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Community-associated methicillin-resistant *Staphylococcus aureus*

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Summary

Methicillin-resistant *Staphylococcus aureus* (MRSA) is endemic in hospitals worldwide and a significant cause of morbidity and mortality. Healthcare-associated MRSA infections occur in individuals with predisposing risk factors for disease, such as surgery or presence of an indwelling medical device. By contrast, community-associated MRSA (CA-MRSA) infections often occur in otherwise healthy individuals who lack such risk factors. In addition, CA-MRSA infections are epidemic in some countries. These observations suggest that CA-MRSA strains are more virulent and transmissible than traditional hospital-associated MRSA strains. Relatively limited treatment options for CA-MRSA infections compound the problem of enhanced virulence and transmission. Although progress has been made toward understanding emergence of CA-MRSA, virulence, and treatment of infections, our knowledge in these areas remains incomplete. Here were review the most current knowledge in these areas and provide perspective on future outlook for prophylaxis and/or new therapies for CA-MRSA infections.

Introduction

Staphylococcus aureus is a leading cause of human bacterial infections worldwide.[1] Severity of these infections is quite varied and can range from minor skin infections to fatal necrotizing pneumonia. The pathogen is also a human commensal organism and ~30% of healthy non-institutionalized individuals are colonized asymptomatically with *S. aureus* in

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Author contributions

All authors participated in conception and writing of the article. Authors were assigned specific sections to write and these sections were then edited by all authors. As corresponding author, F.R.D. had the final responsibility for the decision to submit the article for publication.

Search strategy and selection criteria

We searched PubMed using the terms “CA-MRSA”, “Europe and CA-MRSA”, “Panton-Valentine Leukocidin”, and “USA300”. We selected references primarily from the past 5 years, including cross-references, although landmark and/or highly regarded references were also included. Review articles were cited where appropriate to more detail on a specific topic. We also included references based upon comments from peer reviewers.

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the anterior nares.[2] These observations are of note because *S. aureus* nasal carriage has been associated with subsequent infection.[3]

S. aureus has a remarkable ability to acquire resistance to antibiotics. Infections caused by antibiotic resistant *S. aureus* have occurred in epidemic or pandemic waves over the past 60 years.[4,5] Within 10 years after penicillin was introduced for use in humans, in many cases it was no longer effective for treatment of *S. aureus* infections due to acquisition of plasmid-encoded beta lactamase.[6] Penicillin-resistant *S. aureus* became pandemic throughout the late 1950s and early 1960s.[7] Methicillin-resistant *S. aureus* (MRSA) was first reported in 1961, two years after the antibiotic was introduced to treat penicillin-resistant *S. aureus*.[8] MRSA spread worldwide over the next several decades and is now endemic in most hospitals and healthcare facilities of industrialized countries. In the United States, MRSA is among the leading causes of death by any single infectious agent.[4,9] A major concern for treatment of MRSA infections is the increasing prevalence of resistance to multiple antibiotics (multidrug resistance).

One of the most surprising recent events in the area of infectious diseases is the emergence of community-associated MRSA (CA-MRSA). In contrast to healthcare-associated MRSA (HA-MRSA) infections, for which there is a predisposing risk factor or condition, CA-MRSA infections can occur in otherwise healthy individuals,[10] suggesting that CA-MRSA strains have enhanced virulence compared with traditional HA-MRSA strains. In addition to enhanced virulence, some CA-MRSA strains such as USA300 have the ability to spread readily. These characteristics are perhaps in part the reason CA-MRSA is present in many countries globally (figure 1).[11,12]

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

Epidemiology and disease

Epidemiology

Since its first description in 1961, MRSA has been considered as a nosocomial pathogen and its presence in the community was uncommon. However, this concept has been reshaped dramatically over the past 15 years and CA-MRSA infections are now both prevalent and widespread (figure 1). Although MRSA infections acquired from the community were reported in the Detroit, Michigan area in 1982, these patients all had predisposing risk factors for infection, such as previous hospitalization and/or intravenous drug abuse.[13] The first bona fide cases of CA-MRSA infection were reported among individuals from the Kimberley region of Western Australia in the early 1990s.[14] 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 centers. In addition, the patient MRSA isolates (later known collectively as strain WA-MRSA-1 or WA-1) were non-multidrug resistant and distinct from other MRSA strains present in Australia.[14,15]

During 1997–1999, four otherwise healthy children in the upper Midwestern region of the US died from sepsis and/or necrotizing pneumonia caused by MRSA.[16] These infections were not acquired in a healthcare setting and the children had no risk factors for MRSA infection. This small outbreak was caused by a CA-MRSA strain later known as MW2,[17] a close relative of WA-MRSA-1.[15] An earlier retrospective study by Herold et al. reported an increasing prevalence of CA-MRSA infections during 1988–1995 among children in the Chicago area who had no predisposing risk factors.[10] Cellulitis and abscesses were the most frequent syndromes associated with these infections, whereas those from HA-MRSA

infections were most often (4 of 12 patients) bacteremias.[10] In contrast to the majority of HA-MRSA isolates, most of these CA-MRSA isolates were susceptible to non beta-lactam antibiotics and therefore not multidrug resistant.[10] These early outbreaks were the beginnings of what is now an epidemic of CA-MRSA in North America, especially in the US (figure1).

Whole genome sequencing of MW2 revealed a unique staphylococcal chromosomal cassette *mec* (SCC*mec*) named SCC*mec*IV,[17,18] which harbors the *mecA* gene encoding resistance to methicillin (see below for more details). Unlike SCC*mec* elements I–III, which encode molecules that provide resistance to multiple classes of antibiotics, SCC*mec*IV encodes resistance only to beta-lactam antibiotics,[18] accounting in part for the non-multidrug resistant phenotype of MW2. The antibiogram and gene composition of MW2 give credence to the hypothesis that this was a newly emerging MRSA clone, likely the result of SCC*mec*IV integrating into a methicillin-susceptible *S. aureus* (MSSA) strain. MW2 also contains genes encoding Panton-Valentine leukocidin (PVL), a prophage-encoded bi-component toxin that targets phagocytic leukocytes. SCC*mec*IV and PVL are molecular markers associated with the emergence of CA-MRSA worldwide,[11] although more recent data indicates PVL is not always present among CA-MSA strains (for example, WA-MRSA-1 strains typically lack PVL).[19–22] Association of PVL with CA-MRSA led to a renewed interest in this toxin and its potential role in pathogenesis and this topic is discussed in detail below.

MW2 and closely related strains, collectively known as pulsed-field type USA400 (USA400),[23] multilocus sequence type (MLST or ST) 1 strains,[24] were the most prominent community-associated strains in the US prior to 2001.[16,25] From the early 2000s to the present, in both the scientific community and the lay press, numerous outbreaks and increasing case rates of CA-MRSA were reported. These reports described an inordinate number of skin and soft tissues infections among healthy and diverse populations including inmates in correctional facilities,[26] military personnel,[26] children in day-care centers,[27] men-who-have-sex-with-men,[28] athletes at all levels,[29] Native Americans,[30] and Pacific Islanders.[31] Surprisingly, a new CA-MRSA clone known as USA300, a ST8 strain unrelated to the MW2/ST1 lineage, was identified in the majority of US cases, indicating the rapid replacement of USA400 in most communities.[25] Although USA400 remains a prominent cause of disease in some regions of North America, USA300 is currently the leading cause of community-associated bacterial infections in the US.[23,32–34]

CA-MRSA is currently a human health problem in nearly all industrialized countries, albeit to varied extents. For example, PVL-positive CA-MRSA were isolated from 1–3% of all skin and soft tissue infections in France in 2000–2003,[35,36] whereas the prevalence of these strains was recently reported as >50% in the US.[34] In addition, the most abundant CA-MRSA strains in Europe are distinct from those in North America, Oceania, or other parts of the world (figure 1).[12] Such distinctions are made in part based upon molecular typing schemes that include MLST,[24] SCC*mec* typing,[18] *spa*[37] and/or *agr* typing, and pulsed-field gel electrophoresis (PFGE).[23] These *S. aureus* typing methods have been reviewed recently.[5] The change in epidemiology of MRSA–i.e., its emergence as a community pathogen–correlates with a change in the genetic organization of SCC*mec*. Since the late 1960s, five major MLST-defined pandemic clones of MRSA, ST5, ST8, ST22, ST36, and ST45, spread successfully in different regions of the world and caused significant nosocomial disease. With the exception of ST22, which has only been reported as SCC*mec*IV,[38] these multidrug resistant clones originally harbored three genetically distinct SCC*mec* elements (I, II, and III) that, based on their relatively large size and other properties, likely have limited movement in nature. As discussed above, CA-MRSA clones identified in the US, Europe and Australia carry SCC*mec*IV or a recent variant, and in

contrast to the historic SCC*mec* types, these recent recombinant elements are highly promiscuous and have moved repeatedly into diverse lineages of MSSA.[39] SCC*mec*IV appears critical to the emergence and success of CA-MRSA because the element is smaller and much more mobile than SCC*mec*I–III present in HA-MRSA strains, as it is widely dispersed among numerous MRSA lineages,[39] and it imparts little or no fitness cost in vitro[40,41] or in vivo.[42] Several other SCC*mec* variants and types (e.g., types V, VI, VII, and VIII) have since been identified.[43–45] These SCC*mec* elements, although they tend to be within a similar size range, differ in fine structure and thus demonstrate the remarkable plasticity of the element.[43–45]

Colonization and Disease

S. aureus can be considered normal human flora because approximately a third of the population is colonized by the organism with no associated disease.[46,47] Although CA-MRSA should be similar to other *S. aureus* strains in this regard, i.e., high prevalence of CA-MRSA infections should be reflected by correspondingly high levels of nasal colonization, most individuals in the US that are colonized by *S. aureus* are colonized by MSSA strains despite the higher abundance of CA-MRSA infections.[2] This observation suggests CA-MRSA strains cause infection in the absence of nasal colonization. In addition to the anterior nares, the throat, axilla, groin and perirectal area, and non-intact skin are sites colonized by *S. aureus* and could be considered as potentially important sites for colonization by CA-MRSA.

Nasal carriage studies provide a sentinel approach to determine the burden of *S. aureus* in a population; historically, as a healthcare associated organism, MRSA was rarely recovered from healthy populations. In 1998, among 500 nasal swabs cultured from children and guardians in a New York City vaccination clinic, *S. aureus* carriage rates ranged from 35% in children to 28% in adults, but significantly, only 1 subject (0.26%) harbored MRSA.[48] By comparison, a concurrent study at the University of Chicago Children's Hospital Emergency Department reported a 2.2% MRSA colonization rate (11/500 children),[49] which may reflect the higher burden of CA-MRSA in the upper Midwest region of the US at that time. MRSA carriage in Nashville, Tennessee was reported as 0.8% in 2001; however, when the authors repeated the study in 2005, they found that among 500 swabbed children, 46 or 9.2% of the population were harboring MRSA.[50] These results are consistent with the changing epidemiology of MRSA and its increasing prevalence in the community. *S. aureus* carriers have a higher risk of infection than non-carriers and they are an important source of spread of *S. aureus* strains among individuals. Thus, as the proportion of CA-MRSA increases among 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 other *S. aureus* stains.[51]

CA-MRSA, like all *S. aureus*, is transmitted by directly contacting the organism, and this usually occurs by direct skin-to-skin contact with a colonized or infected individual.[52–54] However, fomites contaminated with CA-MRSA may have a role in transmission in some settings.[30,32] The Centers for Disease Control and Prevention in Atlanta, Georgia have proposed five factors or "5 C's" of MRSA transmission. These factors are Crowding, frequent skin-to-skin Contact, Compromised skin integrity, Contaminated items and surfaces, and lack of Cleanliness (www.cdc.gov/niosh/topics/mrsa/). The "5 C's" are prevalent among the diverse populations with increased numbers of CA-MRSA infections as described above (e.g., military personnel, children in day-care centers, and etc). *S. aureus*, either as a part of normal flora or transmitted by contaminated objects or colonized / infected individuals, circumvents human host defense to cause infection.

The burden of staphylococcal disease has increased worldwide since the emergence of CA-MRSA.[55–58] Skin and soft-tissue infections (SSTIs) constitute approximately 90% of CA-MRSA cases (table 1), and 90% of these are abscesses and/or cellulitis[59] with purulent drainage.[34] In essence, CA-MRSA strains can cause the same types of infections as MSSA strains (table 1). However, some CA-MRSA strains have been associated with particularly severe, invasive disease or syndromes, suggesting they are more virulent than other *S. aureus* strains (see below for details). These syndromes include purpura fulminans with or without Waterhouse-Friderichsen syndrome,[60,61] pyomyositis and myositis,[62] necrotizing fasciitis (virtually unheard of before CA-MRSA),[63] osteomyelitis,[64,65] and pneumonia (sometimes necrotizing) (figure 2).[10,59,65–69]

Virulence and pathogenesis

The ability of bacteria to cause disease in humans is due largely to evasion of innate immunity, which includes resistance to killing by phagocytic leukocytes. *S. aureus* produces numerous molecules–some on the cell surface and others freely secreted–that together elicit a robust inflammatory response. Inasmuch as neutrophils are a key component of the inflammatory response and the most prominent cellular defense against *S. aureus* infections, the pathogen has evolved means to circumvent function of these host cells. For example, *S. aureus* synthesizes molecules that block function of serum complement or antimicrobial peptides, and detoxify reactive oxygen species.[70] In addition, *S. aureus* is notorious for its ability to produce secreted toxins implicated in pathogenesis, including those that are cytolytic for host cells.[70] Some of the secreted toxins are produced by most *S. aureus* strains and are thus not unique to CA-MRSA strains. A comprehensive discussion of *S. aureus* virulence molecules is outside the scope of this Seminar and we refer the reader to several relatively recent reviews on the topic.[70–73] Here we focus our discussion on molecules for which there is information in the context of CA-MRSA transmission, virulence and pathogenesis.

CA-MRSA virulence determinants

CA-MRSA strains cause infections in otherwise healthy people[10,16] and have the capacity to cause unusually severe disease.[60,63] Consistent with these observations, CA-MRSA strains are significantly more virulent than HA-MRSA strains in animal infection models.[74,75] Collectively, these observations suggest CA-MRSA strains have increased virulence and capacity to evade host defenses compared to traditional HA-MRSA strains. Pronounced virulence may contribute not only to disease severity, but also to more persistent disease, which could increase chances of pathogen transmission. Despite significant progress over the past several years, the molecular basis of CA-MRSA pathogenesis remains incompletely determined.

The bi-component leukotoxin Panton-Valentine leukocidin (PVL) has been intensely investigated because the two genes encoding PVL (*lukS-PV* and *lukF-PV*) are the only ones coding for a known virulence determinant that has been epidemiologically linked to CA-MRSA infections.[11] The cytolytic and biochemical properties of the PVL toxin were well established before the appearance of CA-MRSA.[76,77] Although PVL was associated with community *S. aureus* infections caused by phage-type 80/81 in the 1950s and 1960s,[7] the relatively recent epidemiological association of PVL with CA-MRSA prompted examination of the role of PVL in pathogenesis using isogenic *lukS/F-PV* gene deletion mutants in CA-MRSA strains. Surprisingly, many experimental studies in animal models of skin and soft tissue infection, sepsis, and pneumonia, largely have shown no effect or only minor and strain-dependent effects of PVL.[78–84] Although not directly addressing a potential role of PVL in CA-MRSA virulence, an earlier study using transduced *S. aureus* laboratory strains reported that PVL contributed significantly to severe pneumonia in mice.[85] These studies

also found that direct instillation of purified PVL into lungs produced tissue injury. Another potentially intriguing finding was that PVL altered virulence gene regulation as a basis for the contribution to virulence.[85] However, it was shown later that the effects attributed to PVL expressed during infection were due to an unintended genetic mutation causing defective virulence gene regulation, rather than PVL.[86]

The susceptibility of white blood cells to PVL in vitro can differ considerably among mammalian species[76] and is potentially a caveat for the interpretation of experimental studies investigating PVL's effect in animal infection models. For example, mouse neutrophils are more resistant to the cytolytic activity of purified PVL in vitro compared with those from rabbits or humans.[76,87] Although, early studies with partially purified PVL in animal models indicate systemic effects of PVL toward leukocytes are comparable in mice and rabbits in vivo,[88,89] the relative resistance of rodent neutrophils to PVL produced during an actual infection could account in part for the negative data from rodent infection models concerning PVL's role in pathogenesis. To the extent that neutrophils largely mediate the effects of or are targets for PVL, rabbit neutrophils–which similar to those from humans are highly susceptible to PVL–may be a more appropriate model system to study the effects of PVL. Indeed, more recently PVL has been shown to contribute to severity of disease in rabbit models of pneumonia and osteomyelitis, albeit when using relatively high bacterial inocula.[90,91] It seems likely that only under very specific growth conditions will 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.[79,81,87] Clearly, knowledge of PVL activity in vitro is alone insufficient to resolve the question about its role in CA-MRSA pathogenesis. Although most currently available data from experimental studies indicate PVL may not be a major determinant of CA-MRSA virulence, it is still possible that the activity of PVL is largely human-specific and/or the toxin plays a role in pathogenesis under unique conditions, such as those involving host susceptibility factors, and in certain infections such as necrotizing pneumonia and osteomyelitis.[90–92]

While most efforts to understand CA-MRSA pathogenesis have focused on PVL, some recent studies have also addressed the possible role of other cytolytic toxins–namely alpha-toxin and phenol-soluble modulins (PSMs).[82,93] Alpha-toxin (or alpha-hemolysin) is a well described pore-forming toxin that has been reported to lyse many types of host cells, including most types of leukocytes[94] (although not neutrophils)[95] and it has pro-inflammatory effects.[94,96] PSMs are short, amphipathic and alpha-helical peptide toxins, among which those of the alpha-type stimulate and lyse neutrophils and other host cells.[93] Both alpha-toxin and alpha-type PSMs have a dramatic impact on the severity of experimental CA-MRSA disease. CA-MRSA strains lacking alpha-type PSMs caused significantly reduced mortality in a murine sepsis model, and lesion size and area of dermonecrosis were decreased significantly in a murine skin infection model.[93] Alpha-toxin negative CA-MRSA strains (USA300 and USA400) are essentially avirulent in experimental murine pneumonia[82] and antibodies to alpha-toxin protect mice from experimental CA-MRSA pneumonia.[97] By comparison, in the same models there was no difference in virulence between wild-type and isogenic *lukS/F-PV*-negative (PVL negative) strains[81–83] and anti-PVL antibodies were non-protective.[97] These studies demonstrate that alpha-toxin and alpha-type PSMs play a major role of in CA-MRSA disease and pathogenesis, and also underscore the value of parallel investigation to determine the relative contribution of each *S. aureus* virulence determinant to pathogenesis. This information is critical for evaluation of potential targets for prophylaxis or therapeutic agents directed against CA-MRSA.

In contrast to the PVL genes, which are encoded on a mobile genetic element (the acquisition of which is proposed to confer virulence), both alpha-toxin and PSMs are

encoded in the core genome of *S. aureus*. Thus, observed differences in virulence between CA-MRSA and HA-MRSA strains that are attributed to these toxins must be due to differential gene expression. Accordingly, investigation of gene expression within representative subclones of *S. aureus* clonal complex 8 (defined by MLST),[98] which includes USA300 and other closely related strains, revealed that USA300 expresses alpha-toxin, alpha-type PSMs, and other putative determinants of virulence such as secreted proteases to an exceptionally high extent.[74] In addition, changes in gene expression may explain the greater success of USA300 compared to the more distantly-related USA400 strain in the US.[99] These findings indicate that evolution of virulence in CA-MRSA is based, at least in part, on differential gene expression, which may include yet poorly understood rearrangements of gene regulatory networks in CA-MRSA strains.

The question then remains what distinguishes the strains of the pandemic USA300 clone from those of its less successful direct predecessor USA500, as these strains have comparable virulence in mouse infection models.[74] The answer to this question may be found by examining determinants of colonization and transmissibility rather than virulence. For example, USA300 strains harbor a mobile genetic element called arginine catabolic mobile element (ACME), which may contain genes that potentially facilitate survival on human skin.[42,100] ACME, which is absent from other, less successful CA-MRSA strains, may contribute to the noted greater success of USA300 by comparison. Animal models of *S. aureus* colonization are needed to facilitate a better understanding of current and future MRSA pandemics.

Given that a traditional opsonophagocytic vaccine is not available for *S. aureus*, and as there is an escalating increase in multidrug resistance among CA-MRSA strains in some areas of the world,[28,101,102] novel approaches targeting virulence as a means of attenuating disease severity are under development.[103] Such endeavors may be aimed for example at passive immunization using antibodies against *S. aureus* toxins.[104] Given that all studies of PVL in animal infection models, including those that show a contribution of the toxin to virulence, demonstrate PVL-negative CA-MRSA strains retain considerable virulence, therapeutic efforts that target this toxin solely may have limited potential efficacy. The significant contribution of alpha-toxin and alpha-type PSMs to CA-MRSA virulence in animal models suggests that these molecules could be valuable targets for antitoxin-based therapeutic approaches. Clearly, any *S. aureus* antitoxin preparation ideally should be directed against multiple targets and will have to be designed such that functional redundancy of *S. aureus* virulence determinants and the relative contribution of each are taken into account.

Diagnosis

S. aureus infection is diagnosed readily by isolating the organism from cultures of blood, tissue, or pus. Such material is typically loaded with *S. aureus* and as organism is not fastidious it will grow in virtually any non-selective bacterial culture medium. Unless a patient has been previously treated with an effective anti-staphylococcal agent (and several days of effective therapy generally are required to render a site culture-negative), failure to culture *S. aureus* is strong evidence against staphylococcal infection. If *S. aureus* is isolated from blood or other sterile body site, specificity is essentially 100%. Isolation of *S. aureus* from a respiratory specimen is less specific because nasopharyngeal colonization of normal individuals is so prevalent (also the reason isolation of *S. aureus* from a nasal swab or throat culture is not useful for determining 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 as Gram-positive and numerous PMNs and few or no epithelial cells are present, *S. aureus* infection is likely.

Standard antimicrobial susceptibility test methods such as disk diffusion, broth dilution, or automated methods accurately identify MRSA strains. A latex agglutination test that detects PBP2a, the penicillin-binding protein that mediates methicillin resistance, and nucleic acid amplification methods to detect *mecA*, the gene encoding PBP2a, are also available.[105–107] A detailed discussion of the advantages and disadvantages of these various methods is beyond the scope of this article, except to note that sensitivity and specificity of any single test is about 95%, no test is perfect, and most clinical laboratories perform confirmatory testing. Presently, the only way to determine susceptibility to non-beta-lactam antibiotics is by standard susceptibility testing.

Susceptibility tests cannot discriminate between CA-MRSA isolates and other MRSA strains. For example, the characteristic USA300 phenotype is susceptibility to trimethoprim-sulfamethoxazole (TMP-SMX), tetracyclines, and clindamycin, but this pattern is not uniform and the organism can acquire other resistance genes.[28] Moreover, each CA-MRSA lineage has a typical antibiotic resistance pattern.[11,12] Although the current epidemic CA-MRSA clones are now a significant cause of healthcare-associated infections, these clones can be distinguished from traditional HA-MRSA strains by genotyping by PFGE,[23] *spa* typing,[37] or MLST,[24] SCC*mec* typing,[18] and presence of PVL genes.[11] However, these typing methods have no proven value in the clinic, as selecting the appropriate treatment for infection requires careful evaluation of patient history and testing antibiotic susceptibility patterns of any recovered *S. aureus* isolates.

Prevention and treatment

Emergence of CA-MRSA has profoundly impacted the choice of empirical therapy for suspected staphylococcal infection, particularly common skin and soft tissue infections. Beta-lactams, which are relatively inexpensive, non-toxic, and highly effective, have been the drug of choice for treating such infections, but like HA-MRSA, CA-MRSA 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 alternative agents for treatment of CA-MRSA infections is limited. The treatment of choice for cutaneous abscesses caused by *S. aureus*, regardless of antibiotic susceptibility, is incision and drainage.[34,108–112] Antibiotic therapy provides little or no marginal benefit in most cases and is not routinely recommended unless the patient has conditions such as those listed in table 2.[113]

Antimicrobial therapy

Inexpensive oral agents commonly recommended for treatment of CA-MRSA infections include clindamycin, long-acting tetracyclines (doxycycline and minocycline), TMP-SMX, rifampin, and fusidic acid (table 3).[114–116] 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, primarily SSTI.[51,117,118] It is active against group A *Streptococcus*, a common cause of SSTI, which makes it an attractive choice for treatment of skin and soft infections, especially those not accompanied by abscess. Clindamycin resistance, however, may be increasing.[119,120]

The long-acting tetracyclines, doxycycline and minocycline, are commonly used in the treatment of CA-MRSA disease. They have enhanced anti-staphylococcal activity compared to tetracycline,[121] but activity against group A *Streptococcus* is not well defined. Doxycycline and minocycline appear to be effective in the treatment of MRSA SSTI.[122,123] Tetracyclines are not recommended for pregnant women or children under the age of eight years.

TMP-SMX is active against 90–100% of CA-MRSA isolates.[10,59,124] Efficacy data of TMP-SMX for the treatment of MRSA infections are limited,[125–128] but suggest that TMP-SMX is an appropriate for oral therapy of suspected CA-MRSA SSTI. Activity of TMP-SMX against group A *Streptococcus* is unknown and if infection with this organism is suspected, some other agent, such as clindamycin or a beta-lactam, should be used instead. TMP-SMX in not recommended for treatment of women during the third trimester of pregnancy.

Rifampin or fusidic acid may be considered for use as an adjunctive agent in combination with another active agent or used in combination with one another;[114,115] neither agent should be used alone because resistance is likely to emerge during single drug therapy.[129]

Linezolid, an oxazolidinone, is FDA approved for the treatment of complicated SSTI and MRSA pneumonia. Clinically it is comparable to vancomycin in efficacy,[130–133] and resistance so far is rare. Because linezolid is expensive and has the potential for significant toxicity, including myelosuppresion, peripheral neuropathy, optic neuritis, and lactic acidosis,[134–136] it should be reserved for treatment of more serious infections when other oral agents are not an option.

Parenteral therapy

Vancomycin, for the moment, remains the first-line intravenous agent for severe MRSA infections, both CA-MRSA and HA-MRSA. Daptomycin, tigecycline, and linezolid are FDA approved for the treatment of MRSA infections, but to date no clinical trial has demonstrated superiority of any of these agents over vancomycin. Although vancomycin remains a first-line agent for treatment of MRSA infections, it is far from ideal therapy. Persistent or recurrent bacteremia during therapy,[137,138] relatively high treatment failure rates,[139] nephrotoxicity associated with higher doses needed to attain the recommended trough concentrations of 15–20 μg/ml,[140] and emergence of non-susceptible strains[141,142] are all too commonly encountered. Unfortunately, in the absence of demonstrated superiority of any single agent or combination of agents over vancomycin alone, which alternative agent(s) should be used to treat severe MRSA infections, or used for those not responding to vancomycin, is completely unknown.

Experimental agents and adjunctive therapy

Investigational agents that are under development for treatment of MRSA infections include glycopeptides derivatives, such as telavancin, dalbavancin, and oritavancin,[143–145] and anti-MRSA beta-lactams, such as ceftaroline and ceftobiprole.[143–145] Telavancin, dalbavancin, and oritavancin are vancomycin derivatives; all exhibit rapid, concentration-dependent killing in vitro and have good activity in vivo in animal infection models. Randomized clinical trials of these new agents for treatment of skin and soft tissue infections indicate that they are comparable, but not superior to standard therapy.

Anti-MRSA beta-lactams are active because they have high binding affinity for PBP2a. Two cephalosporin compounds, ceftobiprole and ceftaroline, are highly active against MRSA in rabbit endocarditis models[146,147] and have been shown to be as effective as vancomycin for treatment of MRSA skin and soft infections.[148,149] Ceftobiprole has been approved for clinical use in Canada and Switzerland. Further studies are needed to define the role of anti-MRSA beta-lactams in the therapy of MRSA infections.

The glycopeptide-derivatives and beta-lactams can only be administered parenterally and thus there is still a need for oral agents that are active against MRSA. Oxazolidinone compounds, which have good activity against MRSA and are orally bioavailable are in early stages of development.[150]

The facility with which *S. aureus* can acquire or develop resistant to antimicrobials has prompted an interest in non-traditional approaches and agents for treatment and prevention of MRSA. Among these are lysostaphin[151], antimicrobial peptides,[152] natural products (e.g., tea tree oil),[153] and active and passive immunization against *S. aureus*.[97,154,155] Assuming that a development program is even successful, these agents are years away from the clinic. Barriers to development are expensive cost of goods, hypersensitivity that can occur upon repeated administration of protein products, unfavorable pharmacological properties (e.g., short half-life, toxicity), and a notable lack of success in previous efforts at active and passive immunization. With regard to the latter point, there remains a significant need for a vaccine that protects against or controls *S. aureus* infection and this is an active area of research. A vaccine approach directed to prevent or control all *S. aureus* infections is perhaps unrealistic, since all humans have naturally occurring anti-staphylococcal antibodies and are protected already. This natural immunity, coupled with the ability of *S. aureus* to survive after uptake by phagocytosis leukocytes,[156] is presumably one of the key reasons a vaccine approach directed at enhancing opsonophagocytosis has been largely unsuccessful. Factors such as environment, host innate immune status and genetics likely play a significant role in determining susceptibility to severe infection and research is ongoing in these areas. For the foreseeable future physicians will have to rely principally on currently available agents, which must be used judiciously and wisely in order to avoid their further loss from the antimicrobial armamentarium.

Concluding remarks and future outlook

S. aureus has been a cause of human disease throughout recorded history. Alexander Fleming's discovery of penicillin in 1928 and the ensuing modern 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 capacity to develop resistance to antibiotics and these agents have been the impetus for waves of antibiotic resistance in the pathogen over the past 60 years.[5] This problem is perplexing, because antibiotics are absolutely critical for treatment of many types of bacterial infections. One alternative approach is to develop a better understanding of the factors involved in human disease, both host- and pathogen-related, and target those. Undetermined host genetic factors are likely to be important–if not the major–determinants of susceptibility to severe staphylococcal infections. Such factors must be considered in order to have a full understanding the success of CA-MRSA. There are also bacterial factors, some related directly to virulence, that distinguish CA-MRSA strains from hospital relatives in the context of promoting pathogenesis, and such factors should be considered as targets for new therapeutics. In addition, new technologies such as high-throughput whole genome sequencing make it possible to fully understanding the evolution of strains that cause epidemics. In aggregate, this information will ultimately be important in our efforts to limit the impact of antibiotic resistant *S. aureus* infections in the community.

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References

1. Diekema DJ, Pfaller MA, Schmitz FJ, et al. Survey of infections due to *Staphylococcus* species: frequency of occurrence and antimicrobial susceptibility of isolates collected in the United States, Canada, Latin America, Europe, and the Western Pacific region for the SENTRY Antimicrobial

Surveillance Program, 1997–1999. Clin Infect Dis. 2001; 32(Suppl 2):S114–S132. [PubMed: 11320452]

2. Gorwitz RJ, Kruszon-Moran D, McAllister SK, et al. Changes in the prevalence of nasal colonization with *Staphylococcus aureus* in the United States, 2001–2004. J Infect Dis. 2008; 197:1226–34. [PubMed: 18422434]
3. von Eiff C, Becker K, Machka K, Stammer H, Peters G. Nasal carriage as a source of *Staphylococcus aureus* bacteremia. Study Group. N Engl J Med. 2001; 344:11–16. [PubMed: 11136954]
4. DeLeo FR, Chambers HF. Reemergence of antibiotic-resistant *Staphylococcus aureus* in the genomics era. J Clin Invest. 2009; 119:2464–74. [PubMed: 19729844]
5. Chambers HF, DeLeo FR. Waves of resistance: *Staphylococcus aureus* in the antibiotic era. Nat Rev Microbiol. 2009; 7:2464–74.
6. Kirby WM. Extraction of a highly potent penicillin inactivator from penicillin resistant staphylococci. Science. 1944; 99:452–53. [PubMed: 17798398]
7. Roundtree PM, Freeman BM. Infections caused by a particular phage type of *Staphylococcus aureus*. Med J Aust. 1956; 42:157–61.
8. Jevons MP. "Celbenin"-resistant staphylococci. Br Med J. 1961; 1:124–25.
9. Klevens RM, Morrison MA, Nadle J, et al. Invasive methicillin-resistant *Staphylococcus aureus* infections in the United States. JAMA. 2007; 298:1763–71. [PubMed: 17940231]
10. Herold BC, Immergluck LC, Maranan MC, et al. Community-acquired methicillin-resistant *Staphylococcus aureus* in children with no identified predisposing risk. JAMA. 1998; 279:593–98. [PubMed: 9486753]
11. Vandenesch F, Naimi T, Enright MC, et al. Community-acquired methicillin-resistant *Staphylococcus aureus* carrying Panton-Valentine leukocidin genes: worldwide emergence. Emerg Infect Dis. 2003; 9:978–84. [PubMed: 12967497]
12. Tristan A, Bes M, Meugnier H, et al. Global distribution of Panton-Valentine leukocidin--positive methicillin-resistant *Staphylococcus aureus*, 2006. Emerg Infect Dis. 2007; 13:594–600. [PubMed: 17553275]
13. Saravolatz LD, Pohlod DJ, Arking LM. Community-acquired methicillin-resistant *Staphylococcus aureus* infections: a new source for nosocomial outbreaks. Ann Intern Med. 1982; 97:325–29. [PubMed: 7114629]
14. Udo EE, Pearman JW, Grubb WB. Genetic analysis of community isolates of methicillin-resistant *Staphylococcus aureus* in Western Australia. J Hosp Infect. 1993; 25:97–108. [PubMed: 7903093]
15. Coombs GW, Pearson JC, O'Brien FG, et al. Methicillin-resistant *Staphylococcus aureus* clones, Western Australia. Emerg Infect Dis. 2006; 12:241–47. [PubMed: 16494749]
16. From the Centers for Disease Control and Prevention. Four pediatric deaths from community-acquired methicillin-resistant *Staphylococcus aureus*--Minnesota and North Dakota, 1997–1999. JAMA. 1999; 282:1123–25. [PubMed: 10501104]
17. Baba T, Takeuchi F, Kuroda M, et al. Genome and virulence determinants of high virulence community-acquired MRSA. Lancet. 2002; 359:1819–27. [PubMed: 12044378]
18. Ma XX, Ito T, Tiensasitorn C, et al. Novel type of staphylococcal cassette chromosome *mec* identified in community-acquired methicillin-resistant *Staphylococcus aureus* strains. Antimicrob Agents Chemother. 2002; 46:1147–52. [PubMed: 11897611]
19. Rossney AS, Shore AC, Morgan PM, et al. The emergence and importation of diverse genotypes of methicillin-resistant *Staphylococcus aureus* (MRSA) harboring the Panton-Valentine leukocidin gene (*pvl*) reveal that *pvl* is a poor marker for community-acquired MRSA strains in Ireland. J Clin Microbiol. 2007; 45:2554–63. [PubMed: 17581935]
20. O'Brien FG, Lim TT, Chong FN, et al. Diversity among community isolates of methicillin-resistant *Staphylococcus aureus* in Australia. J Clin Microbiol. 2004; 42:3185–90. [PubMed: 15243080]
21. Kim ES, Song JS, Lee HJ, et al. A survey of community-associated methicillin-resistant *Staphylococcus aureus* in Korea. J Antimicrob Chemother. 2007; 60:1108–14. [PubMed: 17884831]

22. Zhang K, McClure JA, Elsayed S, Tan J, Conly JM. Coexistence of Panton-Valentine leukocidin-positive and -negative community-associated methicillin-resistant *Staphylococcus aureus* USA400 sibling strains in a large Canadian health-care region. J Infect Dis. 2008; 197:195–204. [PubMed: 18173361]

23. McDougal LK, Steward CD, Killgore GE, et al. Pulsed-field gel electrophoresis typing of oxacillin-resistant *Staphylococcus aureus* isolates from the United States: establishing a national database. J Clin Microbiol. 2003; 41:5113–20. [PubMed: 14605147]

24. Enright MC, Day NP, Davies CE, Peacock SJ, Spratt BG. Multilocus sequence typing for characterization of methicillin-resistant and methicillin-susceptible clones of *Staphylococcus aureus*. J Clin Microbiol. 2000; 38:1008–15. [PubMed: 10698988]

25. Stemper ME, Brady JM, Qutaishat SS, et al. Shift in *Staphylococcus aureus* clone linked to an infected tattoo. Emerg Infect Dis. 2006; 12:1444–46. [PubMed: 17073100]

26. Aiello AE, Lowy FD, Wright LN, Larson EL. Meticillin-resistant *Staphylococcus aureus* among US prisoners and military personnel: review and recommendations for future studies. Lancet Infect Dis. 2006; 6:335–41. [PubMed: 16728319]

27. Adcock PM, Pastor P, Medley F, Patterson JE, Murphy TV. Methicillin-resistant *Staphylococcus aureus* in two child care centers. J Infect Dis. 1998; 178:577–80. [PubMed: 9697748]

28. Diep BA, Chambers HF, Graber CJ, et al. Emergence of multidrug-resistant, community-associated, methicillin-resistant *Staphylococcus aureus* clone USA300 in men who have sex with men. Ann Intern Med. 2008; 148:249–57. [PubMed: 18283202]

29. Begier EM, Frenette K, Barrett NL, et al. A high-morbidity outbreak of methicillin-resistant *Staphylococcus aureus* among players on a college football team, facilitated by cosmetic body shaving and turf burns. Clin Infect Dis. 2004; 39:1446–53. [PubMed: 15546080]

30. Baggett HC, Hennessy TW, Rudolph K, et al. Community-onset methicillin-resistant *Staphylococcus aureus* associated with antibiotic use and the cytotoxin Panton-Valentine leukocidin during a furunculosis outbreak in rural Alaska. J Infect Dis. 2004; 189:1565–73. [PubMed: 15116291]

31. Community-associated methicillin-resistant *Staphylococcus aureus* infections in Pacific Islanders--Hawaii, 2001–2003. Morb Mortal Wkly Rep. 2004; 53:767–70.

32. Miller LG, Diep BA. Clinical practice: colonization, fomites, and virulence: rethinking the pathogenesis of community-associated methicillin-resistant *Staphylococcus aureus* infection. Clin Infect Dis. 2008; 46:752–60. [PubMed: 18220477]

33. Kennedy AD, Otto M, Braughton KR, et al. Epidemic community-associated methicillin-resistant *Staphylococcus aureus*: recent clonal expansion and diversification. Proc Natl Acad Sci U S A. 2008; 105:1327–32. [PubMed: 18216255]

34. Moran GJ, Krishnadasan A, Gorwitz RJ, et al. Methicillin-resistant *S. aureus* infections among patients in the emergency department. N Engl J Med. 2006; 355:666–74. [PubMed: 16914702]

35. Robert J, Etienne J, Bertrand X. Methicillin-resistant *Staphylococcus aureus* producing Panton-Valentine leukocidin in a retrospective case series from 12 French hospital laboratories, 2000–2003. Clin Microbiol Infect. 2005; 11:585–87. [PubMed: 15966980]

36. Del Giudice P, Blanc V, Durupt F, et al. Emergence of two populations of methicillin-resistant *Staphylococcus aureus* with distinct epidemiological, clinical and biological features, isolated from patients with community-acquired skin infections. Br J Dermatol. 2006; 154:118–24. [PubMed: 16403104]

37. Shopsin B, Gomez M, Montgomery SO, et al. Evaluation of protein A gene polymorphic region DNA sequencing for typing of *Staphylococcus aureus* strains. J Clin Microbiol. 1999; 37:3556–63. [PubMed: 10523551]

38. Enright MC, Robinson DA, Randle G, et al. The evolutionary history of methicillin-resistant *Staphylococcus aureus* (MRSA). Proc Natl Acad Sci U S A. 2002; 99:7687–92. [PubMed: 12032344]

39. Daum RS, Ito T, Hiramatsu K, et al. A novel methicillin-resistance cassette in community-acquired methicillin-resistant *Staphylococcus aureus* isolates of diverse genetic backgrounds. J Infect Dis. 2002; 186:1344–47. [PubMed: 12402206]

40. Lee SM, Ender M, Adhikari R, et al. Fitness cost of staphylococcal cassette chromosome *mec* in methicillin-resistant *Staphylococcus aureus* by way of continuous culture. Antimicrob Agents Chemother. 2007; 51:1497–99. [PubMed: 17283194]

41. Okuma K, Iwakawa K, Turnidge JD, et al. Dissemination of new methicillin-resistant *Staphylococcus aureus* clones in the community. J Clin Microbiol. 2002; 40:4289–94. [PubMed: 12409412]

42. Diep BA, Stone GG, Basuino L, et al. The arginine catabolic mobile element and staphylococcal chromosomal cassette *mec* linkage: convergence of virulence and resistance in the USA300 clone of methicillin-resistant *Staphylococcus aureus*. J Infect Dis. 2008; 197:1523–30. [PubMed: 18700257]

43. Oliveira DC, Milheirico C, de Lencastre H. Redefining a structural variant of staphylococcal cassette chromosome *mec*, SCC*mec* type VI. Antimicrob Agents Chemother. 2006; 50:3457–59. [PubMed: 17005831]

44. Higuchi W, Takano T, Teng LJ, Yamamoto T. Structure and specific detection of staphylococcal cassette chromosome *mec* type VII. Biochem Biophys Res Commun. 2008; 377:752–56. [PubMed: 18926798]

45. Zhang K, McClure JA, Elsayed S, Conly JM. Novel staphylococcal cassette chromosome *mec* type, tentatively designated type VIII, harboring class A *mec* and type 4 *ccr* gene complexes in a Canadian epidemic strain of methicillin-resistant *Staphylococcus aureus*. Antimicrob Agents Chemother. 2009; 53:531–40. [PubMed: 19064897]

46. Graham PL III, Lin SX, Larson EL. A U.S. population-based survey of *Staphylococcus aureus* colonization. Ann Intern Med. 2006; 144:318–25. [PubMed: 16520472]

47. Kluytmans J, van Belkum A, Verbrugh H. Nasal carriage of *Staphylococcus aureus*: epidemiology, underlying mechanisms, and associated risks. Clin Microbiol Rev. 1997; 10:505–20. [PubMed: 9227864]

48. Shopsin B, Mathema B, Martinez J, et al. Prevalence of methicillin-resistant and methicillin-susceptible *Staphylococcus aureus* in the community. J Infect Dis. 2000; 182:359–62. [PubMed: 10882625]

49. Suggs AH, Maranan MC, Boyle-Vavra S, Daum RS. Methicillin-resistant and borderline methicillin-resistant asymptomatic *Staphylococcus aureus* colonization in children without identifiable risk factors. Pediatr Infect Dis J. 1999; 18:410–414. [PubMed: 10353512]

50. Creech CB, Kernodle DS, Alsentzer A, Wilson C, Edwards KM. Increasing rates of nasal carriage of methicillin-resistant *Staphylococcus aureus* in healthy children. Pediatr Infect Dis J. 2005; 24:617–21. [PubMed: 15999003]

51. Crum NF, Lee RU, Thornton SA, et al. Fifteen-year study of the changing epidemiology of methicillin-resistant *Staphylococcus aureus*. Am J Med. 2006; 119:943–51. [PubMed: 17071162]

52. Methicillin-resistant *Staphylococcus aureus* infections among competitive sports participants--Colorado, Indiana Pennsylvania, and Los Angeles County, 2000–2003. Morb Mortal Wkly Rep. 2003; 52:793–95.

53. Kazakova SV, Hageman JC, Matava M, et al. A clone of methicillin-resistant *Staphylococcus aureus* among professional football players. N Engl J Med. 2005; 352:468–75. [PubMed: 15689585]

54. Nguyen DM, Mascola L, Brancoft E. Recurring methicillin-resistant *Staphylococcus aureus* infections in a football team. Emerg Infect Dis. 2005; 11:526–32. [PubMed: 15829189]

55. Kaplan SL, Hulten KG, Gonzalez BE, et al. Three-year surveillance of community-acquired *Staphylococcus aureus* infections in children. Clin Infect Dis. 2005; 40:1785–91. [PubMed: 15909267]

56. Laupland KB, Ross T, Gregson DB. *Staphylococcus aureus* bloodstream infections: risk factors, outcomes, and the influence of methicillin resistance in Calgary, Canada, 2000–2006. J Infect Dis. 2008; 198:336–43. [PubMed: 18522502]

57. Mathews WC, Caperna JC, Barber RE, et al. Incidence of and risk factors for clinically significant methicillin-resistant *Staphylococcus aureus* infection in a cohort of HIV-infected adults. J Acquir Immune Defic Syndr. 2005; 40:155–60. [PubMed: 16186732]

58. Purcell K, Fergie J. Epidemic of community-acquired methicillin-resistant *Staphylococcus aureus* infections: a 14-year study at Driscoll Children's Hospital. Arch Pediatr Adolesc Med. 2005; 159:980–985. [PubMed: 16203945]

59. Fridkin SK, Hageman JC, Morrison M, et al. Methicillin-resistant *Staphylococcus aureus* disease in three communities. N Engl J Med. 2005; 352:1436–44. [PubMed: 15814879]

60. Adem PV, Montgomery CP, Husain AN, et al. *Staphylococcus aureus* sepsis and the Waterhouse-Friderichsen syndrome in children. N Engl J Med. 2005; 353:1245–51. [PubMed: 16177250]

61. Kravitz GR, Dries DJ, Peterson ML, Schlievert PM. Purpura fulminans due to *Staphylococcus aureus*. Clin Infect Dis. 2005; 40:941–47. [PubMed: 15824983]

62. Pannaraj PS, Hulten KG, Gonzalez BE, Mason EO Jr, Kaplan SL. Infective pyomyositis and myositis in children in the era of community-acquired, methicillin-resistant *Staphylococcus aureus* infection. Clin Infect Dis. 2006; 43:953–60. [PubMed: 16983604]

63. Miller LG, Perdreau-Remington F, Rieg G, et al. Necrotizing fasciitis caused by community-associated methicillin-resistant *Staphylococcus aureus* in Los Angeles. N Engl J Med. 2005; 352:1445–53. [PubMed: 15814880]

64. Arnold SR, Elias D, Buckingham SC, et al. Changing patterns of acute hematogenous osteomyelitis and septic arthritis: emergence of community-associated methicillin-resistant *Staphylococcus aureus*. J Pediatr Orthop. 2006; 26:703–8. [PubMed: 17065930]

65. Buck JM, Como-Sabetti K, Harriman KH, et al. Community-associated methicillin-resistant *Staphylococcus aureus*, Minnesota, 2000–2003. Emerg Infect Dis. 2005; 11:1532–38. [PubMed: 16318692]

66. Francis JS, Doherty MC, Lopatin U, et al. Severe community-onset pneumonia in healthy adults caused by methicillin-resistant *Staphylococcus aureus* carrying the Panton-Valentine leukocidin genes. Clin Infect Dis. 2005; 40:100–107. [PubMed: 15614698]

67. Gonzalez BE, Hulten KG, Dishop MK, et al. Pulmonary manifestations in children with invasive community-acquired *Staphylococcus aureus* infection. Clin Infect Dis. 2005; 41:583–90. [PubMed: 16080077]

68. Hageman JC, Uyeki TM, Francis JS, et al. Severe community-acquired pneumonia due to *Staphylococcus aureus*, 2003–04 influenza season. Emerg Infect Dis. 2006; 12:894–99. [PubMed: 16707043]

69. Naimi TS, LeDell KH, Como-Sabetti K, et al. Comparison of community- and health care-associated methicillin-resistant *Staphylococcus aureus* infection. JAMA. 2003; 290:2976–84. [PubMed: 14665659]

70. DeLeo FR, Diep BA, Otto M. Host defense and pathogenesis in *Staphylococcus aureus* infections. Infect Dis Clin North Am. 2009; 23:17–34. [PubMed: 19135914]

71. Rooijakkers SH, Van Strijp JA. Bacterial complement evasion. Mol Immunol. 2007; 44:23–32. [PubMed: 16875737]

72. Kraus D, Peschel A. *Staphylococcus aureus* evasion of innate antimicrobial defense. Future Microbiol. 2008; 3:437–51. [PubMed: 18651815]

73. Foster TJ. Immune evasion by staphylococci. Nat Rev Microbiol. 2005; 3:948–58. [PubMed: 16322743]

74. Li M, Diep BA, Villaruz AE, et al. Evolution of virulence in epidemic community-associated methicillin-resistant *Staphylococcus aureus*. Proc Natl Acad Sci U S A. 2009; 106:5883–88. [PubMed: 19293374]

75. Voyich JM, Braughton KR, Sturdevant DE, et al. Insights into mechanisms used by *Staphylococcus aureus* to avoid destruction by human neutrophils. J Immunol. 2005; 175:3907–19. [PubMed: 16148137]

76. Szmigielski S, Prevost G, Monteil H, Colin DA, Jeljaszewicz J. Leukocidal toxins of staphylococci. Zentralbl Bakteriol. 1999; 289:185–201. [PubMed: 10360319]

77. Woodin, AM. Staphylococcal leukocidin. In: Montje, t; Kadis, S.; Ajl, S., editors. Microbial Toxins. New York and London: Academic Press, Inc; 1970. p. 327-55.

78. Tseng CW, Kyme P, Low J, et al. *Staphylococcus aureus* Panton-Valentine leukocidin contributes to inflammation and muscle tissue injury. PLoS ONE. 2009; 4:e6387. [PubMed: 19633710]

79. Diep BA, Palazzolo-Ballance AM, Tattevin P, et al. Contribution of Panton-Valentine leukocidin in community-associated methicillin-resistant *Staphylococcus aureus* pathogenesis. PLoS ONE. 2008; 3:e3198. [PubMed: 18787708]
80. Montgomery CP, Daum RS. Transcription of inflammatory genes in the lung after infection with community-associated methicillin-resistant *Staphylococcus aureus*: A role for Panton-Valentine Leukocidin? Infect Immun. 2009; 77:2159–67. [PubMed: 19237525]
81. Voyich JM, Otto M, Mathema B, et al. Is Panton-Valentine leukocidin the major virulence determinant in community-associated methicillin-resistant *Staphylococcus aureus* disease? J Infect Dis. 2006; 194:1761–70. [PubMed: 17109350]
82. Bubeck Wardenburg J, Bae T, Otto M, DeLeo FR, Schneewind O. Poring over pores: alpha-hemolysin and Panton-Valentine leukocidin in *Staphylococcus aureus* pneumonia. Nat Med. 2007; 13:1405–6. [PubMed: 18064027]
83. Bubeck Wardenburg J, Palazzolo-Ballance AM, Otto M, Schneewind O, DeLeo FR. Panton-Valentine leukocidin is not a virulence determinant in murine models of community-associated methicillin-resistant *Staphylococcus aureus* disease. J Infect Dis. 2008; 198:1166–70. [PubMed: 18729780]
84. Brown EL, Dumitrescu O, Thomas D, et al. The Panton-Valentine leukocidin vaccine protects mice against lung and skin infections caused by *Staphylococcus aureus* USA300. Clin Microbiol Infect. 2009; 15:156–64.
85. Labandeira-Rey M, Couzon F, Boisset S, et al. *Staphylococcus aureus* Panton-Valentine leukocidin causes necrotizing pneumonia. Science. 2007; 315:1130–1133. [PubMed: 17234914]
86. Villaruz AE, Bubeck Wardenburg J, Khan BA, et al. A point mutation in the *agr* locus rather than expression of the Panton-Valentine leukocidin caused previously reported phenotypes in *Staphylococcus aureus* pneumonia and gene regulation. J Infect Dis. 2009; 200:724–34. [PubMed: 19604047]
87. Hongo I, Baba T, Oishi K, et al. Phenol-soluble modulin alpha 3 enhances the human neutrophil lysis mediated by Panton-Valentine leukocidin. J Infect Dis. 2009; 200:715–23. [PubMed: 19653829]
88. Grojec PL, Jeljaszewicz J. Effect of staphylococcal leukocidin on mouse leukocyte system. Zentralbl Bakteriol Mikrobiol Hyg [A]. 1981; 250:446–55.
89. Szmigielski S, Jeljaszewicz J, Wilczynski J, Korbecki M. Reaction of rabbit leucocytes to staphylococcal (Panton-Valentine) leucocidin in vivo. J Pathol Bacteriol. 1966; 91:599–604. [PubMed: 4224060]
90. Cremieux AC, Dumitrescu O, Lina G, et al. Panton-valentine leukocidin enhances the severity of community-associated methicillin-resistant *Staphylococcus aureus* rabbit osteomyelitis. PLoS ONE. 2009; 4:e7204. [PubMed: 19779608]
91. Diep, BA.; Chan, L.; Tattevin, P., et al. Panton-Valentine leukocidin determines the virulence of USA300 methicillin-resistant *Staphylococcus aureus* in a rabbit model of fulminant necrotizing, hemorrhagic pneumonia. Abstract No. B-1087, 49th ICAAC; San Francisco, CA. Sept 12–15, 2009;
92. Gillet Y, Issartel B, Vanhems P, et al. Association between *Staphylococcus aureus* strains carrying gene for Panton-Valentine leukocidin and highly lethal necrotising pneumonia in young immunocompetent patients. Lancet. 2002; 359:753–59. [PubMed: 11888586]
93. Wang R, Braughton KR, Kretschmer D, et al. Identification of novel cytolytic peptides as key virulence determinants for community-associated MRSA. Nat Med. 2007; 13:1510–1514. [PubMed: 17994102]
94. Bhakdi S, Tranum-Jensen J. Alpha-toxin of *Staphylococcus aureus*. Microbiol Rev. 1991; 55:733–51. [PubMed: 1779933]
95. Valeva A, Walev I, Pinkernell M, et al. Transmembrane beta-barrel of staphylococcal alpha-toxin forms in sensitive but not in resistant cells. Proc Natl Acad Sci U S A. 1997; 94:11607–11. [PubMed: 9326657]
96. Bartlett AH, Foster TJ, Hayashida A, Park PW. Alpha-toxin facilitates the generation of CXC chemokine gradients and stimulates neutrophil homing in *Staphylococcus aureus* pneumonia. J Infect Dis. 2008; 198:1529–35. [PubMed: 18823272]

97. Bubeck Wardenburg J, Schneewind O. Vaccine protection against *Staphylococcus aureus* pneumonia. J Exp Med. 2008; 205:287–94. [PubMed: 18268041]

98. Feil EJ, Enright MC. Analyses of clonality and the evolution of bacterial pathogens. Curr Opin Microbiol. 2004; 7:308–13. [PubMed: 15196500]

99. Montgomery CP, Boyle-Vavra S, Adem PV, et al. Comparison of virulence in community-associated methicillin-resistant *Staphylococcus aureus* pulsotypes USA300 and USA400 in a rat model of pneumonia. J Infect Dis. 2008; 198:561–70. [PubMed: 18598194]

100. Diep BA, Gill SR, Chang RF, et al. Complete genome sequence of USA300, an epidemic clone of community-acquired meticillin-resistant *Staphylococcus aureus*. Lancet. 2006; 367:731–39. [PubMed: 16517273]

101. Larsen AR, Stegger M, Bocher S, et al. Emergence and characterization of community-associated methicillin-resistant Staphyloccocus aureus infections in Denmark, 1999 to 2006. J Clin Microbiol. 2009; 47:73–78. [PubMed: 18971362]

102. Boyle-Vavra S, Ereshefsky B, Wang CC, Daum RS. Successful multiresistant community-associated methicillin-resistant *Staphylococcus aureus* lineage from Taipei, Taiwan, that carries either the novel Staphylococcal chromosome cassette *mec* (SCC*mec*) type VT or SCC*mec* type IV. J Clin Microbiol. 2005; 43:4719–30. [PubMed: 16145133]

103. Alksne LE, Projan SJ. Bacterial virulence as a target for antimicrobial chemotherapy. Curr Opin Biotechnol. 2000; 11:625–36. [PubMed: 11102800]

104. Otto M. Looking toward basic science for potential drug discovery targets against community-associated MRSA. Med Res Rev. 200910.1002/med.20160

105. Shore AC, Rossney AS, O'Connell B, et al. Detection of SCC*mec*-associated DNA Segments in multiresistant methicillin-susceptible *Staphylococcus aureus* (MSSA) and identification of *Staphylococcus epidermidis ccrAB*4 in both methicillin-resistant *S. aureus* (MRSA) and MSSA. Antimicrob Agents Chemother. 2008; 52:4407–19. [PubMed: 18852274]

106. van Hal SJ, Stark D, Lockwood B, Marriott D, Harkness J. Methicillin-resistant *Staphylococcus aureus* (MRSA) detection: comparison of two molecular methods (IDI-MRSA PCR assay and GenoType MRSA Direct PCR assay) with three selective MRSA agars (MRSA ID, MRSASelect, and CHROMagar MRSA) for use with infection-control swabs. J Clin Microbiol. 2007; 45:2486–90. [PubMed: 17537949]

107. Zschock M, Nesseler A, Sudarwanto I. Evaluation of six commercial identification kits for the identification of *Staphylococcus aureus* isolated from bovine mastitis. J Appl Microbiol. 2005; 98:450–455. [PubMed: 15659199]

108. Lee MC, Rios AM, Aten MF, et al. Management and outcome of children with skin and soft tissue abscesses caused by community-acquired methicillin-resistant *Staphylococcus aureus*. Pediatr Infect Dis J. 2004; 23:123–27. [PubMed: 14872177]

109. Llera JL, Levy RC. Treatment of cutaneous abscess: a double-blind clinical study. Ann Emerg Med. 1985; 14:15–19. [PubMed: 3880635]

110. Rajendran PM, Young D, Maurer T, et al. Randomized, double-blind, placebo-controlled trial of cephalexin for treatment of uncomplicated skin abscesses in a population at risk for community-acquired methicillin-resistant *Staphylococcus aureus* infection. Antimicrob Agents Chemother. 2007; 51:4044–48. [PubMed: 17846141]

111. Stevens DL, Bisno AL, Chambers HF, et al. Practice guidelines for the diagnosis and management of skin and soft-tissue infections. Clin Infect Dis. 2005; 41:1373–406. [PubMed: 16231249]

112. Duong M, Markwell S, Peter J, Barenkamp S. Randomized, controlled trial of antibiotics in the management of community-acquired skin abscesses in the pediatric patient. Ann Emerg Med. 2009

113. Stevens DL, Bisno AL, Chambers HF, et al. Practice guidelines for the diagnosis and management of skin and soft-tissue infections. Clin Infect Dis. 2005; 41:1373–406. [PubMed: 16231249]

114. Nathwani D, Morgan M, Masterton RG, et al. Guidelines for UK practice for the diagnosis and management of methicillin-resistant *Staphylococcus aureus* (MRSA) infections presenting in the community. J Antimicrob Chemother. 2008; 61:976–94. [PubMed: 18339633]

115. Barton MD, Hawkes M, Moore D. Guidelines for the prevention and management of community-acquired methicillin-resistant *Staphylococcus aureus*: A perspective for Canadian health care practitioners. Can J Infect Dis Med Microbiol. 2006; 17(Suppl C):4C–24C.

116. Gorwitz, RJ.; Jernigan, DB.; Powers, JH.; Jernigan, JA. Participants in the Centers for Disease Control and Prevention-Convened Experts'Meeting on Management of MRSA in the Community. Strategies for clinical management of MRSA in the community: summary of an experts' meeting convened by the Centers for Disease Control and Prevention. 2006. Available at http://www.cdc.gov/ncidod/dhqp/pdf/ar/CAMRSA_ExpMtgStrategies.pdf

117. Frank AL, Marcinak JF, Mangat PD, et al. Clindamycin treatment of methicillin-resistant *Staphylococcus aureus* infections in children. Pediatr Infect Dis J. 2002; 21:530–534. [PubMed: 12182377]

118. Martinez-Aguilar G, Hammerman WA, Mason EO Jr, Kaplan SL. Clindamycin treatment of invasive infections caused by community-acquired, methicillin-resistant and methicillin-susceptible *Staphylococcus aureus* in children. Pediatr Infect Dis J. 2003; 22:593–98. [PubMed: 12867833]

119. Braun L, Craft D, Williams R, Tuamokumo F, Ottolini M. Increasing clindamycin resistance among methicillin-resistant *Staphylococcus aureus* in 57 northeast United States military treatment facilities. Pediatr Infect Dis J. 2005; 24:622–26. [PubMed: 15999004]

120. Hulten KG, Kaplan SL, Gonzalez BE, et al. Three-year surveillance of community onset health care-associated *Staphylococcus aureus* infections in children. Pediatr Infect Dis J. 2006; 25:349–53. [PubMed: 16567988]

121. Minuth JN, Holmes TM, Musher DM. Activity of tetracycline, doxycycline, and minocycline against methicillin-susceptible and -resistant staphylococci. Antimicrob Agents Chemother. 1974; 6:411–14. [PubMed: 4157335]

122. Ruhe JJ, Menon A. Tetracyclines as an oral treatment option for patients with community onset skin and soft tissue infections caused by methicillin-resistant *Staphylococcus aureus*. Antimicrob Agents Chemother. 2007; 51:3298–303. [PubMed: 17576834]

123. Ruhe JJ, Monson T, Bradsher RW, Menon A. Use of long-acting tetracyclines for methicillin-resistant *Staphylococcus aureus* infections: case series and review of the literature. Clin Infect Dis. 2005; 40:1429–34. [PubMed: 15844065]

124. Liu C, Graber CJ, Karr M, et al. A population-based study of the incidence and molecular epidemiology of methicillin-resistant *Staphylococcus aureus* disease in San Francisco, 2004–2005. Clin Infect Dis. 2008; 46:1637–46. [PubMed: 18433335]

125. Cenizal MJ, Skiest D, Luber S, et al. Prospective randomized trial of empiric therapy with trimethoprim-sulfamethoxazole or doxycycline for outpatient skin and soft tissue infections in an area of high prevalence of methicillin-resistant *Staphylococcus aureus*. Antimicrob Agents Chemother. 2007; 51:2628–30. [PubMed: 17502411]

126. Markowitz N, Quinn EL, Saravolatz LD. Trimethoprim-sulfamethoxazole compared with vancomycin for the treatment of *Staphylococcus aureus* infection. Ann Intern Med. 1992; 117:390–398. [PubMed: 1503330]

127. Proctor RA. Role of folate antagonists in the treatment of methicillin-resistant *Staphylococcus aureus* infection. Clin Infect Dis. 2008; 46:584–93. [PubMed: 18197761]

128. Szumowski JD, Cohen DE, Kanaya F, Mayer KH. Treatment and outcomes of infections by methicillin-resistant *Staphylococcus aureus* at an ambulatory clinic. Antimicrob Agents Chemother. 2007; 51:423–28. [PubMed: 17116664]

129. Howden BP, Grayson ML. Dumb and dumber--the potential waste of a useful antistaphylococcal agent: emerging fusidic acid resistance in *Staphylococcus aureus*. Clin Infect Dis. 2006; 42:394–400. [PubMed: 16392088]

130. Rubinstein E, Cammarata S, Oliphant T, Wunderink R. Linezolid (PNU-100766) versus vancomycin in the treatment of hospitalized patients with nosocomial pneumonia: a randomized, double-blind, multicenter study. Clin Infect Dis. 2001; 32:402–12. [PubMed: 11170948]

131. Stevens DL, Herr D, Lampiris H, et al. Linezolid versus vancomycin for the treatment of methicillin-resistant *Staphylococcus aureus* infections. Clin Infect Dis. 2002; 34:1481–90. [PubMed: 12015695]

132. Weigelt J, Itani K, Stevens D, et al. Linezolid versus vancomycin in treatment of complicated skin and soft tissue infections. Antimicrob Agents Chemother. 2005; 49:2260–2266. [PubMed: 15917519]

133. Wunderink RG, Cammarata SK, Oliphant TH, Kollef MH. Continuation of a randomized, double-blind, multicenter study of linezolid versus vancomycin in the treatment of patients with nosocomial pneumonia. Clin Ther. 2003; 25:980–992. [PubMed: 12852712]

134. Apodaca AA, Rakita RM. Linezolid-induced lactic acidosis. N Engl J Med. 2003; 348:86–87. [PubMed: 12510056]

135. De Vriese AS, Coster RV, Smet J, et al. Linezolid-induced inhibition of mitochondrial protein synthesis. Clin Infect Dis. 2006; 42:1111–17. [PubMed: 16575728]

136. Gerson SL, Kaplan SL, Bruss JB, et al. Hematologic effects of linezolid: summary of clinical experience. Antimicrob Agents Chemother. 2002; 46:2723–26. [PubMed: 12121967]

137. Hawkins C, Huang J, Jin N, et al. Persistent *Staphylococcus aureus* bacteremia: an analysis of risk factors and outcomes. Arch Intern Med. 2007; 167:1861–67. [PubMed: 17893307]

138. Khatib R, Johnson LB, Sharma M, et al. Persistent *Staphylococcus aureus* bacteremia: Incidence and outcome trends over time. Scand J Infect Dis. 2008:1–6.

139. Dombrowski JC, Winston LG. Clinical failures of appropriately-treated methicillin-resistant *Staphylococcus aureus* infections. J Infect. 2008; 57:110–115. [PubMed: 18533269]

140. Lodise TP, Lomaestro B, Graves J, Drusano GL. Larger vancomycin doses (at least four grams per day) are associated with an increased incidence of nephrotoxicity. Antimicrob Agents Chemother. 2008; 52:1330–1336. [PubMed: 18227177]

141. Steinkraus G, White R, Friedrich L. Vancomycin MIC creep in non-vancomycin-intermediate *Staphylococcus aureus* (VISA), vancomycin-susceptible clinical methicillin-resistant *S. aureus* (MRSA) blood isolates from 2001–05. J Antimicrob Chemother. 2007; 60:788–94. [PubMed: 17623693]

142. Wang G, Hindler JF, Ward KW, Bruckner DA. Increased vancomycin MICs for *Staphylococcus aureus* clinical isolates from a university hospital during a 5-year period. J Clin Microbiol. 2006; 44:3883–86. [PubMed: 16957043]

143. Micek ST. Alternatives to vancomycin for the treatment of methicillin-resistant *Staphylococcus aureus* infections. Clin Infect Dis. 2007; 45(Suppl 3):S184–S190. [PubMed: 17712745]

144. Pan A, Lorenzotti S, Zoncada A. Registered and investigational drugs for the treatment of methicillin-resistant *Staphylococcus aureus* infection. Recent Patents Anti-Infect Drug Disc. 2008; 3:10–33.

145. Stryjewski ME, Chambers HF. Skin and soft-tissue infections caused by community-acquired methicillin-resistant *Staphylococcus aureus*. Clin Infect Dis. 2008; 46(Suppl 5):S368–S377. [PubMed: 18462092]

146. Chambers HF. Evaluation of ceftobiprole in a rabbit model of aortic valve endocarditis due to methicillin-resistant and vancomycin-intermediate *Staphylococcus aureus*. Antimicrob Agents Chemother. 2005; 49:884–88. [PubMed: 15728879]

147. Jacqueline C, Caillon J, Le MV, et al. In vivo efficacy of ceftaroline (PPI-0903), a new broad-spectrum cephalosporin, compared with linezolid and vancomycin against methicillin-resistant and vancomycin-intermediate *Staphylococcus aureus* in a rabbit endocarditis model. Antimicrob Agents Chemother. 2007; 51:3397–400. [PubMed: 17591849]

148. Noel GJ, Strauss RS, Amsler K, et al. Results of a double-blind, randomized trial of ceftobiprole treatment of complicated skin and skin structure infections caused by gram-positive bacteria. Antimicrob Agents Chemother. 2008; 52:37–44. [PubMed: 17954698]

149. Parish D, Scheinfeld N. Ceftaroline fosamil, a cephalosporin derivative for the potential treatment of MRSA infection. Curr Opin Investig Drugs. 2008; 9:201–9.

150. Shaw KJ, Poppe S, Schaadt R, et al. In vitro activity of TR-700, the active ingredient of the antibacterial prodrug TR-701, against linezolid resistant strains. Antimicrob Agents Chemother. 2008; 52:4442–47. [PubMed: 18838596]

151. Dajcs JJ, Thibodeaux BA, Hume EB, et al. Lysostaphin is effective in treating methicillin-resistant *Staphylococcus aureus* endophthalmitis in the rabbit. Curr Eye Res. 2001; 22:451–57. [PubMed: 11584345]

152. Lawton EM, Ross RP, Hill C, Cotter PD. Two-peptide lantibiotics: a medical perspective. Mini Rev Med Chem. 2007; 7:1236–47. [PubMed: 18220976]

153. Stapleton PD, Shah S, Ehlert K, Hara Y, Taylor PW. The beta-lactam-resistance modifier (−)-epicatechin gallate alters the architecture of the cell wall of *Staphylococcus aureus*. Microbiology. 2007; 153:2093–103. [PubMed: 17600054]

154. Schaffer AC, Lee JC. Vaccination and passive immunisation against *Staphylococcus aureus*. Int J Antimicrob Agents. 2008; 32(Suppl 1):S71–S78. [PubMed: 18757184]

155. Shinefield H, Black S, Fattom A, et al. Use of a *Staphylococcus aureus* conjugate vaccine in patients receiving hemodialysis. N Engl J Med. 2002; 346:491–96. [PubMed: 11844850]

156. Rogers DE, Tompsett R. The survival of staphylococci within human leukocytes. J Exp Med. 1952; 95:209–30. [PubMed: 14907971]

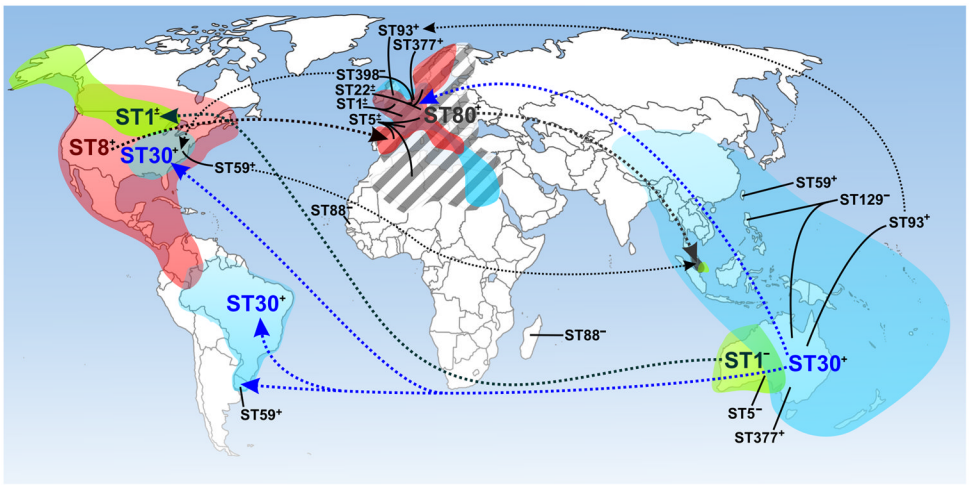

Figure 1. Global distribution of CA-MRSA as indicated by multilocus sequence type (ST)

Dotted lines indicated possible route of dissemination for the indicated clones. Major CA-MRSA clones are indicated by larger font and color. Colored regions are an estimate of the area in which infections have been reported for the indicated clone (not all are shown). ST1, green; ST8, red; ST30, blue; ST80, gray hatched. +, PVL-positive; −, PVL-negative; ±, combination of PVL-positive and PVL-negative strains isolated from the region.

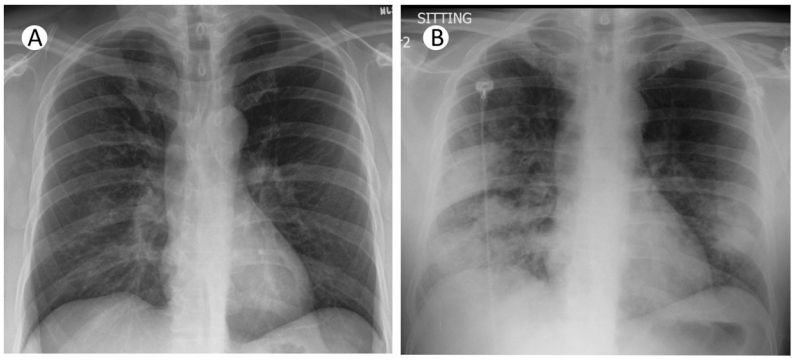

Figure 2. Rapid progression of radiographic findings in a fatal case of CA-MRSA pneumonia complicating novel H1N1 influenza A infection

(A) Chest radiograph at initial presentation of a patient with symptoms of fevers, headache, myalgias, and non-productive cough. (B) Chest radiograph taken 24 hours later with presence of new infiltrates and signs of consolidation in the right upper lobe, right middle lobe and left lower lobe.

Table 1

Distribution of infections caused by CA-MRSA in four observational studies.

	Author (Year of Study)			
	[1] Kaplan[55] (2005)	Fridkin[59] (2005)	Liu[124] (2008)	[1] Purcell[58] (2005)
Patients (N)	2659	1647	2270	826
SSTI (%)	95.6	87	88	94.1
Bone, joint (%)	2.4	3	<1	<1
Respiratory (%)	<1	2	4	<1
Bacteremia (%)	<1	3	4	<1
Urinary (%)	0	4	2	<1
Other (%)	1	4	2	4.5

[1]Children

Table 2

Situations in which to consider use of antimicrobial therapy following incision and debridement of a CA-MRSA SSTI.

Severe or extensive disease and/or rapid progression in presence of associated cellulitis
Signs and symptoms of systemic illness
Associated comorbidities or immune suppression (DM, HIV/AIDS, neoplastic disease)
Extremes of age
Abscess in area difficult to drain
Associated septic phlebitis
Lack of response of treatment with incision and drainage alone

Table 3

Rates of resistance and dosing of oral agents for treatment of CA-MRSA infections.

Antimicrobial agent	Resistance rates	Typical adult oral dosing	Comments
Clindamycin	3–24%	300 TID	D-test should be performed. Excellent activity against strep. Increasing resistance a concern.
Doxycycline Minocycline	[1]9–24%	100 mg BID 100 mg BID	Doxycycline and minocycline probably active against tetracycline resistant strains.
Trimethoprim-sulfamethoxazole	0–10%	1–2 DS (160/800 mg) BID	Low resistance rates in community, reasonable option for empiric therapy.
Rifampin	<1%	600 mg QD	Should not be used alone; potential for significant drug interactions
Fusidic acid	<5%	500 mg TID	Should not be used alone; limited experience in children
Linezolid	< 1 %	600 mg PO BID	Expensive.

[1]Rates shown are for tetracycline and are likely to be < 5% or less for doxycycline and minocycline