Highlights of a Symposium

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Target Audience

This activity has been developed for emergency physicians and other healthcare professionals who treat patients presenting in emergency departments (EDs) with drug-resistant infections.

Educational Needs

The prevalence of resistant infections is increasing in both the community and hospitals, and research has shown that the number of patients presenting with drug-resistant infections to the ED has increased over recent years. Research has also shown that the infections of patients presenting from the community to the ED are increasingly becoming drug-resistant, a phenomenon once seen only in the institutional setting. However, the increased potential for drug-resistant bacteria to be found in infections in patients presenting from the community remains underappreciated.

Learning Objectives

By reading and studying this supplement, participants should be able to:
• Describe the changing epidemiology of community-acquired respiratory, skin, and soft tissue infections.
• Identify key patient risk factors for drug-resistant infections and apply risk stratification tools in the ED.
• Initiate early and appropriate empiric antimicrobial treatment.
• Interact with staff from infectious disease, surgery, critical care, hospital medicine, and pulmonology services to optimize patient management and continuity of care.

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Introduction
David A. Talan, MD, FACEP, FIDSA, Chair

Although the popular press has publicized cases of “flesh-eating” bacteria, antibiotic-resistant Gram-positive pathogens have not traditionally been considered to be a community problem. Today, however, the prevalence of antibiotic-resistant community-associated (CA) Gram-positive pathogens is a major public health issue. For example, multidrug-resistant *Streptococcus pneumoniae* is an increasingly common cause of invasive pneumococcal disease. Methicillin-resistant *Staphylococcus aureus* (MRSA), previously unusual in the community, is now the most common cause of pyogenic skin and soft tissue infections (SSTIs) seen in emergency departments (EDs) and can also produce a life-threatening CA pneumonia. Multidrug-resistant Enterobacteriaceae are now also reported in the community. Thus, resistant species of Gram-negative bacilli must be considered in patients with healthcare-associated infectious disorders such as healthcare-associated pneumonia (HCAP) and diabetic foot infections. While the contributors acknowledge the importance of this issue, the primary focus of this supplement will be drug-resistant staphylococci.

This supplement reviews the evolution of MRSA, with a focus on CA strains. Dr Gregory Moran reviews the epidemiology, clinical features, and treatment of CA-MRSA SSTIs and pneumonia. He also describes HCAP, a disorder associated with MRSA and other multidrug-resistant organisms of institutional origin. Dr Stanley Deresinski provides the perspective of an infectious diseases consultant on diagnostic and treatment issues relevant to patients in the ED. He also addresses issues related to the need for new antibiotics and briefly describes new and investigational agents that can be used to treat MRSA and HCAP. Emergency physicians and hospitalists work closely to ensure continuity of care. Dr Alpesh Amin describes efforts to improve cooperation between the two specialties and also reports on the Centers for Disease Control and Prevention (CDC) campaign to prevent antimicrobial resistance and presents infection control considerations for households of patients with CA-MRSA.

The Changing Epidemiology of Complicated Skin and Skin Structure Infections and Outpatient Pneumonias in the ED
Gregory J. Moran, MD, FACEP

Historically, the bacteriology of skin and soft tissue infections was quite predictable, and emergency physicians were comfortable treating these infections empirically with agents such as cephalexin. Cultures were not felt to be necessary, since an agent with activity against *S. aureus* and *Streptococcus pyogenes* was usually effective. The management of these very common infections has changed considerably in recent years due to the emergence of CA-MRSA, and we are now also seeing CA-MRSA emerge in other types of infections such as pneumonia.

A number of Gram-positive and -negative organisms can secrete β-lactamase into their immediate environment. In
response, investigators have synthesized penicillinase-resistant β-lactams such as isoxazolyl penicillins (eg, oxacillin, dicloxacillin) and methicillin. Resistance to methicillin can be acquired independent of an organism’s ability to produce β-lactamase: a consequence of the acquisition of an additional high-molecular-weight penicillin-binding protein. S aureus strains have been traditionally divided into those that are methicillin-sensitive (MSSA) and those that are methicillin-resistant (MRSA). MSSA strains are resistant to penicillins G and V, but susceptible to the isoxazolyl penicillins and methicillin. MRSA, on the other hand, is resistant to the classic penicillins, penicillinase-resistant penicillins, and methicillin. Although methicillin is no longer available, the term MRSA is still used to describe S aureus resistant to oxacillin and other β-lactams.

**MRSA Infections**

Epidemiologically, invasive MRSA infections can be categorized by setting of acquisition into CA-MRSA, healthcare-associated community MRSA (HA-MRSA, sometimes also known as community-onset HA-MRSA), and hospital-onset MRSA. CA-MRSA is defined as MRSA isolated in a patient from the community without documented community-onset healthcare risk factors. Cases of HA-MRSA have one or more of the following risk factors: (1) history of MRSA colonization or infection; (2) history of surgery, hospitalization, dialysis, or residence in a long-term care facility within the 12 months preceding the culture; and (3) presence of an invasive device at the time of admission to a facility. Hospital-onset invasive MRSA infections are those in which MRSA is cultured from a normally sterile site 48 hours or more after admission. However, the epidemiologic distinctions between these infection types have limitations. It is now recognized that many patients with risk factors for healthcare-associated infections are found to have the strains typical of CA-MRSA when they are characterized in the laboratory.

In a recent survey, 7% of all MRSA infections were invasive (ie, isolated from sterile sites). Invasive MRSA infections can occur in patients without established healthcare risk factors and are associated with significant mortality. In a review of 18 months of data from the Active Bacterial Core Surveillance Emerging Infections Programs Network database, investigators from the CDC estimated that there were 94,360 cases of invasive (sterile-site) MRSA in the United States in 2005. Approximately 20% of the patients with sterile-site MRSA infections died.

**HA-MRSA**

In 1961, shortly after the introduction of methicillin, the first case of MRSA was identified in the United Kingdom. By the late 1960s, MRSA was widespread in Europe, Australia, and Japan and had been isolated in the United States. Since that time, MRSA has been a major nosocomial pathogen. HA-MRSA infections increase mortality, length of hospital stays, and healthcare costs. MRSA comprises approximately one third of all isolates in European and American clinical laboratories. In 2003, 64.4% of S aureus infections in intensive care unit patients in the United States were methicillin-resistant. Of the 8,792 cases of invasive MRSA infections identified in the US from July 2004 to December 2005 by Klevens et al, 86% (7,566) were healthcare-associated (community onset or hospital onset). Of all healthcare-associated cases, in 69% (5,191) of cases, the patient presented from a community setting, but had healthcare associated risk factors such as an invasive device, previous history of MRSA, or significant exposure to the healthcare system within the preceding 12 months.

**CA-MRSA**

Although not a significant cause of community-acquired SSTIs until the beginning of this century, CA-MRSA was first identified in 1980 in outpatients with serious infections admitted to a large urban hospital in Detroit. Approximately 60% of these outpatients were injection
drug users. Other factors associated with CA-MRSA in the Detroit outbreak were underlying illness, previous treatment with cephalosporins or other antibiotics, and prior hospitalization. Once MRSA was identified in the community, the proportion of CA-MRSA infections rose from 3% to 38% over the next 19 months. Concurrently, cases of nosocomial CA-MRSA infections in Detroit appeared and also rapidly increased in numbers. Prior to 2000, CA-MRSA accounted for only 3% of staphylococcal isolates submitted to Minnesota laboratories. Between 2001 and 2004, however, the prevalence of MRSA among patients with SSTI in the author’s Los Angeles-area ED increased from 29% to 64.

CA-MRSA is not just HA-MRSA appearing in the community. CA-MRSA has a number of clinical and molecular features that indicate that it is distinct from HA-MRSA. Pulse-field gel electrophoresis can be used to categorize the strain of S aureus. Typable strains include USA100-800, USA1000, and the Iberian strain. The majority of cases of hospital-onset MRSA and HA-MRSA strains are USA100. CA-MRSA is most often USA300; USA100 strains that have been identified in community-associated outbreaks presumably are healthcare-acquired. Compared to HA-MRSA, CA-MRSA is susceptible to more antibiotics and carries the staphylococcal cassette chromosome mec (SCCmec) with the mecA type IV gene for methicillin resistance. Almost all of the CA-MRSA isolates also carry the Panton-Valentine leukocidin (PVL) gene. The exact role of the PVL gene in the pathogenicity of CA-MRSA is unknown. Scientists recently identified phenol-soluble modulin (PSM) alpha gene cluster of S aureus as a factor that contributes significantly to the leukocytolytic properties of CA-MRSA. Secretion of a PSM protein at the onset of the infection appears to lyse neutrophilic leukocytes that migrate into the initial focus of infection. CA-MRSA also appears to be intrinsically more likely to cause infection among colonized individuals. In a prospective observational study of 812 US Army soldiers, Ellis et al characterized the natural history of CA-MRSA and MSSA nasal colonization in communally housed troops. CA-MRSA and MSSA were isolated from the nares of 3% and 28% of subjects, respectively. During the study period, 38% of the CA-MRSA carriers, but only 3% of those colonized by MSSA, developed SSTIs.

CA-MRSA SSTIs

In 2002, the Los Angeles County Department of Health investigated outbreaks of CA-MRSA SSTIs in athletes, county jail inmates, and men who have sex with men. Other groups that have been identified as being at risk for CA-MRSA skin infections include intravenous drug users, military trainees, homeless people, and people with preexisting skin diseases. The importance of close contact in the spread of CA-MRSA was emphasized in a recent epidemiologic and laboratory investigation of a CA-MRSA SSTI epidemic among members of the 2003 St. Louis Rams football team. During that season, 9% of the players developed CA-MRSA infections—all at the site of turf abrasion injuries. The organism could not be identified in environmental samples. However, it was recovered from nasal swabs of 42% of players and staff as well as from whirlpools and taping gels. Molecular characteristics were those of CA-MRSA and also were identical to isolates from a competing football team.

In an effort to define further the epidemiology of CA-MRSA infections among patients in emergency departments (EDs), Moran et al conducted a prospective study of adult patients with acute, purulent skin infections presenting to EDs during a single month in 11 university-affiliated EDs (Figure 2). Of 422 patients with purulent SSTIs, S aureus was identified in 320 (76%). Of these, 9% of the patients don’t come in saying, “I have MRSA.” –Gregory J. Moran, MD

Most of the patients don’t come in saying, “I have MRSA.” –Gregory J. Moran, MD

CA-MRSA on Board
MRSA was present in 59% (range, 15%-74%, Figure 2). USA300 isolates accounted for 97% of the MRSA strains. SCCmec type IV and PVL were identified in 98% of the strains. The researchers concluded that CA-MRSA was the most common identifiable cause of SSTIs in the ED populations in the study sites. An interesting clinical finding of the study was that patients with MRSA SSTIs often mistakenly attributed their skin lesion to a “spider bite.” Such attribution has been presumed to have been based on the spontaneous appearance of erythema and pain without a preceding injury. Although this study clearly underscores the significance of CA-MRSA as a cause of SSTIs, it is important to note that inclusion in the study required a purulent infection that could be cultured. Thus, the study provided no information on the role of CA-MRSA for nonpurulent SSTI such as pure cellulitis, an infection in which streptococci are thought to be predominant pathogens. Nonetheless, the finding of MRSA in almost 50% of purulent cellulitis cases suggests that MRSA may play a role in at least some cases of nonpurulent cellulitis.

**MRSA Pneumonia**

**CA-MRSA Pneumonia**

MRSA is a well-known cause of nosocomial pneumonia. Over the last several years, there have been increasing numbers of reports of CA-MRSA pneumonia.20-22 The infecting organisms have been USA300, and they have been positive for both SCCmec and PVL. The cases have clustered around the influenza season and have involved previously healthy children and young adults. Clinical characteristics are the abrupt onset of pneumonia shortly after developing an influenza-like illness. In addition, 40% of the cases in the recent report from the CDC had a documented history of MRSA SSTI or close contact with an infected patient.23 Initial reports described a prodrome of constitutional symptoms suggestive of influenza, followed by high fever, respiratory symptoms, respiratory failure, and hemodynamic collapse.20 The mortality rate from CA-MRSA pneumonia has ranged from 25% to 60%.20-22

Clinical features that suggest CA-MRSA pneumonia include a local outbreak of influenza, rapid progression to severe illness, and failure of outpatient therapy (Figure 3). Recently, the CDC has emphasized that some patients may have influenza virus and a MRSA infection concurrently, rather than the classic biphasic pattern of influenza with a secondary bacterial pneumonia. Radiologic features of MRSA pneumonia include a patchy or homogenous bronchopneumonia, cavitary infiltrates, pneumatoceles, pleural effusion, and empyema.21 For cases of severe pneumonia, the American Thoracic Society/Infectious Diseases Society of America (ATS/IDSA) guidelines recommend sputum Gram stains, sputum and blood cultures, and other diagnostic tests.24 In 30% of the CA-MRSA pneumonia cases reported recently by the CDC, MRSA was recovered only from the sputum.22 The results of a Gram stain may be particularly helpful since S aureus may not be suspected in a patient with community-acquired pneumonia (CAP).

**Healthcare-associated Pneumonia (HCAP)**

The rise of multidrug-resistant infections has led to a reexamination of the traditional classification of pneumonia into community and nosocomial types. Recently, ATS and IDSA have defined a fourth category of pneumonia: HCAP.25 Patients with HCAP present from the community with pneumonia caused by antibiotic-resistant organisms that are typically considered pathogens for nosocomial pneumonia (eg, MRSA, *Pseudomonas*). Therefore, all patients presenting with pneumonia should be stratified for their risk of infection by an antibiotic-resistant organism by screening for potential HCAP risk factors (*Table 1*).25 In a study of the microbiology and outcomes of patients with HCAP, Kollef et al determined that *S aureus* accounted for approximately half of the HCAP pathogens.26 In addition, the mortality rate associated with HCAP was similar to that associated with hospital-acquired pneumonia (HAP) and significantly greater than that associated with CAP.
With the properties of HCAP in mind, we should reexamine the exact nature of CA-MRSA pneumonia. In the recent surveillance analysis of invasive MRSA in the United States, Klevens et al reported that the most common presentation of invasive MRSA was as bacteremia. The cases of MRSA pneumonia could be subdivided into CA-MRSA (15%) and HA-MRSA (85%). Cases of HA-MRSA pneumonia were either HCAP (62%) or HAP (38%).

STIs have been variably classified, often with somewhat overlapping terms, including by type (eg, cellulitis, abscess, necrotizing fasciitis), by organism (eg, bacterial, fungal, viral), and by number of infecting pathogens (monomicrobial, polymicrobial), as well as by whether they are superficial or deep, primary or secondary, uncomplicated or complicated. To ensure consistency in clinical trials, the US Food and Drug Administration (FDA) has defined SSTIs as either uncomplicated or complicated, a classification that will be used in this review. Uncomplicated SSTIs are infections that do not involve deeper tissues, are relatively minor clinically, and are not associated with host factors that increase the risk of mortality. Complicated infections involve deeper tissues, may require surgical intervention, and occur in a host with comorbidities that can impair response to treatment.

**Uncomplicated SSTIs**

Uncomplicated SSTIs are generally caused by group A streptococci or *S aureus*. They may be superficial, deeper, associated with hair follicles, or they may form abscesses (Figure 4). *Streptococcus pyogenes* spreads laterally through tissues, at least in part as a result of its production of hyaluronidase: an enzyme that dissolves the hyaluronic acid scaffold of skin, resulting in cellulitis and erysipelas. Staphylococcal infections, on the other hand, tend to be more localized, with greater production of pus that forms, for example, furuncles, carbuncles, and abscesses.

**Complicated SSTIs**

Complicated SSTIs are also most often caused by streptococci and staphylococci. However, to a much greater extent than is seen with uncomplicated infections, the pathogens in this group may include a mixture of Gram-positive and Gram-negative aerobic and anaerobic organisms. Clinical types of complicated SSTIs include acute and chronic wound infections, perianal cellulitis/abscess, diabetic foot infections, and necrotizing fasciitis. Compared to uncomplicated SSTIs, complicated infections are more severe and can be more difficult to treat. Although the clinical characteristics of the patient and the features of the infection are intrinsic clues to the complicated nature of the infection, various local and systemic signs are also evidence of this type of infection (Figure 5).
Although *S. aureus* SSTIs may have a wide variety of manifestations, we will focus on two: diabetic foot infections and necrotizing fasciitis.

**Diabetic Foot Infections**

Approximately 9% of patients with diabetes will, at some time, develop foot infections. Acute diabetic foot infections are most commonly caused by *S. aureus* and β-hemolytic streptococci (groups A, B, C, and G). Chronic infections tend to have more complex bacteriology, which may include Gram-positive organisms and a mixture of enterococci, Enterobacteriaceae, *Pseudomonas*, and obligate anaerobes. Among the commonly isolated pathogens is MRSA, the increasingly high prevalence of which makes it imperative that the clinician include coverage for this resistant pathogen in choosing an initial empiric antibiotic regimen in the treatment of significant diabetic foot infections.

**Necrotizing Fasciitis**

Necrotizing fasciitis is an uncommon but potentially life-threatening form of complicated SSTI. Various subtypes of necrotizing fasciitis have been identified on the basis of etiology, type, and level of tissue involvement, rate of progression, and clinical manifestations. For the sake of simplicity, however, the disorder can be divided into monomicrobial (streptococcal, clostridial) and polymicrobial types. Etiologic agents in polymicrobial infections often include aerobes (eg, *S. aureus*, including MRSA, groups A, B, C, and G streptococci, Enterobacteriaceae), and strict anaerobes (eg, *Bacteroides* sp, *Peptostreptococcus*). Although monomicrobial infection has been generally caused by *S. pyogenes* or, much less frequently, *Vibrio vulnificus*, CA-MRSA has recently emerged as a cause of monomicrobial necrotizing fasciitis.

Miller et al described 14 cases over a period of 15 months. Approximately one third of the patients had no known comorbidities or risk factors.

**Treatment of CA-MRSA SSTIs**

There are several important considerations when first evaluating a patient with an SSTI in the ED:

1. Is the infection potentially life- or limb-threatening?
2. What is the clinical type of infection?
3. Does the patient have risk factors for drug-resistant organisms such as MRSA?

Once these questions have been answered, the principles of therapy consist of source control, acquisition of relevant specimens for culture, and the initiation of appropriate empiric antibiotic therapy. Grayson has conceptualized these principles into a treatment triangle, with each element at one of the vertices of the triangle.

Source control is an important element of both uncomplicated and complicated SSTIs. In patients with an abscess, a simple incision and drainage (I&D) may cure the infection without the need for antimicrobial therapy. In patients with potentially life- and/or limb-threatening infections, immediate surgical consultation should be obtained. In these patients, although antibiotics are an important element of therapy, they are secondary to surgical intervention. Optimal management requires that cultures of the wound be performed in order to better direct definitive antibiotic therapy. The results are necessary for subsequent alteration of therapy if unexpected resistance is encountered. Alternatively, such data are necessary in order to allow the de-escalation of the initial broad-spectrum antibiotic regimen to a more narrowly focused one. Thus, by obtaining appropriate wound cultures, the emergency physician has the opportunity to improve clinical outcomes while decreasing overall healthcare costs and antibiotic pressure that may lead to the development of antimicrobial resistance in patients who are started on empiric broad-spectrum antibiotic therapy and hospitalized.

Clinical judgment and knowledge of local susceptibility data should be used to determine whether antibiotic therapy is indicated and, if it is, the most appropriate empiric regimen. The necessity of antibiotic therapy in the management of adequately drained abscesses has been questioned, but the answer remains uncertain. Rajendran et al conducted a randomized, double-blind, placebo-controlled trial of cephalexin for uncomplicated abscesses in patients at risk...
for CA-MRSA. Following I&D, patients were treated with either placebo or 7 days of cephalaxin (500 mg qid). Clinical cure rates were 90.5% and 84.1% (p=0.25) in the placebo and the oral antibiotic groups, respectively. Further support for a conservative approach comes from the study of ED patients by Moran et al. Most patients in the study were treated with either cephalaxin or dicloxacillin—agents that are not effective against MRSA. Despite the antibiotic susceptibility, the disparity did not adversely influence long-term outcomes. On the other hand, in a large retrospective cohort study, Ruhe and colleagues found that patients treated with an effective anti-MRSA antibiotic (most received doxycycline) were less likely to fail therapy than those given an antibiotic inactive against MRSA, despite the fact that all patients had undergone I&D. No published studies to date have examined additional important outcomes such as the rapidity of response to therapy, the persistence of MRSA colonization, the prevention or delay in recurrence of infection, or the prevention of transmission to contacts.

When systemic antibiotics are indicated for patients with presumed CA-MRSA, they may be administered either orally or parenterally, depending at least in part on the severity of the infection (Table 2). There are several important considerations to keep in mind. Although CA-MRSA is susceptible to trimethoprim-sulfamethoxazole (TMP-SMX), the combination is relatively inactive against streptococci and has not been well studied in patients with SSTIs. Although rifampin is active against MRSA, resistance develops rapidly when the drug is used as monotherapy. Consequently, rifampin is often combined with TMP-SMX or other agents with activity against MRSA. Tetracyclines such as doxycycline and minocycline are effective in approximately 80–90% of infections, but should not be given to children or pregnant women.

The proportion of strains resistant to clindamycin varies widely by geographic regions. Furthermore, routine antibiotic susceptibility testing for resistance to this lincomycin derivative may be misleading because of the presence of inducible resistance, which requires the laboratory to perform a “D-test” for its detection. Finally, in patients with complicated SSTIs and other disorders due to CA-MRSA, the importance of early and appropriate antibiotic therapy cannot be overemphasized. In a retrospective, single-center, observational cohort study, Schramm et al demonstrated that for patients with sterile-site MRSA infections, hospital mortality was significantly greater in patients in whom the initial antibiotic therapy was inappropriate (26.1% vs 16.6%; p=0.015).

**Table 2. Currently Available Antibiotics with Activity Against MRSA**

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<thead>
<tr>
<th>Non–FDA-approved</th>
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<tbody>
<tr>
<td>• Quinupristin-dalfopristin</td>
<td>• Vancomycin</td>
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<tr>
<td>• Minocycline, doxycycline</td>
<td>• Linezolid</td>
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<tr>
<td>• Rifampin</td>
<td>• Daptomycin</td>
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<tr>
<td>• TMP-SMX</td>
<td>• Tigecycline</td>
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<tr>
<td>• Moxifloxacin, levofloxacin</td>
<td>• Clindamycin</td>
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</tbody>
</table>

All but minocycline available as IV formulation

<table>
<thead>
<tr>
<th>We should recognize that since so many of our patients are now coming from long-term care facilities, they need to be considered as if they had hospital-acquired infections.</th>
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**Treatment of CA-MRSA Pneumonia and HCAP**

The identification and appropriate treatment of pneumonia due to CA-MRSA and other potentially antibiotic-resistant pathogens can represent a medical emergency. The principles of the initial management of these infections in the ED are the same as those governing other potentially life-threatening infections. Early goal-directed therapy has been shown to improve outcomes in patients requiring resuscitation. Appropriate cultures should always be obtained. Empiric broad-spectrum antibiotic therapy should be initiated within the first hour after the clinical syndrome is identified, and it must include one or more drugs that have activity against likely pathogens (Table 3). In most cases, the initial regimen should provide coverage of MRSA and, in patients with HCAP, of multidrug-resistant Gram-negative bacilli. The potential for source control should be evaluated (eg, drainage of an empyema). If appropriate cultures are obtained, microbiologic data that become available after 48 to 72 hours can allow de-escalation of antibiotic therapy to drugs with a more restricted spectrum of activity.
New and Investigational Antibiotics

The antibiotic era began with the introduction of the sulfonamides in the 1930s and penicillin in the 1940s, with the subsequent introduction of several newer classes of antibacterial agents. As each class came into widespread use, however, resistance inevitably followed. There is concern that bacteria are winning this ongoing battle: there currently are only 13 new antibiotics in various stages of clinical development, compared to an average of 60 new antibiotics 10 years ago. There are many reasons for this situation. Challenges include:

- High cost of drug development
- Limited return on investment in drugs that are prescribed for only days or weeks, compared with medications such as statins that are taken for decades
- “Capricious” regulation
- Lack of incentives such as those available in the Orphan Drug Act

This has led to a frightening paucity of new antibiotics for the treatment of infections due to resistant Gram-negative pathogens. The immediate prospects for the treatment of MRSA are, fortunately, much better, with the existence of several newly approved or investigational antibiotics that target these pathogens.

Treatment of infections with β-lactam-resistant Gram-positive cocci such as MRSA with vancomycin has been the standard of care for decades. Vancomycin, however, has a number of limitations in the treatment of S aureus infections, including diminishing susceptibility and poor tissue penetration. Linezolid, an oxazolidinone, and newer lipoglycopeptides (such as telavancin, dalbavancin, and oritavancin) are active against MRSA and have been used in the treatment of patients with methicillin- and vancomycin-intermediate infections. Tigecycline, a glycyclycline, is effective against MRSA; however, its lack of activity against Pseudomonas aeruginosa is limiting in its use for empiric therapy of HCAP.

Cephalosporins, while active against a varying range of both Gram-negative and Gram-positive bacteria, have not been effective in the treatment of MRSA infections. Manipulation of the cephalosporin molecule has, however, altered this paradigm, resulting in novel agents such as ceftobiprole and ceftaroline which are the first agents of this class with MRSA activity. Because they also have broad-spectrum activity against aerobic Gram-negative bacilli, which in the case of ceftobiprole includes P aeruginosa, they may prove effective in the empiric treatment of infections such as HCAP. Cefobiprole monotherapy has been demonstrated to be as effective as vancomycin plus ceftazidime in patients with complicated diabetic foot infections, cellulitis, abscesses, and wound infections (Figure 6). The drug has also successfully completed phase III trials in patients with CAP, HAP, and ventilator-associated pneumonia.
Hospital-related costs account for more than one third of overall healthcare expenditures.49 Emergency physicians and hospitalists provide major components of hospital-based care. Unfortunately, although the need for both types of specialists is anticipated to continue to increase, the number of emergency physicians and hospitalists is not increasing at a rate that can meet future requirements.50, 51 Thus, unless anticipated needs are adequately addressed, there is the potential that hospital-based care will be compromised by lack of resources in the future. A 2006 report from the Institute of Medicine (IOM) focused attention on the growing need for emergency physicians. According to the IOM, a “national crisis in emergency care has been brewing and is now beginning to come into full view.”52 Similarly, the shortage of hospitalists and anticipated future requirements have raised concerns that the gap in physicians qualified to practice hospital medicine “may grow into a chasm.”53

To maintain patient care and to address shared concerns in the face of evolving shortages of emergency physicians and hospitalists, benefits can accrue from cooperation between the two specialties. Hospitalists and emergency physicians have similar concerns about patient outcomes (Figure 7).49 Both are trained to deal with acute medical problems that may require hospitalization. This includes providing prompt and efficient treatment, communicating effectively, balancing patient care and the cost-effectiveness of various interventions, and initiating a process that ensures timely consultation and admission for patients who are seriously ill. Importantly, the majority of patients treated by hospitalists come from the ED. Areas of potential cooperation include development and implementation of guidelines for care, early consultation, obtaining cultures in seriously ill patients who are to be admitted to ensure that initial empiric broad-spectrum antibiotics can be appropriately de-escalated once microbiological data become available, and adhering to efforts to decrease antimicrobial resistance.

Preventing Antibiotic Resistance

New drugs are not the only answer to MRSA and other drug-resistant bacteria. The CDC currently has a campaign to prevent the development of drug resistance (Figure 8).54 This initiative is being actively supported by the Society of Hospital Medicine. The CDC campaign’s 12 steps include targeting the specific pathogen, treating infection not contamination, knowing when to say “no” to vancomycin, discontinuing treatment once the patient is cured, and isolating the pathogen.
Target the Pathogen
Appropriate antimicrobial therapy can save lives. Important steps include culturing appropriate patients and tailoring empiric therapy to likely pathogens, with decisions informed by knowledge of local resistance patterns. In addition, once the specific pathogen is known, antibiotic therapy should be de-escalated to target the identified microorganisms according to the antimicrobial susceptibility test results. As shown in Figure 9, inappropriate antibiotic therapy is common in seriously ill patients and is accompanied by increased mortality.56

Use Local Data
The prevalence of resistance can vary by locale, patient population, hospital unit, and length of hospital stay. For example, a study of the development of antibiotic resistance in patients at San Francisco General Hospital demonstrated that the prevalence of E. coli resistance to fluoroquinolones varied in different patient populations such as patients with chronic obstructive pulmonary disease (COPD) and in patients with trauma (Figure 10).56 Thus, it is important not only to know the local antibiogram, but also to be aware of differences in antimicrobial resistance in various patient types.

Know When to Say “No” to Vancomycin
One element contributing in general to the development of antibiotic resistance is inappropriate treatment. Thus, for years the CDC has been emphasizing the importance of restricting the use of vancomycin to prevent the emergence of resistant strains, such as vancomycin-resistant enterococci. With the emergence of CA-MRSA and previously limited parenteral antibiotic alternatives, this has been a difficult task.56 Therefore, it is important to treat the infection, not unexplained fever, bacterial contaminants, or colonizing organisms.

Stop Unnecessary Antimicrobial Treatment
Failure to stop unnecessary antimicrobial treatment contributes to overuse and the development of resistance. Therefore, antibiotic therapy should be discontinued when the infection is cured and when infection is unlikely or cultures are negative. As with all generalizations, however, the actual decision must be based on the judgment and clinical experience of the treating physician.

Infection Control in the Households of Patients with MRSA
Infection control measures are essential, not only in institutions, but also in close contacts of patients with CA-MRSA. Patients with MRSA and their families should practice thorough handwashing and avoid sharing personal items such as towels and razors. Other practical measures include keeping cuts and scrapes clean and covered until healed and avoiding contact with other people’s wounds and bandages. Additional infection control may come with the development of new vaccines. For example, S. pneumoniae vaccination has significantly decreased the morbidity and mortality of invasive pneumococcal disease.
Conclusion

Antibiotic resistance has been a problem in institutions for some time and is now a significant problem in the community. Although multidrug-resistant Gram-negative and Gram-positive organisms are now both widespread in the community, the current crisis is with the increasing prevalence of CA-MRSA, both in uncomplicated and complicated skin and soft tissue infections and in pneumonia. The proper approach to patients with life- or limb-threatening infections includes early risk stratification for the potential for drug-resistant pathogens, source control, and broad-spectrum empiric antibiotic therapy that can be de-escalated when microbiological studies become available.

References

CME Posttest – CA-MRSA on Board

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Section 3 – CME Posttest

1. What is the mortality rate associated with sterile-site MRSA infections?
   - a. 8%
   - b. 15%
   - c. 20%
   - d. 32%
   - e. 40%

2. Which molecular marker is most often identified in CA-MRSA strains?
   - a. Panton-Valentine leukocidin
   - b. Panton Matching System
   - c. cccDNA
   - d. Hyaluronidase
   - e. None of the above

3. The incidence of MRSA in acute, nonpurulent SSTIs in 11 university-affiliated EDs was:
   - a. 29%
   - b. 39%
   - c. 49%
   - d. 59%
   - e. None of the above

4. Which of the following patients would not be considered at high risk for HCAP?
   - a. Nursing home resident
   - b. Resident in a gated retirement community
   - c. Patient receiving dialysis
   - d. Patient with a recent kidney transplant

5. Which of the following is used to initially differentiate risk of HCAP from CAP?
   - a. Sputum cultures
   - b. Blood cultures
   - c. Physical examination
   - d. Chest x-ray
   - e. History

6. According to FDA definitions, the presence of comorbidities that can impair response to treatment is a major differential factor in classification of:
   - a. High-risk vs low-risk patients
   - b. Complicated vs uncomplicated SSTIs
   - c. The need for surgery vs the need for antibiotic therapy
   - d. Inpatient vs outpatient treatment
   - e. Likelihood of Staphylococcus sp vs Streptococcus sp

7. In a patient with an SSTI, all of the following are indicators the infection is probably a complicated SSTI except:
   - a. Local anesthesia
   - b. Tissue gas
   - c. Skin slough
   - d. Temperature > 102.3°F
   - e. Violaceous bullae

8. True or false? Approximately one third of patients with necrotizing fasciitis due to MRSA had no known comorbidities or risk factors.
   - a. True
   - b. False

9. The 3 elements of the treatment for complicated SSTIs are antibiotics, source control, and _____.
   (Select the single best answer.)
   - a. Incision and drainage
   - b. Appropriate cultures
   - c. De-escalation of initial broad-spectrum antibiotic therapy
   - d. Wound and skin precautions

10. True or false? Second- and third-generation cephalosporins have MRSA activity.
    - a. True
    - b. False