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Multi-Drug Resistant Bacteria: Implications for the Emergency Physician

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We could have titled this issue "Antibiotic-resistant bacteria are invading your emergency department (ED)," but you probably already know that. The follow-up question is, what do you do about it? The answers are not glamorous but simple: Suspect resistance, isolate patients at risk for colonization or infection with drug-resistant bacteria, prevent spread by hand washing and infection control methods, and choose antibiotics carefully based on local susceptibility data. Even these simple measures are difficult to maintain in a busy, crowded ED with patients moving in and out, boarding in the hallways, and staff struggling to just keep up with the flow.

The authors of this issue discuss three types of drug-resistant bacteria that can colonize or infect emergency department patients. Community-associated methicillin-resistant Staphylococcus aureus *and, to a lesser extent, vancomycin-resistant enterococci are known to most emergency physicians. Many emergency physicians have modified their antibiotic use to account for these resistant bacteria. Likely, most emergency physicians are not familiar with extended spectrum beta-lactamase producing bacteria, and antibiotic use in the ED for patients with these bacteria has not changed to an extent seen due to the aforementioned organisms.*

Like many other aspects of medicine, you will only find something if you know what to look for. The authors of this issue have provided a description of what to look for regarding these drug-resistant bacteria in the emergency department. The challenge to the practicing emergency physician is to

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take appropriate action when the clues are before us.
—Steve Stapczynski, MD, FACEP, FAAEM, Editor

Methicillin-Resistant *Staphylococcus Aureus* (MRSA)

Introduction. *Staphylococcus aureus*, a common cause of disease, has persistently developed resistance to multiple commonly used antibiotics.[1] Within one year after the introduction of methicillin, outbreaks of methicillin-resistant *Staphylococcus aureus* (MRSA) were reported.[2] These infections, known as health care-associated MRSA (HA-MRSA), were among hospitalized patients or those living in long-term care facilities.[1] Then, in the 1990s, cases of MRSA infection among healthy persons without any identifiable risk factors were reported. Such cases are now commonly labeled community-associated MRSA (CA-MRSA). CA-MRSA refers to MRSA infection that is acquired in the outpatient setting in an individual without HA-MRSA risk factors, such as hospitalization, surgery, close proximity to a patient in the hospital who is infected or colonized with MRSA, and dialysis.[3]

Microbiology. To date, most MRSA strains isolated from patients with CA-MRSA infections have been microbiologically distinct from those endemic in health care settings. Two pulsed-field types, USA300 and USA400, according to a classification scheme established by the CDC, have accounted for the majority of CA-MRSA infections in the United States. The USA300 and USA400 genotypes carry a resistance gene, mecA, which is packaged in a mobile genetic element called the staphylococcal chromosomal cassette (SCC) type IV. This genetic cassette is smaller than types I through III, which are the types found in HA-MRSA strains. It is hypothesized that type IV is more easily transferable between *S. aureus* strains, allowing resistance to spread from one bacterium to another more effectively than antibiotic resistance found in HA-MRSA strains with SCC types I, II, and III.[4,5] CA-MRSA strains also typically possess exotoxin virulence factors. The most common exotoxin is the Panton-Valentine leukocidin (PVL) toxin, which is rarely identified in HA-MRSA isolates. PVL produces cytotoxins that can cause tissue necrosis and leukocyte destruction, which accounts for the tendency of CA-MRSA to form abscesses.[6,7] In addition, CA-MRSA strains often express resistance to beta-lactams alone, in contrast to the multi-drug resistance pattern typical of nosocomial strains.[4] These distinct features of CA-MRSA strains suggest that CA-MRSA did not originate in health care settings, but rather that it originated in the community through the acquisition of methicillin resistant genes by established methicillin-sensitive (MSSA) strains.[8,9]

Epidemiology. Many studies have discovered that the overall percentage of *S. aureus* isolates resistant to methicillin has significantly increased over the past 20 years, with increases as high as 45% in many communities and up to 70% of some public hospitals.[10-12] And, research shows that the incidence of CA-MRSA infection is increasing accordingly. A prospective study of skin and soft-tissue infections among adults presenting to 11 university-affiliated emergency departments during the month of August 2004 found the overall prevalence of MRSA was 59%. Of the MRSA isolates, 97% were subtype USA300 and 98% were positive for PVL toxin. This data emphasizes the pervasiveness of CA-MRSA strains among patients presenting to the emergency departments included in this study. The breakdown of the prevalence by city is listed in Table 1.[13]

Although it affects all age groups, patients with CA-MRSA infections are likely to be younger than those with HA-MRSA infections. A prospective study of 1100 MRSA infections conducted in Minnesota in 2000 found that the median age was 23 years for CA-MRSA infection compared to 68 years with HA-MRSA infection.[9] Among pediatric cases (age < 18 years), dermatological disorders were the most common underlying medical condition documented. Among the adult cases (age > 18 years), tobacco use (19%) followed by diabetes (17%) were the most common underlying medical conditions documented.[9] A similar study found the incidence of CA-MRSA to be significantly higher among those younger than 2 years when compared to those 2 years or older with a relative risk of 1.5.[14] Children in day care centers seem to be particularly at risk.[15,16]

Persons from certain racial minority groups, including Native Americans, Pacific Islanders, and Pacific and Canadian aboriginals have been found to be at increased risk.[7] A population-based surveillance study in Atlanta found the incidence of CA-MRSA

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Table 1. Bacterial Isolates from Purulent Skin and Soft-Tissue Infections in 11 U.S. Emergency Departments*

SITE	NO. OF PATIENTS ENROLLED (N = 422)	MRSA (N = 249)†	MSSA (N = 71)	OTHER BACTERIA (N = 64)‡	NO BACTERIAL GROWTH (N = 38)
				number (percent)	
Albuquerque	42	25 (60)	10 (24)	3 (7)	4 (10)
Atlanta	32	23 (72)	4 (12)	3 (9)	2 (6)
Charlotte, N.C.	25	17 (68)	0	4 (16)	4 (16)
Kansas City, Mo.	58	43 (74)	6 (10)	4 (7)	5 (9)
Los Angeles	47	24 (51)	6 (13)	8 (17)	9 (19)
Minneapolis	28	11 (39)	4 (14)	9 (32)	4 (14)
New Orleans	69	46 (67)	11 (16)	9 (13)	3 (4)
New York	20	3 (15)	8 (40)	5 (25)	4 (20)
Philadelphia	58	32 (55)	12 (21)	12 (21)	2 (3)
Phoenix, Ariz.	30	18 (60)	8 (27)	4 (13)	0
Portland, Oreg.	13	7 (54)	2 (15)	3 (23)	1 (8)

* A total of 31 cultures, including 10 cultures from which MRSA was isolated, were polymicrobial. Because of rounding, percentages may not total 100. MSSA denotes methicillin-sensitive *Staphylococcus aureus*.
† P<0.001 for the test for homogeneity of MRSA prevalence across sites.
‡ Other bacteria isolated were as follows: MSSA (17 percent), streptococcus species (7 percent), coagulase-negative staphylococci (3 percent), and *Proteus mirabilis* (1 percent).

to be significantly higher among blacks compared to whites with an age-adjusted relative risk of 2.7.[17]

CA-MRSA outbreaks have occurred in several distinct populations, including competitive athletes,[18-20] military personnel,[21,22] prisoners,[11,21,23,24] homeless persons,[24,25] and intravenous drug users.[24,25] Factors common to these groups that facilitate the spread of infection include frequent skin-to-skin contact, participation in activities that result in skin trauma, sharing of personal items that may become contaminated, and challenges in maintaining personal hygiene.[26,27] Other risk factors for CA-MRSA include chronic illness, recent or frequent antimicrobial use, recent hospitalization, contact with others who have skin and soft-tissue infections, and living in a crowded environment.[6,11,21-24,26,28,29]

Clinical Disease. The spectrum of disease caused by CA-MRSA is similar to that of methicillin-sensitive *Staphylococcus aureus* (MSSA) in the community.[26] Skin and soft-tissue infections, specifically carbuncles, furuncles, and skin abscesses are the most frequently reported clinical manifestations.[30-32] Carbuncles and furuncles are caused by infection of the hair follicles. Skin abscess is a localized infection involving the dermis and the subcutaneous tissue. Risk factors for the development of abscess infection include nasal or skin colonization with *S. aureus* and minor local trauma such as an insect bite, abrasion, or drug injection.[32] Less commonly, patients have a history of diabetes.[32]

CA-MRSA should always be considered in the differential diagnosis of skin and soft-tissue infections, especially among patients slow to respond to beta-lactam therapy.[4] The previously mentioned study found that MRSA is the most common identifiable cause of skin and soft-tissue infections among patients presenting to 11 urban emergency departments in the United States.[13] Recurrent infection and transmission to close contacts, such as family members and teammates has been shown to occur frequently.[18-20,33,34]

Increasingly, CA-MRSA has been associated with severe invasive pulmonary infections in the community, including necrotizing pneumonia, empyema, and complicated parapneumonic effusions. Reports of lethal community-acquired pneumonia (CAP) due to CA-MRSA are increasing.[4] Invasive infections usually arise from complications of viral respiratory tract infections, particularly influenza. During the 2003-2004 influenza season, 17 cases of *S. aureus* CAP were reported to the Centers for Disease Control and Prevention from nine states; 15 of these cases were associated with MRSA. Influenza virus infection was documented in 71% of the cases. All 17 patients were hospitalized and five (29%) died. Four of the five deaths occurred in patients with MRSA infection. All isolates had community-associated genetic characteristics.[35]

CA-MRSA has also been associated with increasing rates of invasive musculoskeletal infections in the community, including necrotizing fasciitis, myositis, osteomyelitis, and prosthetic joint infection.[36] While these infections are often associated with a previous soft-tissue infection, invasive MRSA infections have occurred in those without any preceding infection or other risk factors.[4,26]

Management. The majority of CA-MRSA infections will present to the emergency department as skin and soft-tissue infections.[1] Incision and drainage alone may be sufficient therapy for cutaneous abscesses in patients with no systemic signs of infection or co-morbidities. Data are conflicting with regard to

the role of antimicrobials in the treatment of uncomplicated CA-MRSA skin and soft-tissue infections.[2] A recent population-based study found that 73% of patients who received empiric therapy for CA-MRSA skin and soft-tissue infections received an antibiotic to which the isolate was resistant. Nevertheless, clinical outcomes were similar regardless of the activity of the antibiotic.[1,26] Additionally, in a randomized, placebo-controlled trial among adults with skin abscesses and surrounding cellulitis, the majority of which were caused by MRSA, treatment success was over 90% for patients treated with incision and drainage alone.[26] A study published in early 2007 determined that patients with CA-MRSA skin and soft-tissue infections had a marginal benefit from the addition of antibiotics to incision and drainage. In addition to indicated incision and drainage, the use of an active antibiotic resulted in a 95% rate of successful outcome compared to an 87% rate without an active antibiotic (absolute difference = 8%, 95% CI 3 to 13%). Furthermore, use of an antibiotic inactive against the isolate was found to be an independent predictor of treatment failure (adjusted OR = 2.80, 95% CI 1.26-6.22).[2]

There are several conditions in which antibiotics are advised in addition to incision and drainage. Such conditions include: rapid progression of infection; the presence of associated cellulitis; signs and symptoms of systemic illness; co-morbidities or immune suppression, such as diabetes, cancer, or HIV; extremes of age; location of the abscess in an area that may be difficult to completely drain or that may extend to important structures, such as facial infections; and failure of treatment with incision and drainage alone.[26] In addition, one study found that patients failed treatment with incision and drainage alone if their abscess was larger than 5 cm in diameter.[37]

When clinical management includes antibiotics, therapy is usually empiric. When prescribing empiric antibiotics for an infection likely caused by *S. aureus*, treatment is best guided by local susceptibility data. However, CA-MRSA strains are uniformly resistant to beta-lactams, which includes penicillins and cephalosporins, as well as most macrolides.[26] If the local prevalence of MRSA is low, generally considered to be less than 15%, penicillin or a cephalosporin is an acceptable first-line therapy in a patient with mild to moderate disease and no significant co-morbidities or risks for CA-MRSA.[26] Resistance of CA-MRSA to other classes of antibiotics, including fluoroquinolones and tetracyclines, has emerged and appears to be increasing in prevalence.[26] One recent study found that 40% of skin and soft-tissue infections caused by CA-MRSA were resistant to fluoroquinolones.[38]

Most CA-MRSA strains are susceptible to trimethoprim-sulfamethoxazole (TMP/SMX), clindamycin, and tetracycline. In a study examining CA-MRSA skin and soft-tissue infections among adults presenting to 11 urban emergency departments, 100% were found to be susceptible to TMP/SMX. Clindamycin and tetracycline had 95% and 92% susceptibility rates, respectively.[38]

TMP/SMX, while not FDA-approved for the treatment of staphylococcal infections, has been shown to have excellent bactericidal activity against MRSA.[1] TMP/SMX is primarily recommended for the treatment of staphylococcal skin and soft-tissue infections.[28,39-43] TMP/SMX, however, does not have good activity against streptococcus spp. So, in cases where *Streptococcus* could be expected (for example, significant cellulitis), TMP/SMX alone would not be sufficient. Either adding cephalexin or switching to clindamycin is an acceptable alternative.

The appropriate dose of TMP/SMX for treatment of CA-MRSA skin infections is unclear. Data from a study that compared TMP/SMX with vancomycin for *S. aureus* infections suggested an appropriate TMP/SMX dose would include approximately 10 mg/kg per day of trimethoprim.[44] For a 70-kg adult, this suggests a trimethoprim dose of 700 mg per day. The standard TMP/SMX double strength (DS) tablet contains 160 mg of trimethoprim and 800 mg of sulfamethoxazole. This suggests that four TMP/SMX DS tablets per day should be used to treat CA-MRSA. That said, these are observational anecdotal comments from physicians who treat many patients with CA-MRSA that two tablets per day (one BID) are adequate for most cases. More definitive recommendations will require prospective studies using different dose regimens.

Clindamycin has been considered a second-line agent to penicillins for the treatment of gram-positive organisms and is commonly used in patients with penicillin allergy. It has the additional advantage of being capable of inhibiting bacterial toxin production, which is important in the treatment of infections that are PVL positive.[38] As discussed earlier, the PVL toxin causes tissue necrosis and leukocyte destruction.[6] Clindamycin is effective in the treatment of skin and soft-tissue infections as well as in more invasive infections. Because clindamycin has good penetration into lung tissue, pleural fluid, wound fluid, bones, and synovial fluid, it is an effective drug in the treatment of osteomyelitis and pleural empyema caused by CA-MRSA.[1,38]

Some MRSA isolates contain genes that encode for macrolide-lincosamide-streptogramin-B (MLSB) resistance. These erythromycin-resistant isolates show sensitivity to clindamycin by routine susceptibility testing, but then express resistance to clindamycin during therapy, termed "inducible clindamycin resistance."[1,26] Therefore, any strain that is erythromycin resistant and clindamycin sensitive should also have a D-zone test, which will identify if the inducible mechanism is present.[1,45] This test is a microbiologic technique that demonstrates bacterial growth in an area of a culture plate that normally inhibition would be expected. Both treatment failures and successes have been reported with the use of clindamycin to treat strains with inducible resistance, so the clinical significance is not established at this time.[46,47]

Long-acting tetracyclines, including doxycycline and minocycline, are alternatives in the treatment of skin and soft tissue infections. A review of nine studies, with a total of 85 patients, found a combined success rate of 85% with use of long-acting tetracyclines for the treatment of staphylococcal infections.[1] In addition, a recent case series found that the tetracyclines may not be appropriate for the treatment of systemic infections, but show effectiveness in the treatment of skin and soft-tissue infections.[1]

Hospital admission should be considered in patients with severe skin and soft-tissue infections, systemic symptoms, or those who have failed appropriate outpatient management. These patients should receive parenteral antibiotics and undergo surgical

Table 2. Antibiotic Choices in Methicillin-Resistant *Staphylococcus Aureus* Infections

DRUG	ADULT DOSE	COMMENTS
Clindamycin	300-450 mg po tid 600-900 mg IV q8h (severe infections)	Inducible resistance Covers staph, strep, anaerobes
TMP/SMX	1-2 (160/800 mg) DS tablets po bid	Group A streptococcal resistance high High MRSA susceptibility rates
Doxycycline	100 mg po bid	Variable susceptibility (85%) Avoid in children and pregnancy
Vancomycin	1 gm IV q12h	Increasing resistance (VRE, VRSA, Hetero-resistant Staph aureus)
Linezolid (Zyvox)	600 mg po/IV bid	Inhibits exotoxin release Reserve use to limit resistance
Quinupristin/dalfopristin (Synercid)	7.5 mg/kg IV q8h	Central line only May not be as efficacious as vancomycin
Daptomycin (Cubicin)	4-6 mg/kg IV q24h	Contraindicated in pneumonia—is inhibited by pulmonary surfactant
Tigecyline (Tygacil)	100 mg IV, then 50 mg IV q12h	Covers gram-negative and anaerobic organisms
Rifampin	300 mg po bid	Rapid resistance if used alone Use for synergy only No conclusive benefit in soft-tissue infections

treatment, if indicated.[4,30] Hospital admission should also be considered for those with serious comorbidities, including diabetes, congestive heart failure, and end stage renal disease, and those who are immunocompromised due to cancer, organ transplantation, or HIV infection.[30] Vancomycin is the first-line antibiotic for empiric treatment of serious skin infections in which MRSA is suspected as a possible pathogen.[4,30,38] While the newer fluoroquinolones (gatifloxacin, moxifloxacin, and levofloxacin) have enhanced activity against *Staphylococcus*, inhospital use of fluoroquinolones has been associated with increased HA-MRSA rates. It is not clear that this might also happen when fluoroquinolones are used to treat CA-MRSA. Until further experience is analyzed, it is probably best to avoid fluoroquinolones as initial therapy for CA-MRSA infections.[4] Recall, however, that fluoroquinolone resistance is increasing,[26] so these should not be used as first-line therapy. Daptomycin and quinupristin-dalfopristin (Synercid) have recently been approved by the Food and Drug Administration (FDA) for the treatment of skin and soft-tissue infections.[4] Additionally, linezolid is effective in treating complicated skin infections and nosocomial pneumonia due to MRSA.[38] Blood and wound cultures should be collected in these patients so that therapy can be directed based on sensitivity data.[30] Tigecycline, a parenteral tetracycline derivative, has activity against gram-positive, gram-negative, aerobic, anaerobic, and many resistant organisms, including tetracycline-resistant isolates.[38,48] The FDA has approved the use of tigecycline for the treatment of skin and soft tissue infections and complicated intraabdominal infections.[38,48] Dalbavancin, a mannopeptimycin currently in Phase 3 trials, has the advantage of once-weekly dosing. Clinical data have demonstrated that the efficacy of dalbavancin is comparable to vancomycin and linezolid.[38] Table 2 outlines the antibiotics and doses commonly used in MRSA infections.

Routine wound culture of purulent wounds is recommended by the CDC to guide therapy in refractory cases, determine local resistance rates, and monitor trends in susceptibility in those communities with known resistance patterns.[26] Patients should have a follow-up visit scheduled within 48 hours of the initial visit to ensure appropriate response to treatment.[26] Patients who present with recurrent infections should have their blood glucose measured to evaluate for the presence of diabetes. Decolonization is not currently routinely recommended as there are no data to support decolonization efforts in the community setting. Nevertheless, patients with recurrent infection, or those recurring in a small associated cohort may benefit from decolonization efforts; consultation with an infectious disease specialist is recommended.[26] A recent study of hospitalized patients did show some promise in decolonization efforts. In this randomized, controlled trial, patients colonized with MRSA received either 7 days of treatment

Table 3. Antibiotic Choices in Vancomycin-Resistant Enterococci (VRE) Infections

DRUG	ADULT DOSE	COMMENTS
Linezolid (Zyvox)	600 mg po/IV bid	Current drug of choice for both *E. faecium* and *E. faecalis* Resistance emerging Major side effect is bone marrow suppression
Quinupristin/dalfopristin (Synercid)	7.5 mg/kg IV q8h	Effective for *E. faecium* Administered through central line Major side effect is arthralgias and myalgias

(2% chlorhexidine washes, 2% mupirocin ointment intranasally and oral doxycycline and rifampin) or no treatment. At three months, 32% of those not treated were MRSA culture negative at 3 months compared to 74% of those treated. Fifty-four percent of the treated subjects were still MRSA culture negative at 8 months.[49] Lastly, standard infection control practices should always be employed, including hand-washing, wearing gloves when managing wounds, and wearing gowns and eye protection during procedures at risk for contamination with body fluids.[26]

Vancomycin-Resistant Enterococci (VRE)

Introduction. Traditionally, vancomycin-resistant Enterococci (VRE) has been most prevalent within inpatient settings. However, the emergency department cares for many patients from long-term care facilities who are colonized or infected with VRE, and therefore serves as a portal of entry for its spread. Furthermore, the control of VRE is imperative to prevent the eventual transmission of vancomycin resistance to *S. aureus*, a virulent organism that is widespread in the patient population serviced in the emergency department. Unfortunately, strains of *S. aureus* exhibiting intermediate resistance to vancomycin have now been isolated,[50-55] and it is only a matter of time before this principal drug for the treatment of serious MRSA infections is ineffective. With the capacity to transfer vancomycin resistance to *S. aureus*, the prolonged survival in the environment, and the ability to overcome infection-control measures, VRE represents an important infectious disease threat, even in the emergency department.[48]

Microbiology. Enterococci, previously classified as group D streptococci, are gram-positive bacteria, and account for approximately 10% of all nosocomial infections.[56] *E. faecalis* and *E. faecium* cause most human infections, with *E. faecalis* being the most common cause of vancomycin resistant enterococci (VRE)-related infections.[56]

Enterococci comprise part of the normal gastrointestinal tract flora. They have also been cultured from the female genitourinary tract and other skin sites, including the axilla, mouth, and hands due to fecal shedding.[56-58]

Epidemiology. Intestinal colonization is the most common clinical manifestation of VRE.[59] Colonization does not result in any symptoms and may persist for months, which is significant because colonized patients serve as a reservoir for the transmission of VRE.[48,58] Patients at high risk for colonization include the severely ill, those in close proximity to others who are colonized, especially those with diarrhea, and those receiving multiple and prolonged courses of antibiotics, in particular vancomycin and cephalosporins.[57,59] Organ transplant recipients and oncology patients are at exceptionally increased risk.[48] The usual risk factors for VRE become unimportant when greater than 50% of a patient population is colonized. When colonization pressure is this high, even health care workers and their household members are at risk of becoming colonized with VRE resulting in spread into the general community.[59]

Residents of long-term care facilities are an important reservoir for VRE. One study found that 45% of patients admitted to an acute care hospital from a long-term care facility had rectal colonization with VRE.[57]

Clinical Disease. Infection with VRE follows colonization.[48] The most common sites of infection include the urinary tract and the bloodstream.[57] Urinary tract infections caused by VRE are usually associated with urinary instrumentation and include cystitis, pyelonephritis, prostatitis, and perinephric abscess.[48] Rarely, patients have developed endocarditis from previous genitourinary tract infection with VRE.[56,60] Risk factors for VRE bacteremia include hemodialysis, organ transplantation, chemotherapy, surgery, parenteral nutrition, and neutropenia.[48,59] Mortality rates for patients with VRE bacteremia can be as high as 70% in liver transplant patients and in those who are critically ill.[48] Intravascular catheter-related sepsis has occurred due to the high prevalence of skin colonization among patients with VRE.[48] Meningitis, pleural space and skin or soft-tissue infections have also been reported.[48]

Management. Controlling the spread of VRE in the health care environment is challenging. Transmission is through direct contact, but VRE can also be transferred from environmental surfaces to patients. A recent study found that health care workers in an ICU spread VRE from a contaminated to an uncontaminated part of a patient's room in nearly 1 in 10 encounters, despite the use of contact precautions.[48] In addition, studies have found that VRE are capable of surviving for days to weeks on environmental surfaces and have been isolated from nearly every surface in health care facilities, including monitoring devices (cardiac monitors, wall-mounted control panels), patient equipment (stethoscopes, blood pressure cuffs, thermometers), other medical equipment (IV poles, ventilators, automated medication dis-

pensers), and even the floor.[61-63] The highest concentration of organisms has been found on bed rails, over-the-bed tables, bed linens, urinals, and bedpans.[58] One study found that VRE contamination persisted even after routine cleaning with phenolics; environmental cultures for VRE were finally negative once a four-hour cleaning protocol was adopted.[57]

Adherence to appropriate contact precautions should be maintained to decrease transmission of VRE. Hand washing is felt to be the single most effective means of preventing spread.[57] In addition, patients known to be colonized or infected with VRE should be isolated and medical care equipment, such as stethoscopes and thermometers, should be dedicated to such patients.[48] Health care workers should put on a gown and gloves before entering a patient's room and remove them prior to leaving. Clothing and ungloved hands should not touch environmental surfaces, including doorknobs or privacy curtains, which could potentially be contaminated with VRE.[48] The CDC also has recently recommended the judicious use of vancomycin to help prevent the spread of vancomycin resistance.[57]

Treatment options for VRE infections are limited. VRE have acquired resistance to vancomycin and many also have high-level resistance to aminoglycosides and penicillins. Quinupristin-dalfopristin is available for the treatment of serious VRE infections caused by *E. faecium*. However, as discussed previously, the majority of infections are associated with *E. faecalis*. In addition, quinupristin-dalfopristin must be administered through a central line and is associated with clinically significant arthralgias and myalgias. Linezolid, an oxazolidinone agent, has become the drug of choice for many types of VRE infections caused by both *E. faecium* and *E. faecalis*.[58,64] Linezolid can be administered orally or intravenously. The primary side effect of linezolid is bone marrow suppression, with thrombocytopenia being most common.[58,64] (*See Table 3.*) Unfortunately, cases of linezolid-resistant enterococci have already emerged.[48] In 2001 the Mayo Clinic reported linezolid resistance in seven clinical isolates of vancomycin-resistant *E. faecium*.[64] Daptomycin is effective against VRE.[65] Dalbavancin, which currently is undergoing Phase 3 clinical trials, is effective in the treatment of VanB resistant enterococci, however it has little activity against the more common VanA phenotype enterococci.[48] An alternative approach is the prevention of VRE infection through the elimination of gastrointestinal colonization. The most promising agent currently under study is ramoplanin.[58]

To prevent further resistance to quinupristin-dalfopristin and linezolid, these medications must be used prudently. In general, antibiotics should be used to treat infection, not colonization.[66] And, susceptibility testing is recommended for any infection that is being treated with linezolid or quinupristin-dalfopristin.

ESBL-Producing Bacteria

Introduction. The advent of extended spectrum cephalosporins in the 1980s greatly expanded the clinician's ability to combat bacterial resistance conferred by beta-lacatamase. However, resistance to these new antibiotics was soon to follow; organisms with beta lactamases capable of hydrolyzing these new drugs were first described in 1983 in Europe.[67] The new beta-lactamases were given the name extended spectrum beta-lactamases (ESBLs). Since that time, reports of outbreaks from ESBL-producing organisms have been increasing both in Europe and the United States. An appreciation of the epidemiology and resistance patterns of these ESBL-producing bacteria is important for the emergency physician so that appropriate empiric antibiotic coverage can be started early.

Microbiology. Many gram-negative bacteria produce a chromosomally mediated beta-lactamase, such as the one initially discovered in 1940.[68] The first discovery of a plasmid-mediated -lactamase was in 1965 in a strain of *E. coli*.[69] It was coined TEM-1 after the patient's name. Once plasmidborne, this gene rapidly spread to other enterobacteriaceae, *Pseudomonas aeruginosa,* and others. Another plasmid-mediated beta-lactamase, SHV-1, was discovered in *Klebsiella pneumoniae*.[70] These enzymes conferred resistance to many of the beta-lactam antibiotics available at the time.

The third-generation cephalosporins were developed as beta-lactams able to overcome resistance caused by these beta-lactamases. Within a few years, however, some hospital-acquired bacteria began producing beta-lactamases capable of conferring resistance to these drugs. These extended spectrum beta-lactamases (ESBLs) were designated SHV- and TEM-type. Since then, other beta-lactamases have been described; they are termed CTX-M (due to greater activity against cefotaxime than ceftazidime) and OXA. As of 2005, more than 200 ESBLs have been characterized.[71] Interestingly, there is not a precise consensus definition of what constitutes an ESBL. Generally, these are beta-lacatamases that hydrolyze the penicillins, first-, second-, third- generation cephalosporins and aztreonam, thereby conferring bacterial resistance. They are less active against cefamycins (e.g., cefotetan, cefoxitin, cefmetazole) and carbapenems (e.g., imipenem, carbapenem), and are inhibited by beta-lactamase inhibitors (e.g., clavulanic acid).

Other beta-lactamases have been discovered that do show activity against extended-spectrum cephalosporins (like the cephamycins) and/or carbapenems.[72] They are also resistant to inhibition by beta-lactamase inhibitors.[72] AmpC and carbapenemases are two such entities.

As stated above, the genes coding for ESBLs are typically found on plasmids, facilitating transmission among and between bacterial species. Additionally, the plasmids, which carry the genes for ESBLs, are usually large; therefore, they also frequently code for genes that confer resistance to other classes of antibiotics: aminoglycosides, trimethoprim-sulfamethoxazole, and fluoroquinolones.[71]

ESBL producing organisms are typically Enterobacteriaceae. *Klebsiella pneumoniae* was the first bacteria described to produce an ESBL.[67] Since that time, *Klebsiella pneumoniae*, *Escherichia coli,* and Enterobacter spp. have become increasingly problematic. The National Nosocomial Infections Surveillance System report from 2004 showed resistance of these organisms to third-generation cephalosporins at the following levels: 20.6% (*Klebsiella*), 5.8% (*E. coli*), and 31.1% (*Enterobacter*).[73] Non-enterobacteriaceae such as *Pseudomonas aeruginosa* and *Acinetobacter* spp. may also produce ESBLs.[74,75]

Epidemiology. The prevalence of ESBL-producing organisms is less in the United States than in many other parts of the world. Among isolates obtained from 1997-1999 in the United States, 7.6% of *Klebsiella pneumoniae* and 3.3% of *E. coli* isolates expressed ESBL. Expression rates for the two bacterial isolates were much higher in Latin America (45.4 and 8.5 respectively) and Europe (22.6 and 5.3 respectively).[76] However, rates in all locales are on the increase according to another surveillance study done from1997-2003.[77]

Intensive care units are typically the epicenter of production. In isolates collected in the United States from 1998 to 2001, ceftazidime resistance was present in 9.6% of *K. pneumoniae* from intensive care units and 6.6% from other hospital locations.[78]

Seriously ill patients with prolonged hospital stays and those with indwelling medical devices are at risk for colonization or infection with ESBL-producing organisms.[71,79-81] Some studies have specifically linked gastrostomy tubes,[82] nasogastric tubes,[83] and arterial lines[84] to these infections. Antibiotic use has also been associated with acquisition of ESBL-producing bacteria. Third-generation cephalosporins in particular have been linked to infection with these organisms in a number of studies.[80,83,85,86]

Nursing homes may serve as a reservoir for these bacteria. One point prevalence study in Chicago found 46% of residents were colonized with ESBL-producing organisms.[82] Other studies have described outbreaks of ESBL producing bacteria in these facilities.[87-89] Within nursing homes, antibiotic use, particularly a third-generation cephalosporin, has been identified as one of the leading risk factors for colonization with an ESBL-producing organism.[85,89] Importantly, poor hand washing rates exist among nursing home personnel.[90] Efforts targeted at improving hand washing compliance have decreased ESBL clinical isolates in at least one study.[91]

Like MRSA above, ESBL-producing organisms are moving into the community setting. In 1993, a French survey of isolates from non-hospitalized patients revealed no truly community-acquired infections from ESBL-producing organisms. These bacteria were present in the community (5 of 107 strains of *K. pneumoniae*), but all were hospital-acquired in patients living in nursing homes.[92] More recently, there has been an increase in community isolates.[93-96] Typically, the patient has developed a urinary tract infection from an ESBL-producing *E. coli*.[93] These reports are from outside the United States, but the trend is worrisome. In fact, a recent study of fecal isolates in hospital and ambulatory patients in Spain revealed equivalent prevalence of ESBL-producing organisms in the two populations.[94]

The risk factors for disease in the community setting may be different than those in the hospital setting. A multivariate analysis of a small case-control study showed admission during last year, fluoroquinolone use, diabetes mellitus, and recurrent UTIs to all be associated with increased risk of community-acquired infection with an ESBL-producing organism.[93] Fluoroquinolone use has been associated with subsequent infection with an ESBL-producing infection in other studies as well.[81,82]

Clinical Disease. Gram-negative Enterobacteriaceae are important causes of intra-abdominal infections, urinary tract infections (UTIs), nosocomial-acquired pneumonias, and bacteremia. The spectrum of clinical disease for ESBL-producing organisms is not significantly different than disease caused by the same species of non-ESBL-producing organisms. The diagnosis of an Enterobacteriaceae-mediated infection, whether it is cystitis or ascending cholangitis, is routine emergency medicine practice. It is the recognition of the patient at risk for these infections that may be caused by an ESBL-producing organism that is the challenge.

As mentioned above, community-acquired ESBL-producing infections will most often be UTIs, but cholangitis and bacteremia have been seen in this population.[93] It is clear that certain populations are at higher risk for infections with ESBL-producing Enterobacteriaceae. Nursing home residents, especially those recently on antibiotics, should be considered high risk for infection with ESBL-producing organisms. Residents of long-term care facilities are at particular risk for fluoroquinolone-resistant *K. pneumoniae* and *E. coli*.[97]

Management. The presence of an ESBL-producing organism greatly reduces the number of antibiotics available for appropriate coverage. These bacteria typically are resistant to multiple antibiotic classes, including the aminoglycosides, trimethoprim/sulfamethoxazole, and the fluoroquinolones.[71] Infection with an ESBL-producing organism by itself may not significantly impact mortality.[98,99] However, appropriate initial antibiotic therapy may impact mortality in patients infected with these organisms. One study showed higher mortality of patients bacteremic with ESBL-producing organisms who did not receive appropriate antibiotics.[98] Another study of patients with ESBL-producing *K. pneumoniae* pneumonia showed higher mortality rates in those patients treated with a noncarbapenem antibiotic.[100]

Beta-lactam/beta-lactamase inhibitor combinations are effective against most organisms that produce a single ESBL. However, resistance to this combination therapy is increasing, likely due to the production of multiple ESBLs in a single organism.[71] Resistance to piperacillin/tazobactam among ESBL-producing isolates rose from 31% in 1994 to 63% in 1998 according to one study in Europe.[101] This class of antibiotics should not be used as first-line therapy for serious infections.

Cefepime, an extended-spectrum cephalosporin initially useful for ESBL-producing organisms is seeing increasing resistance and should no longer be considered a first-line agent.[71,79,102] High dose cefepime (2 g b.i.d.) may be used in combination with amikacin, however, with increased effect.[103]

Carbapenems, such as imipenem-cilastin (Primaxin) or meropenem (Merrem), are the drugs of choice for serious infections likely to be caused by ESBL-producing bacteria. They demonstrate consistent in vitro activity and favorable clinical outcomes against ESBL-producing organisms.[81,102,104] In nosocomial meningitis, meropenem should be used as the drug of choice.[70] When using a carbapenem, combination therapy is not indicated; there is no evidence that this improves outcome.[100,105] Although rare, organisms carrying carbapenemases have now been identified.[106] This may impact outcome. In a recent analysis of 298 patients with nosocomial pseudomonas infections, those patients with *Pseudomonas* carrying a metallo-beta-lactamase gene (carbapenemase) had a

higher mortality than those without the gene (51.2% vs. 32.1%).[107] In these cases, tigecycline or polymyxins can be used.

Conclusion

The emergence of resistant bacteria has complicated the treatment of nosocomial infections for years. With the spread of these organisms into the community, the emergency physician must now be attuned to populations at risk and local resistance patterns. This will hopefully optimize initial antibiotic choices and improve patient outcomes.

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Physician CME Questions

121. Which of the following people is *not* at increased risk for CA-MRSA

infection?
A. An athlete on a football team
B. A child who attends day care
C. An elderly female
D. An intravenous drug user

122. Which choice appropriately describes the treatment of a 2 cm arm abscess in an otherwise healthy 24 year-old male?
A. Cephalexin plus trimethoprim/sulfamethoxazole, return in 48 hours for wound check
B. Incision and drainage, mupirocin nasal ointment, chlorhexidine body wash, wound culture, return in 48 hours for wound check
C. Incision and drainage, wound culture, cephalexin plus trimethoprim/sulfamethoxazole, return in 48 hours for wound check
D. Incision and drainage, wound culture, return in 48 hours for wound check

123. Which of the following patients should receive an antibiotic in addition to incision and drainage of their abscess?
A. A 40-year-old healthy male with a 2 cm abscess with 5 cm of surrounding cellulitis on his arm
B. A 17-year-old healthy female with a 3 cm abscess on her distal thigh
C. A 65-year-old diabetic female with poorly controlled blood glucose with a 4 cm abscess on her abdominal wall
D. A 39-year-old male with a 2 cm abscess on his back and a fever of 38.9°
E. Answers A, C, and D are correct.

124. Which antibiotic regimen would *not* be appropriate for a septic patient with known community-acquired MRSA infection?
A. Clindamycin
B. Levofloxacin
C. Linezolid
D. Vancomycin

125. Which is *not* a risk factor for infection with VRE?
A. Hemodialysis
B. Organ transplantation
C. Recent course of a third-generation cephalosporin
D. Recent urinary instrumentation

126. Appropriate initial antibiotic therapy for a patient infected with VRE could include which of the following?
A. Linezolid
B. Piperacillin/tazobactam
C. Tetracycline
D. Tobramycin

127. The spread of VRE is best prevented by which of the following means?
A. Decolonization of individuals with mupirocin nasal ointment and chlorhexidine body washes
B. Dedicated stethoscopes and other medical care equipment for colonized or infected patients
C. Handwashing before and after contact with a colonized or infected patient
D. Treatment of all infected patients with quinupristin/dalfopristin

128. Which of the following is *not* a risk factor for infection with an extended-spectrum beta-lactamase producing organism?
A. Indwelling Foley and gastric tubes
B. Intravenous drug use
C. Nursing home resident
D. Recent treatment with a third-generation cephalosporin

129. Which antibiotic would be the first choice for the empiric treatment of a septic 72-year-old nursing home patient with chronic recurrent urinary tract infections who has been treated multiple times with a fluoroquinolone?
A. Ampicillin/sulbactam
B. Ceftriaxone
C. Imipenem
D. Trimethoprim/sulfamethoxazole

130. Which of the following organisms have *not* been known to produce an extended-spectrum beta-lactamase?
A. *Escherichia coli*
B. *Klebsiella pneumoniae*
C. *Pseudomonas aeruginosa*
D. *Staphylococcus aureus*

CME Answer Key

121. C; 122. D; 123. E; 124. B; 125. C; 126. A; 127. C; 128. B; 129. C. 130. D

Emergency Medicine Reports CME Objectives

To help physicians:

- quickly recognize or increase index of suspicion for specific conditions;
- understand the epidemiology, etiology, pathophysiology, and clinical features of the entity discussed;
- apply state-of-the-art diagnostic and therapeutic techniques (including the implications of pharmaceutical therapy discussed) to patients with the particular medical problems discussed;
- understand the differential diagnosis of the entity discussed;
- understand both likely and rare complications that may occur.

Emergency Medicine Reports®
The Practical Journal for Emergency Physicians

Multi-Drug Resistant Bacteria

Bacterial Isolates from Purulent Skin and Soft-Tissue Infections in 11 U.S. Emergency Departments*

SITE	NO. OF PATIENTS ENROLLED (N = 422)	MRSA (N = 249)†	MSSA (N = 71)	OTHER BACTERIA (N = 64)‡	NO BACTERIAL GROWTH (N = 38)
				number (percent)	
Albuquerque	42	25 (60)	10 (24)	3 (7)	4 (10)
Atlanta	32	23 (72)	4 (12)	3 (9)	2 (6)
Charlotte, N.C.	25	17 (68)	0	4 (16)	4 (16)
Kansas City, Mo.	58	43 (74)	6 (10)	4 (7)	5 (9)
Los Angeles	47	24 (51)	6 (13)	8 (17)	9 (19)
Minneapolis	28	11 (39)	4 (14)	9 (32)	4 (14)
New Orleans	69	46 (67)	11 (16)	9 (13)	3 (4)
New York	20	3 (15)	8 (40)	5 (25)	4 (20)
Philadelphia	58	32 (55)	12 (21)	12 (21)	2 (3)
Phoenix, Ariz.	30	18 (60)	8 (27)	4 (13)	0
Portland, Oreg.	13	7 (54)	2 (15)	3 (23)	1 (8)

* A total of 31 cultures, including 10 cultures from which MRSA was isolated, were polymicrobial. Because of rounding, percentages may not total 100. MSSA denotes methicillin-sensitive *Staphylococcus aureus*.
† P<0.001 for the test for homogeneity of MRSA prevalence across sites.
‡ Other bacteria isolated were as follows: MSSA (17 percent), streptococcus species (7 percent), coagulase-negative staphylococci (3 percent), and *Proteus mirabilis* (1 percent).

Antibiotic Choices in Methicillin-Resistant *Staphylococcus Aureus* Infections

DRUG	ADULT DOSE	COMMENTS
Clindamycin	300-450 mg po tid 600-900 mg IV q8h (severe infections)	Inducible resistance Covers staph, strep, anaerobes
TMP/SMX	1-2 (160/800 mg) DS tablets po bid	Group A streptococcal resistance high High MRSA susceptibility rates
Doxycycline	100 mg po bid	Variable susceptibility (85%) Avoid in children and pregnancy
Vancomycin	1 gm IV q12h	Increasing resistance (VRE, VRSA, Hetero-resistant Staph aureus)
Linezolid (Zyvox)	600 mg po/IV bid	Inhibits exotoxin release Reserve use to limit resistance
Quinupristin/dalfopristin (Synercid)	7.5 mg/kg IV q8h	Central line only May not be as efficacious as vancomycin
Daptomycin (Cubicin)	4-6 mg/kg IV q24h	Contraindicated in pneumonia—is inhibited by pulmonary surfactant
Tigecyline (Tygacil)	100 mg IV, then 50 mg IV q12h	Covers gram-negative and anaerobic organisms
Rifampin	300 mg po bid	Rapid resistance if used alone Use for synergy only No conclusive benefit in soft-tissue infections

Antibiotic Choices in Vancomycin-Resistant Enterococci (VRE) Infections

DRUG	ADULT DOSE	COMMENTS
Linezolid (Zyvox)	600 mg po/IV bid	Current drug of choice for both *E. faecium* and *E. faecalis* Resistance emerging Major side effect is bone marrow suppression
Quinupristin/dalfopristin (Synercid)	7.5 mg/kg IV q8h	Effective for *E. faecium* Administered through central line Major side effect is arthralgias and myalgias

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