Community-associated meticillin-resistant Staphylococcus aureus

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Meticillin-resistant Staphylococcus aureus (MRSA) is endemic in hospitals worldwide, and causes substantial morbidity and mortality. Health-care-associated MRSA infections arise in individuals with predisposing risk factors, such as surgery or presence of an indwelling medical device. By contrast, many community-associated MRSA (CA-MRSA) infections arise in otherwise healthy individuals who do not have such risk factors. Additionally, CA-MRSA infections are epidemic in some countries. These features suggest that CA-MRSA strains are more virulent and transmissible than are traditional hospital-associated MRSA strains. The restricted treatment options for CA-MRSA infections compound the effect of enhanced virulence and transmission. Although progress has been made towards understanding emergence of CA-MRSA, virulence, and treatment of infections, our knowledge remains incomplete. Here we review the most up-to-date knowledge and provide a perspective for the future prophylaxis or new treatments for CA-MRSA infections.

Introduction

Staphylococcus aureus is a leading cause of human bacterial infections worldwide.1 The severity of these infections varies widely—from minor skin infections to fatal necrotising pneumonia. The pathogen is also a commensal organism in people, and about 30% of healthy individuals who are not in institutions are colonised asymptomatically with S aureus in the nostrils.2 These findings are noteworthy because nasal carriage of S aureus has been associated with subsequent infection.3

S aureus has outstanding ability to acquire resistance to antibiotics. Epidemics or pandemics of antibiotic-resistant S aureus have arisen in the past 60 years.4,5 Benzylpenicillin was no longer effective for treatment of most S aureus infections within 10 years after its introduction for use in people because of the acquisition of plasmid-encoded β-lactamase.4 Penicillin-resistant S aureus became pandemic throughout the late 1950s and early 1960s.6 Metillin-resistant S aureus (MRSA) was first reported in 1961, 2 years after the antibiotic was introduced to treat the penicillin-resistant strain.7 MRSA spread worldwide over the next several decades and is now endemic in most hospitals and health-care facilities in industrialised countries. In the USA, MRSA is among the leading causes of death by any single infectious agent.8 A major concern for treatment of MRSA infections is the increasing prevalence of resistance to several antibiotics (multidrug resistance).

By contrast with health-care-associated MRSA (HA-MRSA) infections, for which there is a predisposing risk factor or illness, community-associated MRSA (CA-MRSA) infections can occur in otherwise healthy individuals,9 suggesting that these bacterial strains have greater virulence than do traditional HA-MRSA strains. In addition to enhanced virulence, some CA-MRSA strains, such as USA300, have the ability to spread readily. These characteristics perhaps partly explain why CA-MRSA is present in many countries (figure 1).10,11

In this Seminar, we review our current understanding of CA-MRSA emergence, the basis for enhanced transmission and virulence, and provide an update of the most recent strategies for diagnosis and treatment of CA-MRSA infections.

Epidemiology and disease

Epidemiology

Since MRSA was first described in 1961, it has been regarded as a nosocomial pathogen that is not normally present in the community. However, this notion has changed greatly in the past 15 years, and CA-MRSA infections are now prevalent and widespread (figure 1). Although MRSA infections acquired from the community were reported in Detroit, MI, USA, in 1982, all patients had predisposing risk factors for infection, such as previous hospital admission or intravenous drug abuse.12 The first genuine cases of CA-MRSA infection were reported among individuals from Kimberley, Western Australia in the early 1990s.13 Notably, these patients were from remote and sparsely populated areas, and thus did not have close contact with individuals who had access to large medical centres. Additionally, the MRSA isolates (later known collectively as strain WA-MRSA-C1 or WA-1) from the patients were not multidrug resistant, and were distinct from other MRSA strains present in Australia.14,15

Four otherwise healthy children in the upper midwestern region of the USA died from sepsis or necrotising pneumonia that was caused by MRSA during 1997–99.16

Search strategy and selection criteria

We searched PubMed using the terms “CA-MRSA”, “Europe and CA-MRSA”, “Panton-Valentine leukocidin”, and “USA300”, without any language restrictions. We selected references mainly from the past 5 years, including cross-references, although landmark or highly regarded references were also included. Review articles were cited when appropriate for further detail about a specific topic. We also included references on the basis of comments from peer reviewers.

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These infections were not acquired in a health-care setting, and the children had no risk factors for MRSA infection. This small outbreak was caused by a CA-MRSA strain that later became known as MW2, a close relative of WA-MRSA-1. In a retrospective study, Herold and colleagues reported an increasing prevalence of CA-MRSA infections during 1988–95 among children in Chicago, IL, USA, who had no predisposing risk factors. Cellulitis and abscesses were the most frequent features associated with these infections, whereas bacteraemia was the feature most often associated with HA-MRSA infections (four of 12 patients). By contrast with most HA-MRSA isolates, most CA-MRSA isolates were susceptible to non-β-lactam antibiotics and therefore were not multidrug resistant. These early outbreaks were the beginning of what is now an epidemic of CA-MRSA in North America, particularly the USA (figure 1).

Whole-genome sequencing of MW2 showed a staphylococcal chromosomal cassette mec (SCCmec), named SCCmecIV, which contains the meca gene that encodes resistance to meticillin. Unlike SCCmec elements I–III, which encode molecules that provide resistance to several classes of antibiotics, SCCmecIV encodes resistance only to β-lactam antibiotics, partly accounting for the non-multidrug-resistant phenotype of MW2. The anti-biogram and gene composition of MW2 lend support to the hypothesis that this was a newly emerging MRSA clone, probably the result of SCCmecIV integrating into a meticillin-susceptible S aureus (MSSA) strain. MW2 also contains genes encoding Panton-Valentine leukocidin (PVL), a prophage-encoded bicomponent toxin that targets phagocytic leucocytes. SCCmecIV and PVL are molecular markers associated with the emergence of CA-MRSA worldwide, although PVL does not seem to be present in all CA-MRSA strains (eg, WA-MRSA-1 strains typically do not have PVL). Association of PVL with CA-MRSA led to renewed interest in this toxin and its potential role in pathogenesis.

MW2 and closely related strains, collectively known as pulsed-field type USA400, multilocus sequence type (MLST or ST) 1 strains, were the most prominent community-associated strains in the USA before 2001. From the early 2000s to now, many outbreaks and increasing rates of CA-MRSA were reported by the scientific community and lay press. Many skin and soft-tissue infections were reported in healthy and diverse populations, including inmates in correctional facilities, military personnel, children in day-care centres, men who have sex with men, athletes, Native Americans, and Pacific Islanders. A new CA-MRSA clone known as USA300, an ST8 strain unrelated to the MW2/ST1 lineage, was identified in most cases in the USA, indicating the rapid replacement of USA400 in most communities. Although USA400 remains a prominent cause of disease in some regions of North America, USA300 is now the leading cause of community-associated bacterial infections in the USA.

CA-MRSA is a health problem in nearly all industrialised countries, albeit to varied extents. For example, PVL-positive CA-MRSA strains were isolated...
from 1–3% of all skin and soft-tissue infections in France in 2000–03, whereas the prevalence of these strains was reported as being greater than 50% in the USA. Additionally, the most abundant CA-MRSA strains in Europe are distinct from those in North America, Oceania, or other parts of the world (figure I).

Such distinctions are made partly on the basis of molecular typing schemes that include MLST, SCCmec, spa, or agr, and pulsed-field gel electrophoresis. The emergence of MRSA as a community pathogen is associated with a change in the genetic organisation of SCCmec. Since the late 1960s, five main MLST-defined pandemic clones of MRSA—ST5, ST8, ST22, ST36, and ST45—spread successfully in different regions of the world and caused substantial nosocomial disease. With the exception of ST22, which has only been reported as SCCmecIV, these multidrug-resistant clones originally contained three genetically distinct SCCmec elements (I, II, and III) that, on the basis of their large size and other properties, probably have little movement in nature. CA-MRSA clones identified in the USA, Europe, and Australia have SCCmecIV or a recent variant. By contrast with the historic SCCmec types, the recent recombinant elements are highly promiscuous, and have moved repeatedly into diverse lineages of MSSA.

SCCmecIV seems to be essential for the emergence and success of CA-MRSA because the element is smaller and much more mobile than is SCCmecI–III, which is present in HA-MRSA strains, because it is widely dispersed among several MRSA lineages and imparts little or no fitness cost in vitro or in vivo. Several other SCCmec variants and types (eg, V, VI, VII, and VIII) have since been identified that tend to be of a similar size, but differ in fine structure and thus show plasticity.

**Colonisation and disease**

*S. aureus* can be regarded as part of normal human flora because about one in three people are colonised by it without any associated disease. Although CA-MRSA should be similar to other *S. aureus* strains in this respect—ie, high prevalence of infections should be matched by correspondingly high levels of nasal colonisation, most individuals in the USA who are colonised by *S. aureus* are colonised by MSSA strains despite the higher abundance of CA-MRSA infections. This finding suggests that CA-MRSA strains cause infection in the absence of nasal colonisation. In addition to the nostrils, the throat, axilla, groin and perirectal area, and non-intact skin are sites colonised by *S. aureus* and can be regarded as potentially important sites for colonisation by CA-MRSA.

Studies of nasal carriage provide a sentinel approach to assess the burden of *S. aureus* in a population; previously, as a health-care associated organism, MRSA was rarely recovered from healthy populations. In 1998, among 500 nasal swabs cultured from children and their carers in a New York City vaccination clinic, NY, USA, carriage rates of *S. aureus* were from 35% in children to 28% in adults, but importantly, only one person (0·26%) had MRSA. By comparison, in a concurrent study at the University of Chicago Children’s Hospital emergency department, the reported colonisation rate with MRSA was 11 (2·2%) of 500 children, which might indicate the higher burden of CA-MRSA in the upper midwest region of the USA at that time. MRSA carriage in Nashville, TN, USA, was 0·8% in 2001; however, when the investigators repeated the study in 2005, they noted that among 500 swabbed children, 46 (9·2%) tested positive for MRSA. These results are consistent with the changing epidemiology of MRSA, and its increasing prevalence in the community. Carriers of *S. aureus* have a higher risk of infection than do non-carriers, and they are an important source of spread of infection. Thus, as the proportion of CA-MRSA increases in carriage isolates, so does its transmission within a population of exposed individuals. Moreover, the rapid dissemination of CA-MRSA strains and the high attack rate in outbreak settings suggest that they are more easily transmitted than are other *S. aureus* strains.

CA-MRSA, like all strains of *S. aureus*, is transmitted by direct contact with the organism, usually by skin-to-skin contact with a colonised or infected individual. However, fomites contaminated with CA-MRSA might have a role in transmission in some settings. The Centers for Disease Control and Prevention in Atlanta, GA, USA, have proposed five factors or five Cs of MRSA transmission—ie, Crowding, frequent skin-to-skin Contact, Compromised skin integrity, Contaminated items and surfaces, and lack of Cleanliness. These factors are prevalent in the diverse populations, with increased numbers of CA-MRSA infections—eg, among military personnel and children in day-care centres. *S. aureus*—as part of normal flora, or transmitted by contaminated objects or colonised or infected individuals—circumvents human host defence to cause infection.

The burden of staphylococcal disease has increased worldwide since the emergence of CA-MRSA. Skin and soft-tissue infections represent about 90% of cases of...
CA-MRSA infection (table 1), and 90% of these are abscesses or cellulitis with purulent drainage. Essentially, CA-MRSA strains can cause the same types of infections as MSSA strains (table 1). However, some CA-MRSA strains have been associated with very severe, invasive disease or syndromes, suggesting that they are more virulent than are other S aureus strains. These syndromes include purpura fulminans with or without Waterhouse-Friderichsen’s syndrome, pyomyositis and myositis, necrotising fasciitis (virtually unheard of before CA-MRSA), osteomyelitis, and pneumonia (sometimes necrotising; figure 2).

**Virulence and pathogenesis**

*Staphylococcus aureus* immune evasion

The ability of bacteria to cause disease in human beings is due largely to evasion of innate immunity, which includes resistance to killing by phagocytic leukocytes. *S aureus* produces several molecules—some on the cell surface and others freely secreted—that together elicit a robust inflammatory response. In as much as neutrophils are a key component of the inflammatory response and are the most prominent cellular defence against *S aureus* infections, the pathogen has evolved means to circumvent function of these host cells. For example, *S aureus* synthetises molecules that block the function of serum complement or antimicrobial peptides, and detoxify reactive oxygen species. Additionally, *S aureus* produces secreted toxins that are implicated in pathogenesis, including those that are cytolytic for host cells. Some of these toxins are produced by most *S aureus* strains and are thus not specific to CA-MRSA strains. A comprehensive discussion of the virulence molecules is outside the scope of this Seminar, and we therefore refer the reader to several reviews about the topic. Here we focus our discussion on molecules for which there is information in the context of CA-MRSA transmission, virulence, and pathogenesis.

**Determinants of CA-MRSA virulence**

CA-MRSA strains cause infections in otherwise healthy people and have the ability to cause unusually severe disease. Consistent with these findings, CA-MRSA strains are much more virulent than are HA-MRSA strains in models of animal infections. Together, these results suggest CA-MRSA strains have greater virulence and ability to evade host defences than traditional HA-MRSA strains have. Pronounced virulence might contribute not only to disease severity, but also to persistent disease, which could increase chances of pathogen transmission. Despite much progress in the past several years, the molecular basis of the pathogenesis of CA-MRSA has not been completely established.

PVL has been intensely investigated because the two genes encoding it (*lukS-PV* and *lukF-PV*) are the only genes coding for a known virulence determinant that has been epidemiologically linked to CA-MRSA infections. The cytolytic and biochemical properties of PVL were well established before the emergence of CA-MRSA. Although PVL was associated with community-acquired infections of *S aureus* that were caused by phage-type 80/81 in the 1950s and 1960s, the epidemiological association of PVL with CA-MRSA prompted the assessment of the role of PVL in pathogenesis by use of isogenic *lukS/F-PV* gene deletion strains. Generally, results from experimental studies in animal models of skin and soft-tissue infection, sepsis, and pneumonia, have shown no effect or only minor and strain-dependent effects of PVL. In one study, direct instillation of purified PVL into lungs produced tissue injury, and PVL was thought to contribute to disease by altering virulence gene regulation in *S aureus*. However, the effects attributed to PVL expressed during infection were actually due to an unintended genetic mutation that resulted in defective virulence gene regulation.

The susceptibility of white blood cells to PVL in vitro can differ greatly among mammalian species, and is potentially a caveat for the interpretation of experimental studies in which the effects of PVL are investigated in animal models of infection. For example, mouse neutrophils are more resistant to the cytolytic activity of purified PVL in vitro than are those from rabbits or human beings. Although results from studies of partially purified PVL in animal models suggest that the systemic effects on leukocytes are similar in mice and rabbits, the resistance of rodent neutrophils to PVL produced during an actual infection could partly account for the negative findings for its role in pathogenesis in rodent models of infection. Since neutrophils largely mediate the effects of or are targets for PVL, rabbits—which like human beings have neutrophils that are highly susceptible to PVL—might be an appropriate model system to study the effects of PVL. Indeed, PVL has been shown to contribute to severity of disease in rabbit models of pneumonia and...
osteomyelitis, albeit with high bacterial inocula. These findings might be consistent with those in vitro—ie, only under specific growth conditions do PVL-positive CA-MRSA strains produce sufficient toxin to promote lysis of human neutrophils to a greater extent than the corresponding PVL-negative isogenic mutants. In any case, PVL's role in CA-MRSA pathogenesis cannot be resolved on the basis of only its activity in vitro. Although most available data from experimental studies suggest that PVL is not the main determinant of CA-MRSA virulence, the activity of PVL might largely be specific to man or the toxin could play a part in pathogenesis under unique conditions, such as those involving host susceptibility factors, and in some infections such as necrotising pneumonia and osteomyelitis.

Although the focus of most efforts to understand the pathogenesis of CA-MRSA has been on PVL, the possible role of other cytolytic toxins—namely, α toxin and phenol-soluble modulins, has also been investigated. α toxin (or α haemolysin) is a well described pore-forming toxin that lyases many types of host cells, including most types of leucocytes (although not neutrophils), and has proinflammatory effects. Phenol-soluble modulins are short, amphipathic, and α-helical peptides; the α-type toxins stimulate and lyse neutrophils, and other host cells. α-toxin and α-type phenol-soluble modulins greatly affect the severity of experimental CA-MRSA infection. The mortality rate in infection with CA-MRSA strains that do not have α-type phenol-soluble modulins was substantially reduced in a murine model of sepsis, and lesion size and area of dermonecrosis were reduced substantially in a murine model of skin infection. α-toxin-negative CA-MRSA strains (USA300 and USA400) are essentially avirulent in experimental murine pneumonia, and antibodies to α toxin protect mice from experimental CA-MRSA pneumonia. In the same models, virulence did not differ between wild-type and isogenic lukS/F-PV-negative (PVL negative) strains and anti-PVL antibodies were not protective. These studies show that α toxin and α-type phenol-soluble modulins play a major part in CA-MRSA disease and pathogenesis, and also emphasise the value of parallel investigation to assess the contribution of each S aureus virulence determinant to pathogenesis. This information is essential for assessment of potential targets for prophylaxis or therapeutic agents directed against CA-MRSA.

By contrast with the PVL genes, which are encoded on a mobile genetic element, α toxin and phenol-soluble modulins are encoded in the core genome of S aureus. Thus, differences in virulence between CA-MRSA and HA-MRSA strains that are attributed to these toxins should be caused by differential gene expression. Accordingly, investigation of gene expression within representative subclones of S aureus clonal complex 8 (defined by MLST), which includes USA300 and other closely related strains, showed that USA300 has exceptionally high expression of α toxin, α-type phenol-soluble modulins, and other putative determinants of virulence, such as secreted proteases. Additionally, changes in gene expression might explain the greater success of USA300 than the more distantly related USA400 strain in the USA. These findings suggest that the basis of the evolution of virulence in CA-MRSA, at least partly, is the differential gene expression, which might include yet poorly understood rearrangements of gene regulatory networks in these strains.

The question then remains what distinguishes the strains of the pandemic USA300 clone from those of its less successful direct predecessor USA500, since these strains have similar virulence in mouse models of infection. The answer might be obtained by assessment of the determinants of colonisation and transmissibility rather than virulence. For example, USA300 strains have a mobile genetic element—ie, arginine catabolic mobile element, which might contain genes that potentially help survival on human skin. This genetic element, which is absent from other, less successful CA-MRSA strains, could contribute to the noted success of USA300. Animal models of colonisation with S aureus are needed to improve our understanding of current and future MRSA pandemics.

Because a traditional opsonophagocytic vaccine is not available for S aureus, and multidrug resistance is increasing among CA-MRSA strains in some parts of the world, novel approaches to target virulence as a means of attenuating disease severity are in progress. Such endeavours might be aimed, for example, at passive immunisation with antibodies against S aureus toxins. Since the results from all studies of PVL in animal models of infection, including those that show a contribution of the toxin to virulence, show PVL-negative CA-MRSA strains retain most of their virulence, therapeutic efforts that target only this toxin might have little efficacy. The substantial contribution of α toxin and α-type phenol-soluble modulins to CA-MRSA virulence in animal models suggests that these molecules could be valuable targets for antitoxin-based therapeutic approaches. Any S aureus antitoxin preparation ideally should be directed against several targets, and will have to be designed to take into account
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co-trimoxazole, tetracyclines, and clindamycin, but this between CA-MRSA isolates and other MRSA strains—antibiotics is with standard susceptibility tests. The only way to assess susceptibility to non-β-lactam confi rmatory tests are done in most clinical laboratories. Of sterile body sites, specifi  city is essentially 100%. Isolation in infection. If the bacterium is isolated from blood or other \( S\) aureus is strong evidence against staphylococcal to render a site culture-negative), failure to culture an organism will grow in virtually any non-selective bacterial culture medium. Unless a patient has been previously treated with an effective antistaphylococcal drug (and generally several days of effective treatment are needed to render a site culture-negative), failure to culture \( S \) aureus is strong evidence against staphylococcal infection. If the bacterium is isolated from blood or other sterile body sites, specifi city is essentially 100%. Isolation of \( S \) aureus from a respiratory specimen is not specifi c because nasopharyngeal colonisation of normal individuals is common (hence isolation from a nasal swab or throat culture is not useful for assessment of whether an infection at some other site is caused by \( S \) aureus). However, in the clinical setting of pneumonia, if staphylococci are the predominant organisms that stain gram-positive and many polymorphonuclear neutrophils and few or no epithelial cells are present, \( S \) aureus infection is likely.

Standard methods to test antimicrobial susceptibility, such as disc diffusion, broth dilution, or automated methods, can be used to accurately identify MRSA strains. A latex agglutination test that detects PBP2a, the penicillin-binding protein that mediates meticillin resistance, and nucleic acid amplifi cation methods to detect \( m\)ecA, the gene encoding PBP2a, are also available. A detailed discussion of the advantages and disadvantages of these various methods is beyond the scope of this Seminar, except to note that sensitivity and specifi city of any test is about 95%, no test is perfect, and confi rmatory tests are done in most clinical laboratories. The only way to assess susceptibility to non-β-lactam antibiotics is with standard susceptibility tests.

Susceptibility tests cannot be used to discriminate between CA-MRSA isolates and other MRSA strains—eg, the characterist ic \( S\) USA300 phenotype is susceptible to co-trimoxazole, tetracyclines, and clindamycin, but this pattern is not uniform and the organism can acquire other resistance genes. Moreover, each CA-MRSA lineage has a typical antibiotic resistance pattern. Although the epidemic CA-MRSA clones are now a substantial cause of health-care-associated infections, they can be distinguished from traditional HA-MRSA strains by genotyping by PFGE, spa, MLST, or SCCmec, and presence of PVL genes. However, these typing methods have no proven value in the clinic, because selection of the appropriate treatment for infection requires careful assessment of the patient’s history and antibiotic susceptibility patterns of any recovered \( S \) aureus isolates.

**Diagnosis**

\( S \) aureus infection is diagnosed readily by isolating the organism from cultures of blood, tissue, or pus. The organism will grow in virtually any non-selective bacterial culture medium. Unless a patient has been previously treated with an effective antistaphylococcal drug (and generally several days of effective treatment are needed to render a site culture-negative), failure to culture \( S \) aureus is strong evidence against staphylococcal infection. If the bacterium is isolated from blood or other sterile body sites, specifi city is essentially 100%. Isolation of \( S \) aureus from a respiratory specimen is not specifi c because nasopharyngeal colonisation of normal individuals is common (hence isolation from a nasal swab or throat culture is not useful for assessment of whether an infection at some other site is caused by \( S \) aureus). However, in the clinical setting of pneumonia, if staphylococci are the predominant organisms that stain gram-positive and many polymorphonuclear neutrophils and few or no epithelial cells are present, \( S \) aureus infection is likely.

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**Prevention and treatment**

**Antimicrobial therapy**

Emergence of CA-MRSA has profoundly aff ected the choice of empirical treatment for suspected staphylococcal infection, particularly common skin and soft-tissue infections. \( \beta \)-lactams, which are inexpensive, not toxic, and highly eff ective, have been the drugs of choice for treatment of such infections, but, like HA-MRSA, CA-MRSA strains are broadly resistant to almost all \( \beta \)-lactam antibiotics, making these an undesirable option when the prevalence of CA-MRSA strains is high. Clinical evidence supporting the efficacy of other agents for treatment of CA-MRSA infections is insuffi cient. The treatment of choice for cutaneous abscesses caused by \( S \) aureus, irrespective of antibiotic susceptibility, is incision and drainage. Antibiotics provide little or no benefi t in most cases, and are not routinely recommended unless the patient has conditions such as those listed in the panel.

Inexpensive oral agents commonly recommended for treatment of CA-MRSA infections include clindamycin, long-acting tetracyclines (doxycycline and minocycline), co-trimoxazole, rifampicin, and fusidic acid (table 2). Clindamycin is active in vitro against 80% or more of CA-MRSA strains, and has been used with success in the treatment of CA-MRSA infections, mainly skin and soft-tissue infections. It is active against group A streptococcus, a common cause of skin and soft-tissue

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<thead>
<tr>
<th>Resistance rates</th>
<th>Typical adult dosing</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Clindamycin</td>
<td>3–24%</td>
<td>300 mg three times a day</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>9–24%&lt;sup&gt;*&lt;/sup&gt;</td>
<td>100 mg twice a day</td>
</tr>
<tr>
<td>Minocycline</td>
<td>9–24%&lt;sup&gt;*&lt;/sup&gt;</td>
<td>100 mg twice a day</td>
</tr>
<tr>
<td>Co-trimoxazole</td>
<td>0–10%</td>
<td>1–2 double-strength tablet (trimethoprim 150 mg and sulfamethoxazole 800 mg) twice a day</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>&lt;1%</td>
<td>600 mg once a day</td>
</tr>
<tr>
<td>Fusidic acid</td>
<td>&lt;5%</td>
<td>500 mg three times a day</td>
</tr>
<tr>
<td>Linezolid</td>
<td>&lt;1%</td>
<td>600 mg twice a day</td>
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<sup>*</sup>Rates shown are for tetracycline and are likely to be 5% or less for doxycycline and minocycline.

Table 2: Rates of resistance and dosing of oral antimicrobial agents for treatment of community-acquired meticillin-resistant Staphylococcus aureus infections
infections, so it is an attractive choice for treatment of these infections, especially those not accompanied by abscess. Clindamycin resistance, however, seems to be increasing.128,129

Doxycycline and minocycline are commonly used in the treatment of CA-MRSA infection. They have greater antistaphylococcal activity than tetracycline has,122 but activity against group A streptococcus is not well defined. Doxycycline and minocycline seem to be effective in the treatment of skin and soft-tissue infections caused by MRSA.111,112 Tetracyclines are not recommended for pregnant women, or children younger than 8 years.

Co-trimoxazole is active against 90–100% of CA-MRSA isolates.130,131 Efficacy data to support the use of this drug combination for MRSA infections are inadequate,132–135 but suggest that it is an appropriate oral treatment for suspected CA-MRSA infection of skin and soft tissues. Activity of co-trimoxazole against group A streptococcus is unknown; if infection with this organism is suspected, some other agent, such as clindamycin or a β-lactam antibiotic, should be used instead. Co-trimoxazole is not recommended for treatment during the third trimester of pregnancy.

Rifampicin or fusidic acid could be used as adjunctively with another active drug or together;136,137 neither agent should be used alone because resistance is likely to emerge during single-drug therapy.138

Linezolid, an oxazolidinone, is approved by the US Food and Drug Administration (FDA) for complex skin and soft-tissue infections and MRSA pneumonia. Clinically, it has similar efficacy to vancomycin,139–141 and resistance so far is rare. Because linezolid is expensive and has the potential for substantial toxicity, including myelosuppression, peripheral neuropathy, optic neuritis, and lactic acidosis,142–144 it should be reserved for serious infections when other oral drugs are not an option.

Parenteral therapy
Vancomycin is the first-line intravenous drug for severe MRSA (CA-MRSA and HA-MRSA) infections. Daptomycin, tigecycline, and linezolid are FDA-approved for the treatment of MRSA infections, but these drugs have not been shown to be better than vancomycin in clinical trials. However, vancomycin is far from ideal. Persistent or recurrent bacteremia during treatment,145,146 high treatment-failure rates,147 nephrotoxicity associated with high doses needed to attain the recommended trough concentrations of 15–20 μg/mL,148 and emergence of non-susceptible strains149,150 are all too common. Since there is no evidence of whether any one drug or combination of drugs is better than vancomycin alone, which other drug(s) should be used to treat severe MRSA infections, or those not responding to vancomycin, is completely unknown.

Experimental agents and adjunctive therapy
Drugs that are in development for treatment of MRSA infections include glycopeptide derivatives, such as telavancin, dalbavancin, and oritavancin,151–153 and anti-MRSA β-lactams, such as ceftaroline and ceftobiprole.154–156 Telavancin, dalbavancin, and oritavancin are derivatives of vancomycin; all have shown rapid, concentration-dependent bactericidal activity in vitro, and have good activity in vivo in animal models of infection. In randomised clinical trials, these derivatives had similar efficacy for treatment of skin and soft-tissue infections, but were not better than standard treatments.157 Telavancin is now FDA approved for complicated skin and soft-tissue infections.

Anti-MRSA β-lactams are active because they have high binding affinity for PBP2a. Two cephalosporin compounds, ceftobiprole and ceftaroline, are highly active against MRSA in rabbit models of endocarditis158,159 and were as effective as vancomycin for MRSA infections of skin and soft tissues.160,161 Ceftobiprole has been approved for clinical use in Canada and Switzerland. Further studies are needed to define the role of anti-MRSA β-lactams for treatment of MRSA infections.

The glycopeptide derivatives and β-lactams can only be administered parenterally, and thus drugs that are active against MRSA by oral administration are still needed. Oxazolidinones, which have good activity against MRSA and are orally bioavailable, are in early stages of development.

The ease with which S aureus can acquire or develop resistance to antimicrobials has prompted an interest in non-traditional approaches and drugs for treatment and prevention of MRSA. Among these are lysostaphin,162 antimicrobial peptides,163 natural products (eg, tea tree oil),164 and active and passive immunisation against S aureus.165,166,167,168 Even if a development programme is successful, these agents are still years away from being used in the clinical setting. Barriers to development are expensive cost of goods, hypersensitivity that can arise with repeated administration of protein products, unfavourable pharmacological properties (eg, short half-life, toxicity), and a notable absence of success in previous efforts at active and passive immunisation.

With respect to immunisation, a vaccine is needed that will protect against or control S aureus infection, and this is an active area of research. A vaccine directed to prevent or control S aureus infections is perhaps unrealistic, since all individuals have naturally occurring antistaphylococcal antibodies and are protected already. This natural immunity, coupled with the ability of this bacterium to survive after uptake by phagocytic leucocytes,169 is presumably one of the main reasons a vaccine directed at enhancing opsonophagocytosis has been largely unsuccessful. Factors such as environment, host innate immune status, and genetics probably play a substantial part in determining susceptibility to severe infection, and research of these
factors is in progress. Physicians will have to rely mainly on the available drugs, which should be used judiciously and wisely to avoid their further loss from the antimicrobial armamentarium.

Conclusions and future

*S. aureus* has been a cause of human disease throughout recorded history. The antibiotic era was perhaps largely expected to eliminate *S. aureus* (and other bacterial pathogens) as a leading cause of human infections. However, *S. aureus* has extraordinary ability to develop resistance to antibiotics, which have been the impetus for waves of antibiotic resistance over the past 60 years. 1 This resistance is perplexing, because antibiotics are absolutely crucial for treatment of many types of bacterial infections. Another approach is to develop an improved understanding of the host-related and pathogen-related factors involved in human disease, and target those. Unknown host genetic factors are likely to be important—if not the major—determinants of susceptibility to severe staphylococcal infections. Such factors must be considered to have a full understanding for the successful treatment of CA-MRSA. There are also bacterial factors, some related directly to virulence, that distinguish CA-MRSA strains from those that arise in hospitals in the context of promoting pathogenesis, and such factors should be regarded as targets for new treatments. Additionally, new technologies, such as high-throughput whole-genome sequencing, allow complete elucidation of how strains that cause epidemics evolve. Together, this information will ultimately be important in our efforts to restrict the effect of antibiotic-resistant *S. aureus* infections in the community.

Contributors

All authors participated in the conception and writing of the Seminar, and were assigned specific sections to write, which were then edited by all authors.

Conflicts of interest

HFC has been a consultant for Johnson and Johnson, and has been a consultant and has received research grant support from Pfizer. The other authors declare that they have no conflicts of interest.

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