and obtaining cultures, and had initially responded to therapy with penicillin, ampicillin and gentamicin. No molecular typing was performed, but it is probable that the MRSA was acquired during the first admission. The second case involved MRSA endocarditis in an otherwise healthy young woman (54). Detailed investigation failed to reveal a risk factor for the acquisition of MRSA, and the isolate were shown to be distinct from known nosocomial strains by molecular typing methods (54).

AUSTRALIA AND NEW ZEALAND

In Australia, MRSA has been known to be present in the eastern states since the mid-1970s (55,56) and an eastern MRSA strain was reported to cause outbreak in Western Australia in the early 1980s (57). Following this outbreak, Western Australian hospitals remained remarkably free of MRSA until Udo et al (58) reported the emergence of a community-based strain of MRSA in Western Australia. These researchers described 25 cases of MRSA colonized **or?** infected patients who were detected on admission to hospital and who had no prior histories of hospitalization. Interestingly, 20 of 25 (80%) of the patients were from isolated communities from the Kimberley region of Western Australia, suggesting a community focus. PFGE analysis of all 25 community isolates revealed that the majority were either the same strain or that the strains were closely related, yet distinct from nosocomial strains. Follow-up studies have shown that this strain has increased in prevalence and has spread to surrounding rural areas as well as metropolitan regions in the south (59,60). The geographic isolation of the cases as well as the PFGE data strongly imply the emergence of a community-based MRSA strain in this region.

Collignon et al (61) have reported a dramatic increase in MRSA infections occurring in outpatients with no history of hospitalization from several Australian cities. Sensitivity patterns were found to be different from nosocomial strains as were the phage types on isolates where phage typing was performed. Similar trends have been noted upon review of laboratory isolates from New Zealand by Riley et al (62), although community-acquired disease was not defined.

Perhaps the most telling indication that community-acquired MRSA strains have emerged in Australia is the recent report by O'Brien et al (63) of a hospital outbreak of MRSA caused by the community-based Kimberly MRSA strain (63). Subsequent screening of the remote communities where the index patient originated revealed that 24% to 42% of residents were colonized with MRSA, of which 17% to 39% were found to be carrying the outbreak strain.

EUROPE

May et al (64) described 62 cases of invasive MRSA infections from 15 French hospitals over a one-year period. Less than 10% of cases were considered to be community acquired when community acquired was defined as isolation of the organism within 48 h of admission. No epidemiological information was provided regarding hospitalization histories of

the community-acquired patients nor was molecular typing data presented for the isolates. It is impossible to determine the origin of the MRSA strains (ie, community versus nosocomial); however, it is likely that these patients were infected with nosocomial strains.

Simpson et al (65) reported a family outbreak of MRSA in England following the development of an MRSA otitis media by a child hospitalized for the insertion of tympanic tubes. Both parents were injection drug users, and both developed MRSA endocarditis with strains of the same susceptibility pattern and phage type as the child and the known nosocomial strain.

CONCLUSIONS

It appears from the above review of the literature that MRSA has indeed emerged as a community pathogen in some populations. This epidemiological shift appears to have occurred over a much longer period than was the case with PRSA. This may be because of differences in the transmissibility of resistance genes between MRSA and PRSA, but also may be in part because of the overall effectiveness of hospital-based infection control programs, which have become commonplace over the past two decades. Furthermore, one cannot rule out the possibility that MRSA is some how slightly less evolutionarily 'fit' as a community pathogen than PRSA. It is possible that the presence of the *mec* locus may put MRSA at a slight evolutionary disadvantage unless positive selective factors such as beta-lactamase-resistant, beta-lactam antibiotics are widely present in the environment.

There appear to be two mechanisms for the introduction of MRSA into a nonhospitalized community. The first mechanism involves the likely inevitable spread of nosocomial strains into a community following the discharge of MRSA colonized patients. The majority of the earlier studies describing community-acquired MRSA cases have in fact involved previously hospitalized patients or those who may have had close contact with the hospital milieu. While previously hospitalized patients may be found to be colonized or infected with MRSA at the time of readmission, they are perhaps more correctly classified as nosocomial rather than community-acquired cases, especially if there are additional molecular epidemiological data indicating that their isolates are similar to known nosocomial strains.

The second mechanism appears to involve the de novo appearance of community-based MRSA strains. There is evidence to suggest that such strains have arisen independently from nosocomial strains. Several clusters of MRSA infection have occurred in patients from geographically distinct regions who have never been hospitalized, yet have been found to be colonized or infected with MRSA at the time of admission. In these instances, antibiotic sensitivity patterns and molecular subtyping analysis have shown the isolates to be distinct from nosocomial strains. Case control studies have indicated that these cases appear to be associated with certain communities such as native populations, inner city paediatric populations or inhabitants of remote areas. Although no phylogenetic analysis has been performed comparing community-acquired strains from different populations and geographic locales, it is probable that these strains have arisen independently from each other. This would suggest that horizontal transfer of genetic material between *S aureus* and other bacteria has occurred at different geographic locations and times.

Determining the origins of community-acquired MRSA strains is more than just an academic exercise. Faced with growing evidence that MRSA has become a community pathogen, a large number of authors have questioned the use of beta-lactamase-resistant, beta-lactam antibiotics such as methicillin or cloxacillin for the empirical treatment of community infections due to *S aureus.* To change empirical therapy broadly for all patients to another class of antibiotics such as the glycopeptides is not a decision to be made lightly because it would likely have a profound effect on the emergence of resistant Gram-positive organisms.

Given the data presented in this review, the empirical use of vancomycin for the treatment of the majority of community-acquired *S aureus* infections is not justifiable at the present time. However, there are circumstances where empiric vancomycin therapy may be appropriate, especially when confronted with a serious *S aureus* infection. It is likely prudent to treat with vancomycin empirically those patients who were previously hospitalized in institutions with a high prevalence of MRSA, and who have risk factors for nosocomial acquisition of MRSA. For the vast majority of patients with community-acquired *S aureus* infections who do not have risk factors for the acquisition of nosocomial strains, a beta-lactamase-stable, beta-lactam antibiotic should remain the empirical therapy of choice. In patients belonging to populations where community-based MRSA strains are prevalent, it would be prudent to avoid empirical beta-lactam therapy. In these circumstances, however, the community strains often remain sensitive to other antibiotics such as clindamycin, providing an alternative therapy to vancomycin. Regardless of the choice of empirical therapy, it is crucial to obtain material for culture whenever possible and perform sensitivity testing on all *S aureus* isolates.

Currently, there is no evidence to suggest that the empirical treatment of common community-acquired infections where *S aureus* might potentially be a cause should be altered to account for MRSA. For example, studies examining the etiology of community-acquired pneumonia have either not reported MRSA as a cause of disease, or have not provided the necessary information to determine whether an extremely rare MRSA isolate was of community or nosocomial origin (66-69).

Although the present review has described outbreaks of MRSA in several nonhospital-based populations, the actual overall prevalence of MRSA in most of these communities is essentially unknown because population-based surveillance studies have not been performed. The majority of information is available from the small subset of patients who have developed MRSA infections serious enough to require hospitalization. Because we know that more patients are colonized with PRSA in the community than develop invasive infections, it is likely that the prevalence of MRSA colonization in some communities is many-fold greater than the number of cases with invasive MRSA disease. This has been shown to be the case in

the Kimberly region of Western Australia (63). A direction for future research must therefore include surveillance studies of those populations identified at high risk for community-acquired invasive MRSA disease such as intravenous drug abusers, Aboriginal communities and paediatric populations. Subsequent surveillance studies should then focus on the prevalence of MRSA in the general population. As more community MRSA strains become known, phylogenetic trees could be constructed that would help to elucidate the origin of these strains.

There is little information regarding the clinical course of community-acquired MRSA infections. A synthesis of the studies presented in this review suggests that community-acquired MRSA infection may behave similarly to community-acquired infection caused by methicillin-sensitive *S aureus*, as long as appropriate therapy is given early on in the course of the disease. Clearly, if serious or life-threatening community-acquired MRSA infections are treated empirically with beta-lactam antibiotics for prolonged periods because delays in sensitivity testing, the clinical outcome will be worse than for methicillin-sensitive infections.

The emergence of MRSA as a community pathogen seems have followed two routes: through the spread of nosocomial strains into the community from discharged patients, and through the de novo development of community strains. It appears likely that the prevalence of MRSA in both the hospital and community setting will continue to increase with time due to continued selective pressure from antibiotic use. It is curious that the majority of reports of community-acquired MRSA infections have come from only two continents while MRSA is known to be a worldwide nosocomial pathogen. Whether this reflects an absence of community-acquired MRSA disease in other parts of the world or whether such disease exists but has not been reported in indexed journals is not known.

Eventually, a large percentage of community-acquired *S aureus* infections from many geographically distinct regions will be caused by methicillin-resistant strains. At that point in time, the empirical treatment of essentially all community-acquired *S aureus* infections will have to be changed to vancomycin or newer nonbeta-lactam antibiotics. As has happened several times in the antibiotic era, this will inevitably promote the emergence of the next wave of antibiotic-resistant *S aureus* strains.

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