NEW APPROACHES IN THE MANAGEMENT OF METHICILLIN-RESISTANT STAPHYLOCOCCUS AUREUS (MRSA)

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ABSTRACT

Methicillin-resistant Staphylococcus aureus (MRSA) skin and soft tissue infections (SSTIs) are a growing issue worldwide with significant economic impact. As a pharmacist, you should be familiar with all the risk factors and treatment available now a day. A new antibiotic, tedizolid phosphate, appears to be a reasonable alternative to linezolid for the treatment of acute bacterial skin and skin structure infections (ABSSSI): A short (6-day) course of tedizolid phosphate was as effective as a 10-day course of linezolid with regard to both early and sustained clinical responses. Recently, new and unusual antibiotic compound has been extracted from a marine microorganism found in sediments off the coast of California, researcher also found that wearing gloves and gowns in intensive care units does not reduce overall rates of acquiring Methicillin-resistant Staphylococcus aureus (MRSA).

Keywords: new approaches, methicillin-resistant staphylococcus aureus, management, antibiotic, prevention.

INTRODUCTION

Staphylococcus aureus is a group of bacteria that live on the surface of people's skin and inside the nose. It is normally harmless: most people who are carrying it are totally unaware
that they have it. In fact, it is thought that up to 30% of the general UK population carries these bacteria in their nose or on their skin.

This group of bacteria can be spread quite easily from person to person through contact.\(^1\) Methicillin-resistant Staphylococcus aureus (MRSA) skin and soft tissue infections (SSTIs) are a growing issue worldwide with significant economic impact. As a pharmacist, you should be familiar with all the risk factors and treatment available now a day. The pharmacist is often the first-line health care professional that people seek, and he or she should be able to make an educated professional referral based upon the discussion with the patient. Patients need to be educated regarding the risk factors of a staphylococcal infection in order to seek medical attention when necessary.\(^2\)

**Management**

Hospital-acquired MRSA (HA-MRSA) has been defined by the Centers for Disease Control and Prevention (CDC) as an MRSA infection occurring in individuals who have been hospitalized or received surgery within the last year, who have a permanent indwelling medical device, who reside in a long-term care facility, or who have recently received dialysis. HA-MRSA strains are genetically and phenotypically different than Community-associated MRSA infections (CA-MRSA) strains. CA-MRSA has been associated with a smaller composition, a higher incidence of virulence, and a lack of multidrug resistance (i.e., retaining susceptibility to tetracyclines, trimethoprim-sulfamethoxazole [TMP-SMX], rifampin, clindamycin, and fluoroquinolones).\(^2\)

Problems occur if Staphylococcus aureus bacteria are able to enter the body through a cut or wound. On the skin, MRSA infection may begin as a reddish rash with lesion(s) that looks like a pimple or small boil. Often it progresses to an open, inflamed area of skin that may weep pus or drain other similar fluid. In some instances, it may appear as an abscess, a swollen, tender area, often with reddish skin covering. When the abscess is cut open or spontaneously bursts open, pus drains from the area.\(^3\)

Your doctor may order a “culture.” This is a sample from a wound, blood, urine, or sputum (spit). The sample is sent to the lab for testing. This testing can take a few days to finish.\(^4\) MRSA spreads from person to person usually by direct skin-to-skin contact. MRSA is usually caught from hospitals. Spread may also occur by touching sheets, towels, clothes, dressings,
etc, which have been used by someone who has MRSA. Ways to prevent spread of MRSA include:

- Washing your hands regularly. You may be asked to use an alcohol hand rub when entering and leaving a hospital.
- Ensuring all cuts are covered with a waterproof dressing.
- Wearing gloves if you are in contact with a person with MRSA. This does not mean if you are just talking to someone though.
- Avoid sharing towels, face cloths, etc with people who have MRSA.

Patients with infections due to Staphylococcus aureus often need antibiotics. Infections due to normal strains of Staphylococcus aureus are often treated with flucloxacillin (eg Floxapen), but this is ineffective against MRSA. To make matters worse, MRSA are often also resistant to other types of antibiotics such as erythromycin (eg Erythroped) and ciprofloxacin (eg Ciproxin). Antimicrobial dosing recommendation for MRSA given in table 1.

Since MRSA is ever evolving and has progressed to the community setting--even in patients without identifiable risk factors--it is crucial to include Community-associated MRSA infections CA-MRSA in the differential diagnosis of any patient who presents to a medical facility with an SSTI. It is also important to keep in mind that few antimicrobial agents have been studied for the treatment of CA-MRSA; thus, their true efficacy has not yet been proven. Because randomized, prospective data on the treatment of CA-MRSA is lacking, no single antibiotic regimen is indicated over others for primary treatment. Moreover, resistance to these agents has been observed at varying rates throughout different regions. A number of prevention strategies are recommended to avoid becoming infected with MRSA there are as follow:

Prevention in the hospital — in the hospital, MRSA is commonly spread to patients from the hands of healthcare workers. To minimize this risk, patients and family members can help to ensure that anyone who comes in contact with the patient washes their hands or uses an alcohol-based hand sanitizer before and after touching the patient. Patients with active infection should also wash their hands frequently.

Hospitalized patients who are colonized or infected with MRSA should have "contact precautions". This means that anyone who enters the patient's room, even family and friends must wash their hands and wear gloves and a clean cover gown to prevent contamination of their clothing.
Prevention in the community — the best way to prevent and control MRSA in the community is not clear. The Center for Disease Control and Prevention has made the following recommendations 10:

- Keep hands clean by washing thoroughly with soap and water. Hands should be wet with water and plain soap, and rubbed together for 15 to 30 seconds. Special attention should be paid to the fingernails, between the fingers, and the wrists. Hands should be rinsed thoroughly, and dried with a single use towel (eg, paper towels).
- Alcohol-based hand sanitizers are a good alternative for disinfecting hands if a sink is not available. Hand sanitizers should be rubbed over the entire surface of hands, fingers, and wrists until dry, and may be used several times. Hand sanitizers are available as a liquid or wipe in small, portable sizes that are easy to carry in a pocket or handbag. When a sink is available, visibly soiled hands should be washed with soap and water.
- Keep cuts and scrapes clean, dry, and covered with a bandage until healed.
- Avoid touching other people’s wounds or bandages.
- Avoid sharing personal items such as towels, washcloths, razors, clothing, or uniforms. Other items that should not be shared include brushes, combs, and makeup.
- Students who participate in team sports should shower after every athletic activity using soap and clean towels. Athletes with skin infections should receive prompt treatment and should not compete when they have draining or active skin infections.
- People who use exercise machines at sports clubs or schools should be sure to wipe down the equipment, including the hand grips, with an alcohol-based solution after using it.

TEDIZOLID PHOSPHATE A ALTERNATIVE TO LINEZOLID 11, 12

A new antibiotic, tedizolid phosphate, appears to be a reasonable alternative to linezolid for the treatment of acute bacterial skin and skin structure infections (ABSSSI): A short (6-day) course of tedizolid phosphate was as effective as a 10-day course of linezolid with regard to both early and sustained clinical responses.

Philippe Prokocimer, MD, from Trius Therapeutics in San Diego, California, and colleagues published the results of their efficacy and safety trial in the February 13 issue of JAMA. The study was conducted from August 2010 through September 2011 at 81 centers throughout North America, Latin America, and Europe. The intent-to-treat analysis included data from 667 adults with ABSSSI treated with either tedizolid phosphate (n = 332) or linezolid (n = 335).
When early clinical response was measured 48 to 72 hours after initiating therapy for an ABSSSI, tedizolid phosphate (79.5% response rate; 95% confidence interval, 74.8% - 83.7%) was found to be statistically noninferior to linezolid (79.4% response rate; 95% confidence interval, 74.7% - 83.6%).

Although many disease states create markets for long-term or even lifelong drugs, infectious disease experts increasingly seek a shorter duration of therapy. Moreover, these experts closely guard new antibiotics and are reluctant to prescribe them until emerging antibiotic resistance makes the current arsenal of antibiotics ineffective. In Dr. Schaffner's words, "The economic incentives for developing new antibiotics have been a disaster." The new FDA environment allows new drugs to be tested against established first-line drugs, which makes it possible for researchers to gather much better comparative efficacy and safety data for new drugs.

Dr. Schaffner described tedizolid phosphate as the first drug to make it through a new, well-lubricated maze created by the October 1, 2012, Generating Antibiotic Incentives Now (GAIN) Act. The GAIN Act mandates priority reviews for antibiotic new drug applications and adds an additional 5 years of market exclusivity for new antibiotics. The GAIN Act also adds a pathogen-focused pathway that allows a new drug application to be supported by multiple clinical trials of the same infection, but in different parts of the body.

The current study therefore represents a larger societal interest than a typical phase 3 clinical trial, in that it suggests that the GAIN Act will lead to the development of new antibiotics that are desperately needed as antibiotic resistance becomes increasingly widespread. Although infectious disease experts have many reasons to be hopeful about antibiotic drug development, the practicing clinician should know that, "We have a new antibiotic that is effective against these seemingly superficial, but possibly serious, skin infections," he added. Dr. Schaffner also noted that the once-daily dosing and shorter dosing of tedizolid phosphate are likely to improve patient compliance.

**ANTIBIOTIC THAT ATTACKS MRSA FOUND IN OCEAN MICROBE**

Completely new and unusual antibiotic compound has been extracted from a marine microorganism found in sediments off the coast of California. The discovery of genuinely novel antibiotics is rare, and experts say resistance to the drugs poses a grave threat to human health. US scientists say the new compound, called anthracimycin, and seems to be effective
against MRSA and anthrax. The unique chemical structure of the compound could lead to a new class of antibiotic medicines. Thomas Frieden, director of the US Centers for Disease Control and Prevention, recently warned of the risk posed by antibiotic-resistant "nightmare" bacteria while Sally Davies, UK Chief Medical Officer, described them as a "ticking time bomb" that threatens national security. The Infectious Disease Society of America has expressed concern that the rate of antibiotic development to counter resistance is insufficient. This makes this latest discovery particularly welcome news.

The compound was extracted from Streptomyces bacteria that had been collected by Christopher Kauffman in Pacific Ocean sediments. Research team leader William Fenical commented: "The real importance of this work is that anthracimycin has a new and unique chemical structure. The discovery of truly new chemical compounds is quite rare. This discovery adds to many previous discoveries that show that marine bacteria are genetically and chemically unique." Initial testing of the antibiotic compound has demonstrated its efficacy in attacking anthrax, a bacterial disease that has been used as a bioterrorism weapon. But it also showed significant activity against Staphylococcus aureus, the MRSA superbug. The discovery highlights the potential resource for new materials and compounds offered by the oceans, much of which remains unexplored.

**GLOVES AND GOWNS DO NOT PROTECT AGAINST MRSA**

The CDC urges four core actions to focus on in the fight against antibiotic-resistance:

- **Prevention:** if you prevent infections, you do not need to use antibiotics in the first place. This in turn prevents spread of resistance. Actions include hand washing, safe food handling, infection prevention in hospitals and immunization.

- **Surveillance:** the CDC already tracks antibiotic-resistant infections and their causes, and analyzes underlying risk factors. This helps experts develop new approaches to prevention.

- **Stewardship:** probably the single action that could most effectively reduce the problem - there needs to be a shift toward more sparing and judicious use of antibiotics to vastly reduce the nearly 50% of misuse that goes on.

- **Development:** of new drugs and diagnostics. Antibiotic resistance is a natural step in the evolution of bacteria, so we will always need new drugs and new tests to keep one step ahead. Researchers have found that wearing gloves and gowns in intensive care units does not reduce overall rates of acquiring MRSA, a study published online by *JAMA* has revealed. Bacteria MRSA is the primary causes of health care-associated infections. And these, as the
study notes, are the most common complication of hospital care, affecting an estimated 5% of inpatients. The study also records that the cost of antibiotic-resistance in the US is estimated at more than $4 billion per year. The Centers for Disease Control and Prevention (CDC) estimate that 1 in 3 people carry the Staphylococcus bacteria in their noses, usually without any ill-effects. However, two in 100 people carry the antibiotic-resistant strain - MRSA. In health care settings, MRSA infections are more serious and potentially life-threatening, as the bacteria can enter the bloodstream through surgical sites.

**Wearing gloves and gowns**

The CDC recommends wearing gloves and gowns when caring for patients infected with antibiotic-resistant bacteria. However, as infection with MRSA or other antibiotic-resistant bacteria is often not detected, these precautions may not be applied. It has not been known whether wearing gloves and gowns for all patient contact - not just for patients with known infections - decreases acquisition of antibiotic-resistant bacteria in the intensive care unit (ICU).

**Collecting swabs**

Swabs were collected from 26,180 ICU patients on both admission and discharge from both the intervention and control ICUs. Cultures were grown from the 92,241 swabs collected to check for infection of MRSA or VRE. In the intervention ICUs, all health care workers were required to wear gloves and gowns for all patient contact and when entering any patient room. The researchers found that there was a decrease in both the intervention and control ICUs in the composite rate of MRSA or VRE acquisition over the study periods, but the difference in change was not statistically significant. There was a borderline statistically significant reduction in MRSA that was greater in the intervention group. The intervention did not reduce VRE acquisition, but it did reduce MRSA acquisition, although the authors noted that there was better hand hygiene compliance on room exit in the intervention ICUs. Good hygiene is vital for preventing MRSA infection. Simple measures, such as using antibacterial soap and ointment can be extremely effective. It is also worth noting that a CDC study has shown that MRSA infections are declining. They claim that invasive MRSA infections that began in hospitals have fallen by over 50% between 2006 and 2011.
### Table 1: Antimicrobial dosing recommendation for MRSA

<table>
<thead>
<tr>
<th>Drug</th>
<th>Adult IV dose</th>
<th>Adult oral dose</th>
<th>Pediatric IV dose</th>
<th>Streptococcus pyogenes activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>clindamycin</td>
<td>1200-2700mg/day divided every six to eight hrs</td>
<td>300-450 mg every six hrs</td>
<td>Age&gt;1month 20-40mg/kg/day divided every 8 hrs</td>
<td>Yes</td>
</tr>
<tr>
<td>daptomycin</td>
<td>4mg/kg every 24 hrs</td>
<td>N/A</td>
<td>N/A</td>
<td>Yes</td>
</tr>
<tr>
<td>Doxyocycline/Minocycline</td>
<td>100 mg every 12 hrs</td>
<td>100mg every 12 hrs</td>
<td>Age&lt;8 years contraindicated</td>
<td>No</td>
</tr>
<tr>
<td>linezolid</td>
<td>600 mg every 12 hrs</td>
<td>600 mg every 12 hrs</td>
<td>Age&lt;10 years, 10mg/kg/Every eight to 12 hrs</td>
<td>Yes</td>
</tr>
<tr>
<td>Quinupristin/Dalfopristin</td>
<td>7.5mg/kg every eight to 12 hrs</td>
<td>N/A</td>
<td>7.5 mg every eight hrs</td>
<td>Yes</td>
</tr>
<tr>
<td>Rifampin</td>
<td>600 mg every 12 hrs</td>
<td>600 mg every 12 hrs</td>
<td>15-20mg/kg/day divided in one to two doses. maximum 600 mg/dose</td>
<td>No</td>
</tr>
<tr>
<td>Tigecycline</td>
<td>100 mg once, 15 mg every 12 hrs</td>
<td>N/A</td>
<td>Not established</td>
<td>Yes</td>
</tr>
<tr>
<td>TMP/SMX</td>
<td>15-20mg/kg/day divided every six hrs</td>
<td>One to two double strength tablets every 12 hrs</td>
<td>Age&gt;2 months. 15-20mg/kg/day divided every six hrs</td>
<td>No</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>15-20 mg/kg/dose every 12 hrs then dosage and interval adjusted to trough level</td>
<td>N/A</td>
<td>15-20 mg/kg/dose every 8 hrs then dosage and interval adjusted to trough level</td>
<td>Yes</td>
</tr>
</tbody>
</table>
CANCER TREATMENT SEARCH LEADS SCIENTISTS TO MRSA KILLER, IMMUNE BOOSTER

In the August issue of Bioorganic and Medicinal Chemistry, researchers detail the results of a study that began 10 years ago, when Ching-Shih Chen, professor of medicinal chemistry at Ohio State College of Pharmacy and a team of researchers were creating a library of anti-cancer agents built around the scaffold of the molecules of celecoxib, a popular arthritis treatment in a family of drugs known as cyclooxygenase-2 (COX-2) inhibitors. This effort yielded OSU-03012 (AR12), a compound that is currently in a Phase I clinical trial as anticancer agent at the OSU Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute.

After observing how OSU-03012 acted within breast cancer cells, Hao-Chieh Chiu realized that the derivatives were suppressing a mechanism that bacteria use to take over their host cells. Chiu decided, with the support of Dr. Chen, to focus his research on testing this compound library against a variety of bacteria. When these compounds showed anti-bacterial activity against Salmonella and Francisella, they began testing efficacy against a variety of pathogenic bacteria, including Staphylococcus aureus, Enterococcus, and Streptococcus. It became clear that these analogues had a unique anti-bacterial activity, and they appeared to be most potent against Staph aureus and other MRSA strains.

The researchers narrowed the library down to a single agent (dubbed “compound 46”) and moved to testing in MRSA-infected mice. Published in the August issue of Bioorganic and Medicinal Chemistry, the authors report that an intraperitoneal administration of compound 46 resulted in increased survival in MRSA-infected mice versus untreated mice.

It is particularly gratifying to see that these compounds, originally designed as anticancer agents, work as a novel class of anti-bacterial agents based on the same principle in bacterial cells.

The researchers are hopeful that this early work will ultimately provide insights on the development of a treatment for antibiotic resistant infectious diseases.

MRSA DNA tells scientists where it’s been – and where it might go next

Investigators in the Division of Infectious Diseases at the Ohio State College of Medicine have created a state-wide “roadmap” of MRSA infections that is helping them better predict how – and where – MRSA will spread. The team, funded by the Centers for Disease Control and Prevention (CDC), used diverse methods from geographic analysis to molecular
genotyping to track more than 1,000 MRSA cases from the Wexner Medical Center and community hospitals across Ohio. Experts say using a variety of tracking methods is essential to stopping infections before they start.

With data from different sources, they’ve markedly improved their understanding of how MRSA is acquired and then spread among healthcare facilities. For example, they identified a very rare strain in the US, ST-239, which originated in Asia, spread to hospitals in Western Europe, and was introduced to Ohio sometime in the past two decades. It’s that level of knowledge that will help to change the course of transmission. Stevenson, whose research on ST-239 Stevenson’s team has also applied these tracking methods to bloodstream isolates from hospitals in Franklin County, Ohio, as well as skin and soft tissue infections among patients receiving primary care in a variety of settings. The results not only demonstrated the value of rapid molecular typing in examining the distribution and transmission of individual MRSA strains, but showed that particular strains tended to cluster in specific places. These studies have demonstrated that specific molecular types of MRSA are linked to specific types of infections, or even specific settings. For instance, there are strains that tend to colonize catheters, strains that are more commonly found in nursing homes. As we understand why certain MRSA strains behave as they do, more targeted interventions for prevention and treatment can be tested. Stevenson is hopeful that technology will someday provide a quick and inexpensive on-site genomic analysis of MRSA. In anticipation of that day, the team is using the “roadmap” data to create a MRSA molecular library that provides a detailed background on individual strains, including its drug resistance, weaknesses, and most likely source of transmission.

REFERENCES