Case Seventeen: A Critical Case of Community Acquired Pneumonia

Matthew O. Henson, Rachel Sheridan, and Joel E. Mortensen

Autopsy examination revealed the cause of death to be from a severe bilateral necrotizing acute pneumonia involving predominantly the lower lobes of the lung (Figure 2). An extensive acute inflammatory infiltrate was noticeable in the alveolar spaces and respiratory bronchioles as well as areas of hemorrhage. Hemorrhagic pleural effusion was also present. Numerous micro-abscesses containing bacteria were found throughout both lungs (Figure 3). The trachea and bronchial mucosa also showed a diffuse necrotizing inflammation with destruction of the surface epithelium. In addition to the necrotizing pneumonia, there was also evidence of disseminated intravascular coagulation with microthrombi in the capillaries of not only the lungs, but glomeruli. Furthermore, damage from hemorrhagic shock was found on the intestinal mucosa and adrenal glands.

Clinical cultures were all sent to the microbiology laboratory for evaluation. The blood cultures showed no growth after five days and were discarded appro-

Figure 2. Necrotic lung found at the time autopsy. Numerous abscesses and abnormal lung tissue is notable. Photo taken by R. Sheridan 2/19/2009.

Figure 3. Microscopic images of the lung tissue at the time of autopsy. (Left) Hematoxylin and eosin stain at 100x magnification: Lung parenchyma showing diffuse necrotizing pneumonia with focal abscess formation and cavitations. There are also scattered areas of hemorrhage. (right) Hematoxylin and eosin stain at 200x magnification: Alveolar spaces filled with neutrophils, nuclear debris and bacterial colonies. Photo taken by R. Sheridan 2/19/09.
appropriately. The urine culture was read after 24 hours as 1,000-9,000 cfu/mL of normal flora present. However, the endotracheal specimen received a day prior to the patient’s demise was positive. After 18 hours of incubation the plates showed growth of beta-hemolytic golden colonies on 5% sheep blood agar and Chocolate agar with normal flora largely absent. A Gram-stain of the organism showed Gram-positive cocci in clusters. The catalase and slide coagulase tests were both positive and the organism was identified as Staphylococcus aureus. Growth on the chromogenic agar showed mauve colonies suggestive of methicillin resistance, thus the identification of the organism was updated to methicillin resistant S. aureus (MRSA) isolated. Susceptibility testing was then performed using the VITEK 2 automated system (bioMérieux, Inc.). The organism was reported resistant to methicillin, but sensitive to erythromycin, clindamycin, trimethoprim-sulfamethoxazole, gentamicin, tetracycline, and vancomycin. Cultures obtained at the time of autopsy were also positive for MRSA with identical susceptibilities.

Molecular characterization of the isolate revealed that the strain harbored the SCCmec type IV gene, and was positive for the PVL gene. This classified the strain to be of the community-associated origin. The viral cultures were held for 14 days and were negative for the observation of any cytopathic effects. Molecular PCR revealed that the patient was positive for Influenza B.

**Background**

Methicillin-resistant Staphylococcus aureus (MRSA) first appeared in the 1960s and has since become a global problem. In 1997 the National Healthcare Safety Network (NHSN) released an estimate that hospitalized patients in the United States develop 2 million health care associated infections each year, causing 90,000 deaths and $4.5 billion in health care costs. The majority of this impact is caused by MRSA and it is estimated that MRSA causes upwards of $2.5 billion in non-reimbursable costs. The CDC reports that more people die annually from MRSA than AIDS.

Now that hospital-acquired MRSA (HA-MRSA) has gained the attention of the general population and health care employees worldwide, a new problematic strain has arisen. In the late 1990’s, a new strain of MRSA was identified. Once defined as a problem impacting only those with predisposing risk factors such as recent hospitalization, hemodialysis, or residence within a nursing home, MRSA now was occurring in patients who had no prior history of health care exposure. Therefore, these strains were given the name of community-associated MRSA (CA-MRSA) and have since been proven to be of a new genetic lineage. Like HA-MRSA, CA-MRSA is seen in a variety of clinical settings. Although the majority of CA-MRSA infections are generally not associated with high mortality rates, given the opportunity they can be fatal.

**The Molecular Characteristics of CA-MRSA**

Initially, it was believed HA-MRSA, not CA-MRSA, was somehow establishing itself outside the healthcare setting. However, upon further investigation it appeared that these CA-MRSA strains were distinctly different from those seen in the hospital setting by both genetic and epidemiological evidence (Table 1). First, it was noted that the CA-MRSA strains were causing a different type of clinical syndromes in populations with risk factors more similar to methicillin-sensitive strains. Also, they were more susceptible to non-β-lactam antimicrobials such as tetracycline and clindamycin, rendering them open to a wider variety of treatment options. Most importantly, the discovery of unique genotypic differences and virulence factors soon solidified the recognition that CA-MRSA was entirely separate in origin from HA-MRSA.

Both CA-MRSA and HA-MRSA share the common ability for high levels of resistance to all penicillinase-resistant penicillins and cephalosporins. Their resistance is mediated by the production of a unique penicillin binding protein 2a (PBP2a), a peptidoglycan transpeptidase, encoded by the mecA gene. The PBP2a protein has a lower affinity to β-lactams than the native staphylococcal penicillin binding proteins found in ancestral strains. Thus, the native penicillin binding proteins are bound by β-lactams and inactivated, allowing PBP2a to continue cell wall synthesis.

The mecA gene is located on a mobile genetic element, the staphylococcal chromosomal cassette mec (SCCmec). Through horizontal transfer, this
gene was thought to be acquired by *S. aureus* from coagulase-negative staphylococci. So far there have been five individual SCCmec types described and each varies in size, genetic composition, and antimicrobial resistance patterns. These differences in the SCCmec types are used to categorize MRSA.

Unlike HA-MRSA strains that carry the larger genetic elements SCCmec I-III, CA-MRSA strains carry much smaller SCCmec variants; either SCCmec IV or the newly discovered SCCmec V. The larger variants carried by the HA-MRSA strains are typically multiply drug resistant, due to the presence of genes which encode for non-β-lactam antibiotic resistance. CA-MRSA variants of the SCCmec element IV and V are much smaller and only carry resistance to methicillin, allowing them to be pan susceptible to non-β-lactam antibiotics. Although lacking multiple drug resistance genes, it is thought that these smaller variants of SCCmec element found in CA-MRSA strains are in part responsible for its noticeable impact. For example, the small SCCmec IV allele carries little evolutionary fitness cost allowing it to spread rapidly outside the hospital environment. In contrast, the larger SCCmec I-III alleles require a hospital milieu for survival and expression, making them much more difficult to transfer carriers and thus thrive.

In addition to the newly formed SCCmec cassettes IV and V, many CA-MRSA strains hold the *pvl* gene that encodes for Panton-Valentine leukocidin (PVL), a novel *S. aureus* specific exotoxin. This gene is known to be transmitted by a mobile lysogenic phage, phiSLT. To date this gene has been largely absent in HA-MRSA strains and is thought to be a major factor in both the increased virulence, alongside the success of CA-MRSA as a non-opportunistic pathogen. It has been estimated that a total of 40%-90% of CA-MRSA strains carrying the SCCmec IV allele have the ability to produce PVL.

The PVL bicomponent exotoxin is largely responsible for CA-MRSA’s ability to cause their characteristic necrotic skin and soft tissue infections and in some cases much more invasive diseases such as necrotizing pneumonia. It works by initiating neutrophil chemotaxis to the infected area. Once the host’s immune response is assembled, the neutrophils are activated by the toxin and release cytotoxic elements into the surrounding milieu causing localized tissue damage. In the latter stages the toxin ultimately causes the neutrophils to lyse in large numbers, resulting in leukopenia.

With the discovery of these genotypic differences we now have a good understanding of how CA-MRSA strains arose independently and abruptly in the community. It is generally believed that CA-MRSA arose during the 1990’s when methicillin sensitive *S. aureus* (MSSA) epidemics began occurring in communities worldwide. These ancestral MSSA strains acquired the SCCmec elements through horizontal transfer from commensal strains of neighboring coagulase-negative staphylococci. However, the *pvl* gene added selective pressure to those CA-MRSA strains. This was possible because MSSA strains carrying the ability to encode for PVL were more likely to survive as CA-MRSA strains due to their increase in virulence.

### Epidemiology and Associated Risk Factors:

*S. aureus* has been recognized for years as a human commensal pathogen, and it is estimated that nearly 50% of humans are asymptomatic carriers. Epidemiologists have defined three principle types of carriage for *S. aureus*: (1) persistent carriers, (2) intermittent carriers, and (3) non-carriers. The major ecological niche in humans for this organism is the anterior nares, although it can also be isolated from the skin, axilla, groin, or gastrointestinal tract as it has the natural ability to be a colonizer of mucous membranes. Thus, in the nares the organism is most likely to survive as CA-MRSA strains due to their increase in virulence.

<table>
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<th>TABLE 1: Comparison of CA-MRSA and HA-MRSA.</th>
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<td>Mean age at infection</td>
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<td>Resistance gene</td>
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<td>PVL toxin gene</td>
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<td>Types of infections</td>
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by several integral pieces of evidence. The primary line of evidence is that when elimination of the organism from the nares by topical antimicrobial agents such as mupirocin is successful, disappearance from other body sites is soon followed. In fact, the strains found at other body sites are usually identical to the primary strain found in the nares. Also, colonized hospitalized patients who are successfully treated have a lower rate of nosocomial infections and strains causing infections in carriers are identical to those from the nares.

CA-MRSA also shares this ability to colonize successfully in the anterior nares of humans in both the community and health care settings. However, unlike MSSA and HA-MRSA, colonization of the nares does not seem to be a major precursor to infections. It has been suggested that alternative sites of colonization other than the nares or fomites (i.e. wound dressings, bedding, locker room furnishings, saunas, athletic equipment, and towels) may be important reservoirs. Yet, most evident to date is that CA-MRSA seems to play a hit and run strategy in which person-to-person contact with active infected person’s wounds results in immediate infection skipping the role of colonization all together.

The risk group most affected by CA-MRSA appears to be otherwise healthy younger individuals with no underlying comorbidities, or disease, and it is now being found in virtually all settings including hospitals and nursing homes. Nonetheless, it has become apparent that physical crowding, socioeconomic status, and hygiene have been the significant players in the recent emergence of CA-MRSA. Unfortunately, since the majority of skin and soft tissue infections are caused by strains of CA-MRSA, pinpointing specific risk factors has been a daunting task as clusters of infection have been isolated in numerous at-risk populations (Table 2).

According to a laboratory-based surveillance program at the San Francisco Community Health Network from 1996 to 2004 the frequency of CA-MRSA disease increased 15-fold. Overall, the clone most responsible for the CA-MRSA epidemic has been the USA300 clone. The USA400 clone is also found, however, it appears to be a much smaller player. This has been determined through multilocus sequence typing and pulse-field gel electrophoresis studies. First isolated in 2000, USA300 has been associated with outbreaks of at least 38 states, but more importantly has been responsible for >50% of all S. aureus infections, most of which emerge as sporadic cases. Even more astonishing, the CA-MRSA epidemic is not unique to the United States and has been noted with drastic importance worldwide. Depending on the geographical locations and the different backgrounds within the specific regions different genetic clones can be found with unique frequencies.

**Clinical Significance**

The clinical manifestations of CA-MRSA differ from those caused by HA-MRSA in that approximately 80%-90% present as skin and soft tissue infections. This includes the wide variety of cutaneous infections often associated with traditional MSSA ranging from impetigo to life-threatening necrotizing fasciitis. Other forms can be more life-threatening; including a deadly form of community acquired necrotizing pneumonia, pyomyositis, osteomyelitis, and septic arthritis. The majority of the CA-MRSA epidemic is seen in the emergency department (ED) and is consequently followed up in the outpatient setting where inappropriate therapy of the organism has repeatedly become an issue. Thus, the ED has become a first line of defense against CA-MRSA and a front runner in modeling novel therapies for the medical community. This is most likely because they were first to recognize the association between CA-MRSA and the increase in skin and soft tissue infections.

The largest numbers of CA-MRSA skin and soft tissue manifestations are seen in the form of lesions, most commonly abscesses (50-75%) and cellulitis (25-50%). These lesions are often encountered as single lesions involving the extremities and appear to have the ability to arise spontaneously on uncompromised skin. They also have been reported to complicate atopic dermatitis and other skin associated conditions in which the skin barrier is compromised. Patients may exhibit systemic signs of inflammation

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**TABLE 2: At-risk populations and Risk Factors Associated with CA-MRSA**

- Daycare attendees
- Individuals with active draining wounds and recurring SSTI
- Household contacts of known infected persons
- Athletes and participants of contact sports
- Homeless persons
- Tattoo recipients
- Men who have sex with men
- HIV-infected persons
- Diabetics
- Pregnant and postpartum women
- Newborns
- Urban dwellers of low socioeconomic status
- Ethnic populations (i.e., African-Americans, Pacific Islanders, and Native Americans)
- Military personnel
- Intravenous drug users
- Prisoners and jail detainees
- Overcrowded living areas
such as fever and leukocytosis; however, more often than not these symptoms are absent. Furuncles (boils) are very characteristic of CA-MRSA infections and most commonly arise due to the blockage of the hair follicle by skin oil (sebum), although minor trauma from friction caused by clothes rubbing the skin can be another precursor. These types of infections often form large abscesses with localized necrosis, caused by the PVL exotoxin, that begin as a red nodule and ultimately become purulent. They are often mistaken for spider bites or bug bites due to their similarity in appearance. Complication of these furuncles can cause the infection to spread into deeper layers of the dermis and surrounding subcutaneous tissues resulting in carbuncles. Folliculitis is less frequent than furuncles and often appears in discrete areas in the form of multiple pustules. CA-MRSA also causes impetigo, scalded-skin syndrome, staphylococcal toxic-shock syndrome, paronychia, deep subcutaneous abscesses, necrotizing fasciitis, and surgical site infections as it begins its hospital invasion. Even more rarely it has been known to be associated with purpura fulminans and Waterhouse-Friderichsen syndrome in cases of patients with PVL positive forms of CA-MRSA pneumonia. Overall, the prognosis for patients with CA-MRSA associated skin and soft tissue infections is very good and death is quite uncommon.

Life-threatening infections are rarely the cause of CA-MRSA, but in the recent years its ability to cause necrotizing community acquired pneumonia has gained considerable attention. Despite accounting for at most only 2% of the CA-MRSA disease burden, community acquired pneumonia due to CA-MRSA is associated with unparalleled morbidity and mortality in patients of all ages. Community acquired pneumonia due to S. aureus is not a new clinical syndrome. In fact, historically S. aureus has been well-recognized as a cause of pneumonia and is responsible for approximately 1%-5% of community acquired pneumonia cases each year. However, CA-MRSA strains, mainly the PVL positive USA300 clone, have been slowly increasing in incidence over the last few years as a cause of community acquired pneumonia. Many physicians fear CA-MRSA could soon emerge as the leading cause of community acquired pneumonia in the coming years, similar to its role in skin and soft tissue infections.

In most cases the largest risk factor, or more likely prerequisite, for community acquired pneumonia due to CA-MRSA is recent or concomitant influenza-like illness. Accordingly, it has been closely tied with the viral respiratory season during the fall and winter months when influenza is active. Most cases precede Influenza A infections and less frequently Influenza B. This type of secondary-infection is often rapidly progressive and it is believed CA-MRSA opportunistically adheres to the damaged bronchial epithelial basement membrane. Patients often experience high fevers, tachypnea, tachycardia, hypotension, and hypoxemia. Leukopenia is common and radiographic chest x-rays include the findings of uni- or multilobar infiltrates as alveolar hemorrhage. In the latter stages lesions become evident due to necrotic lung tissue and septic shock ultimately becomes the final fate resulting in mortality rates as high as 42%. These signs and symptoms are for the most part caused solely by the effects of the PVL exotoxin.

**Treatment**

Proper treatment of CA-MRSA infections remains controversial and to date no one standardized approach has yet to be defined. Until this decade, vancomycin had been the treatment of choice for MRSA infections; as well studied alternatives were not yet available. Today, CA-MRSA is known to have in-vitro susceptibilities to an assortment of non-ß-lactam antimicrobial agents making it appear to have several treatment options available. However, multiple drug resistance CA-MRSA strains are becoming increasing evident. Studies involving the therapeutic management of this infection have been lacking and their efficacy in the clinical setting is still under investigation. Thus, treatment of suspected or diagnosed CA-MRSA infections has made empirical and directed therapy potentially confusing for clinicians. Nevertheless, reasonable guidelines for the clinical management of MRSA in the community are beginning to take shape.

For the majority of CA-MRSA skin and soft tissue infections, surgical incision and drainage of the purulent lesions are the primary therapy. Although many studies show that completion of successful surgical drainage is adequate enough, empiric antimicrobial therapy often follows. Supplemental antibiotic therapy includes several options that need to be directed with the knowledge of local susceptibility patterns of CA-MRSA and the severity of the infection. For children under eight years old and adults with complicated infections or known underlying conditions, oral clindamycin or trimethoprim-sulfamethoxazole (TMP-SMX) combined with cephalaxin to cover for group A Streptococcus is suggested. Adult and adolescent patients with uncomplicated skin and soft tissue infections often respond well to the administration of doxycycline, tetracycline, and minocycline. Fluoroquinolones, such as ciprofloxacin, and macrolides, such as azithromycin, are not effective choices for therapy against CA-MRSA. This is due to their high prevalence of resistance in CA-MRSA and the ability for resistance to rapidly develop.

For more serious infections with CA-MRSA vancomycin, daptomycin, and linezolid are reasonable
therapeutic choices. However, they must be used with caution and appropriate therapy should follow after MRSA susceptibilities are known or the patient has improved. Linezolid has become increasingly important in the treatment of CA-MRSA associated pneumonia due to its ability to concentrate in alveolar fluid. Also, like clindamycin, it is known to inhibit the production of PVL, a major virulence factor for CA-MRSA.

Role of the Clinical Laboratory

Since the diagnosis of CA-MRSA is largely based on clinical findings and antibiotic susceptibility patterns, the clinical microbiology laboratory plays a pivotal role in the clinical management of CA-MRSA by providing fast, accurate, and cost effective tests for clinicians. However, it is important to note that laboratory testing to confirm the diagnosis of CA-MRSA by SCCmec typing is largely limited to reference laboratories and for the use of epidemiological studies. Therefore, identification is almost entirely limited to the goal of confirming the isolate as MRSA.

Laboratory diagnosis for *S. aureus* begins with the collection of clinical specimens. Clinicians are encouraged to collect specimens for culture and antimicrobial susceptibility testing from all patients where MRSA is considered in the differential diagnosis. Appropriate clinical specimens for MRSA consideration include: fluid from a purulent lesion or abscess cavity, respiratory secretions (e.g. sputum, bronchial alveolar lavage, tracheal aspirates), or pleural fluid, blood, and specimens from other normally sterile body sites (e.g. bone, tissue, joint aspirates). This is important for not only patient management but also to determine the local prevalence of MRSA and antimicrobial susceptibilities.

The first approach to the identification of MRSA in the laboratory is a Gram-stain of the specimen and its cultivation. *S. aureus* and other staphylococcal species appear as Gram-positive cocci, usually in clusters. The media of choice for cultivation of *S. aureus* is 5% sheep blood agar and chocolate agar incubated at 35°C 5% CO₂ or ambient air. They will also grow in nutrient broth and growth usually appears within 24 hours of culture. The appearance of large raised β-hemolytic colonies, often producing a golden yellow pigment, that are catalase and coagulase positive are suggestive of *S. aureus*. Identification normally occurs within 24 hours of culture.

Once isolated in pure culture, antimicrobial susceptibility testing is performed to confirm the presence of MRSA. Today, the Clinical Laboratory Standards Institute (CLSI) provides extensive guidelines for antimicrobial susceptibility testing. Currently, culture based methods such as disk diffusion and the ETEST (AB Biodisk) method or breakpoint method are still the mainstay for MRSA detection. These tests require 24 hours of incubation after pure culture on an agar medium for reliable detection of MRSA. According to CLSI guidelines, MRSA is defined as any *S. aureus* isolate with an oxacillin minimum inhibitory concentration (MIC) greater than or equal to 4μg/mL or a cefoxitin zone of inhibition of ≤21mm. The CLSI no longer recommends methicillin for antimicrobial susceptibility testing as it is not commercially available in the United States and does not maintain its activity when stored for long periods of time. Most importantly, it runs a greater risk of failing to detect heteroresistant strains, a phenomenon in which the variability in culture conditions may affect phenotypic expression of resistance. This occurs when only a small portion of the bacterial cells from a pure culture of *S. aureus* are actively expressing resistance through the mecA gene, allowing for MRSA to go undetected. For this reason oxacillin is now used for antimicrobial susceptibility testing. In the disc diffusion method, cefoxitin is now recommended by CLSI guidelines. It holds the advantage of being a superb inducer of the mecA gene and is less affected by penicillinase hyper-producing isolates than oxacillin. Thus, it is more reliable for the detection of MRSA in instances where breakpoint detection is not being used. Less commonly used is an agar screening method, in which an agar medium containing 6μg/mL of oxacillin limits the growth to MRSA isolates only. However, this is more commonly used as a confirmatory method for suspect isolates in which antimicrobial susceptibility testing was already carried out.

Automated bacterial identification and antimicrobial susceptibility testing systems are now becoming widely used in clinical laboratories. These systems offer the ability to provide susceptibility results with shorter incubation times than culture based methods and identify bacteria simultaneously. MRSA detection in an automated setting is possible in <12 hours after pure culture with >98% sensitivity and >99% specificity. The automated testing systems available for use in the United States include the Vitek 2 system (bioMérieux, Inc.), the MicroScan Walkaway system (Dade International), Sensititre ARIS 2x (Trek Diagnostics), and the Phoenix system (BD Microbiology Systems). Each system is unique in regards to how the inoculum is prepared, the extent in which inoculation is automated, and the methods used to detect growth. Also, each uses different algorithms to interpret and assign MIC values in categorical fashion (i.e. susceptible, intermediate, and resistant).

As alternative technologies become readily available the pressure for labs to provide novel rapid diagnostic tests for MRSA continues to mount. Some tests work by rapidly identifying phenotypic characteristics of MRSA and provide accuracy relatively comparable to culture based methods. One of these
novel tests is based on a slide latex agglutination method targeted at the PBP2a and provides detection of MRSA in 10 minutes from pure culture. Available from several suppliers, the test involves the extraction of the PBP2a from a suspension of colonies and detection by agglutination through latex particles coated with monoclonal antibodies to the PBP2a. Another new method provides detection of MRSA in 5 hours through a broth assay (Crystal MRSA, Becton-Dickenson). Here the fluorescence quenching of an oxygen-sensitive indicator detects inhibition of growth in the presence of oxacillin by oxygen remaining in the broth. Although they allow for faster detection of MRSA than culture based methods, phenotypic tests do not provide full antimicrobial sensitivities for isolates which is the main concern for clinicians in the long run.

Recently the use of active surveillance methods to identify MRSA colonized patients and carriers have become an integral part of infection control strategies. The ability for laboratories to adapt simple screening strategies to identify MRSA quickly, accurately, and in a cost effective manner has become its own challenge. Unlike conventional culture and antimicrobial susceptibility testing which may cause costly delays in the implementation of infection control strategies, these surveillance methods are designed not with patient therapy in mind, but rather with the intention of limiting transmission to others and preventing outbreaks in at-risk populations. Since the nares appear to be the primary site for MRSA colonization swabs of the nares are currently the most encountered screening specimen submitted to laboratories. However, other sites that may be useful are the rectum, groin, and axilla. Active surveillance methods today rely almost entirely on rapid methods such as chromogenic agars and real-time PCR.

Culture based surveillance methods for MRSA involve selective and differential agar based media that permit for the direct detection of MRSA through the incorporation of specific chromogenic substrates and cefoxitin. Additional selective agents are incorporated for the suppression of gram-negative organisms, yeast, and some gram-positive cocci. MRSA strains that grow on these agars produce unique colored colonies resulting from hydrolysis of the chromogenic substrates. For example, BBL™CHROMagar™ (Becton-Dickenson) utilizes a chromogenic substrate that produces mauve-colored colonies in the presence of MRSA. Bacteria other than MRSA may utilize other chromogenic substrates in the medium resulting in blue to blue/green colored colonies or if no chromogenic substrates are utilized, the colonies appear as white or colorless. These agars can produce results with sensitivities >80% and specificity upwards of 99% when incubated for 18-24 hours and sensitivities of 95-100% and specificity of >90% when incubated for 42-48 hours. Although created solely for screening purposes, these chromogenic agars appear to be so promising that many laboratories have validated them for identification of MRSA from wound and respiratory specimens where MRSA is considered as the pathogen.

Real time PCR-based methods for surveillance of MRSA colonization are very rapid and sensitive (>90%), with turnaround times ranging from 2-4 hours, making it the current gold standard for identifying MRSA. These genotypic methods work by identifying the meca gene usually in the presence of a second gene such as femA, femB, orfX, sa422, or the S. aureus specific gene nuc. Currently two molecular assays that target the detection of the SCCmec-orfX junction using real-time PCR are available in the U.S.: the BD GeneOhm MRSA (BD Microbiology Systems) and the Xpert MRSA assay (Cepheid). Both assays are currently limited to screening by nasal swabs only and have yet to be fully perfected. In some instances anatomic sites containing MSSA and competing normal flora, such as coagulase-negative staphylocci, may cause false-positive results. Also, S. aureus variants with a deletion of the meca gene may appear to be methicillin susceptible resulting in false-negative results.

Laboratories considering PCR-based technology for screening purposes have found it very difficult to provide enough evidence to consider it a cost effective method. To date these assays have been largely limited to reference laboratories where specially trained technicians are available. Yet, the push for a more simplified PCR-based technique available around the clock requiring limited specimen preparation and technician interaction has made the technology more readily accessible, especially in instances where high-volume MRSA surveillance is necessary. A testament to this has been the development of the Xpert MRSA assay which is categorized as a moderately-complex test by CLIA (Clinical Laboratory Improvement ACT) that can be performed on demand by virtually any laboratory technician without batching patient specimens. Nonetheless, the cost of this type of instrumentation has kept it from replacing the use of chromogenic agar based screening methods in most laboratories. However, in regards to MRSA management the future of molecular based methods will soon become undoubtedly noticeable. This will become apparent as newer multiplex PCR-based technologies are able to target multiple resistance genes in S. aureus making them ideal not only for screening, but for antimicrobial susceptibility testing.

**Prevention and Control**

Guidelines for the prevention and control of MRSA in the healthcare setting are readily available,
but lacking in regards to the outpatient and community settings. Although screening methods have been shown to reduce the number of MRSA infections in hospitals, most notably in preoperative patients, they have yet to play a key role in the prevention of CA-MRSA. This is due to the fact that it is not rational to screen all patients presenting to the ED or in an outpatient setting. Thus, control strategies for CA-MRSA focus on wound care and containment, enhanced hygiene, and regular cleaning of frequently touched environmental surfaces. Open wounds need to be properly covered with dressing and any persons coming into contact with drainage need to carefully wash their hands. Also, athletes and persons with close contact should avoid sharing towels, equipment, and razors. Any athlete with active lesions should be prohibited from participating in practices and competitions until the lesion has healed. Most importantly, proper hygiene such as hand washing and frequent showering with soap and hot water is recommended for persons at-risk for infections or that can potentially spread CA-MRSA is recommended.

The large number of recurrent CA-MRSA infections and household clusters of CA-MRSA infections have forced clinicians to focus on the eradication of MRSA from the colonized individual. This method is becoming increasingly popular despite the evidence for the association between MRSA colonization and CA-MRSA infection. Decolonization strategies include the use of topical nasal antimicrobials, such as mupirocin, to eradicate nasal colonization and chlorhexidine, hexachlorophene, and dilute bleach solutions for skin eradication. However, it is important to note that these methods to date have yet to provide any overwhelming success in the prevention of MRSA and much more data is needed to support their usefulness.

Conclusions

Today, the distinction between CA-MRSA and HA-MRSA is becoming increasingly difficult to define due to the emergence of CA-MRSA in areas once noted for HA-MRSA infections and vice versa. Nonetheless, CA-MRSA has undoubtedly emerged as the most predominant cause of S. aureus infections and holds the ability of causing numerous types of infections in otherwise healthy individuals, some of which can become life-threatening. Although it appears to be readily transmissible from person-to-person, evidence predicting specific risk-factors has been unsuccessful. Also, more investigations regarding treatment and prevention are necessary in order to establish standardized approaches for clinicians and infection control programs to follow.

References

1. MRSA is responsible for more deaths in the U.S. than AIDS according to the Centers for Disease Control and Prevention.
   A. True  
   B. False  

2. Which of the following can be used to direct supplemental antimicrobial therapy for patients infected with CA-MRSA?
   A. Knowledge of local susceptibility patterns  
   B. Severity of infection  
   C. Age  
   D. All of the above  

3. What is the largest known risk factor, or prerequisite, for developing necrotizing community acquired pneumonia due to CA-MRSA?
   A. Recent influenza-like illness  
   B. Recent hospitalization  
   C. Chemotherapy  
   D. Prolonged antimicrobial therapy  

4. Which of the following colony morphologies on 5% sheep blood agar is suggestive for the presence of S. aureus?
   A. Large raised α-hemolytic colonies producing a golden yellow pigment that are catalase and coagulase positive.  
   B. Small raised α-hemolytic colonies producing a golden yellow pigment that are catalase and coagulase negative.  
   C. Large raised β-hemolytic colonies producing a golden yellow pigment that are catalase and coagulase negative.  
   D. Small raised β-hemolytic colonies producing a golden yellow pigment that are catalase and coagulase negative.  

5. Which of the following SCCmec types are found in CA-MRSA strains?
   A. Types IV, V  
   B. Types IV, III  
   C. Types I, II, III  
   D. Types II, V  

6. Which strategy for MRSA prevention is most important in the control of CA-MRSA?
   A. Screening with PCR prior to surgery  
   B. Proper hygiene and hand-washing  
   C. Antibiotic therapy  
   D. Eradication of the colonized individual via mupirocin  

7. The toxin most commonly association with CA-MRSA virulence is known as what?
   A. Tissue factor IV  
   B. Urease  
   C. Mutase  
   D. Panton-Valentine leukocidin  

8. CA-MRSA most often causes which of the following types of infections?
   A. Pneumonia  
   B. UTIs  
   C. Skin and soft tissue infections  
   D. Sepsis  

9. CA-MRSA risk factors include which of the following?
   A. Newborns  
   B. Household contacts with infected persons  
   C. Persons in crowded living spaces  
   D. All of the above  

10. Which of the following methods is the most sensitive for the surveillance of MRSA colonization and is considered the "gold standard"?
    A. Automated bacterial identification systems  
    B. Chromagenic agars  
    C. Real-time PCR based methods  
    D. None of the above  

Questions for STEP Participants

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