Contemporary Issues in Wound Infection: Managing the Risks, Treating the Problem

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The Emerging Problem of Infectious Diseases:  
The Impact of Antimicrobial Resistance in Wound Care

Jose A. Vazquez, MD, FACP, FIDSA

INTRODUCTION

Wound care clinicians face a continuum of dilemmas on a daily basis. Whether facing an immunologic deficit in the host, the possibility of drug-resistant organisms, or selection of the type of antimicrobials required, clinicians must take into account many different factors when managing these complicated patients on a continuing basis. A major problem facing clinicians today is the impact of a particular group of organisms, the gram-positive cocci, specifically methicillin-resistant Staphylococcus aureus (MRSA). These bacteria have presented a major challenge in the hospital setting for many years. Recent epidemiologic surveys demonstrate that these organisms are also producing severe and invasive infections in the community setting. This newer strain of MRSA is called community-acquired MRSA (CA-MRSA). These organisms have become a problem for clinicians who practice wound care in hospitals, in the community, and in long-term care facilities. Because of the high prevalence of wound colonization and/or infection in wound care, a critical issue is how to prevent altering the normal flora of these patients so that it does not develop into a multidrug-resistant flora. This involves selective usage of parenteral antimicrobials only when absolutely necessary and the predominant usage of effective, nontoxic local antimicrobials. In addition to MRSA and other gram-positive cocci, the gram-negative bacteria, especially Pseudomonas aeruginosa, Serratia marcescens, Acinetobacter, Enterobacter, and Citrobacter, are also problematic for clinicians because of their frequent occurrence and their resistance patterns. Another group of resistant gram-negative pathogens, Burkholderia spp, have become a significant threat, especially in hosptialized patients and patients in long-term care facilities. Several Burkholderia outbreaks have been reported across the country in major teaching institutions because of poor hygiene and the misuse of systemic antibiotics.

Host resistance is also an important factor that needs to be addressed in wound care. The patient that is immunocompromised, neutropenic, HIV positive, and/or malnourished has difficulty with wound healing and has an increased rate of bacterial colonization. In essence, the best place to manage a patient with a wound infection is at home, since hospitals are known breeding grounds for multidrug-resistant gram-negative bacteria, MRSA, and vancomycin-resistant Staphylococcus aureus (VRSA) to name a few. It is important for clinicians to be aware of the different antimicrobial resistance patterns not only across North America but also across the world.

Bacterial quantity, quality, and virulence are other factors that need to be considered in wound care. Many bacteria, specifically the gram-positive bacteria, produce virulence factors, such as biofilms, adhesins, and polysaccharide capsules, that make them virtually indestructible.

Systemic risk factors associated with poor wound healing include venous insufficiency, arterial insufficiency (macrovascular or microvascular), uncontrolled diabetes mellitus, corticosteroid...
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use, malnutrition, alcoholism, and generalized edema (Table 1). For example, parenteral antibiotics reach the infected area via the vascular system and then via diffusion into the surrounding tissue. If there are several inches of tissue edema between the blood stream and the infected wound, the concentration of antimicrobial that will be achieved at the site of infection will decrease exponentially with any increase in distance for the blood supply. In these situations, in addition to decreasing the amount of tissue edema, a topical or local antibiotic may be of great benefit. Other risk factors associated with poor wound healing include prior surgery, prior hospitalization, radiation therapy, and, less commonly, an inherited immune defect.

Local factors that need to be assessed when examining a wound include the depth of the wound, the degree of chronicity, and the wound location. Some of the most challenging wounds to treat are those in the perineal and perianal region. These wounds are difficult to keep clean and to heal, especially in patients that are bedridden and have a multitude of systemic risk factors.

Another difficult management problem is an infected foreign body. It is almost impossible to eradicate bacteria from any wound that contains foreign bodies because antibiotics are not able to penetrate these objects. The key to treating these types of wounds is to remove all foreign bodies and necrotic tissue. The mechanism of injury as well as reduced perfusion to the affected area are also problems. When blood flow and oxygenation are absent, nutrients and antibiotics are not able to reach the infection site.

A major concern when managing wounds is deciding when the wound is colonized versus when the wound is truly infected. Bacterial contamination is frequently seen in any open wound, and characteristically, the bacterial colony counts are relatively low. However, these bacteria—despite being found in low numbers and because of the production of several virulence factors, especially exotoxins, endotoxins, and metalloproteinases—do not allow the wound to heal. In the presence of these virulence factors, healthy tissues are damaged along with the bacteria. This prevents adequate granulation tissue formation, which is essential to wound health (Figure 1). Thus, the removal of bacteria, endotoxins, and protease production is crucial to wound healing. If the bacterial density (colony-forming units or CFUs) in the wound increases, the wound progresses from a state of colonization, during which phase the bacteria start to reproduce and further increase in CFUs, to a state of localized infection. During this phase, the infection remains located adjacent to the wound but on occasion may extend deeper into the subcutaneous tissues and produce systemic infection. Overall, bacteremia is uncommon in wound infections but may be found in approximately 10% to 20% of severely infected wounds. For example, in patients with cellulitis or infections of skin and skin structures without open wounds, the rate of bacteremia is in the range of 10% to 20%. Thus, even a wound

**TABLE 1. WOUND INFECTION: RISK FACTORS**

<table>
<thead>
<tr>
<th>Systemic</th>
<th>Local</th>
</tr>
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<tbody>
<tr>
<td>• Vascular disease</td>
<td>• Large wound area</td>
</tr>
<tr>
<td>• Edema</td>
<td>• Increased wound depth</td>
</tr>
<tr>
<td>• Malnutrition</td>
<td>• Degree of chronicity</td>
</tr>
<tr>
<td>• Diabetes mellitus</td>
<td>• Anatomic location (distal extremity, perineal)</td>
</tr>
<tr>
<td>• Alcoholism</td>
<td>• Presence of foreign bodies</td>
</tr>
<tr>
<td>• Prior surgery or radiation</td>
<td>• Necrotic tissue</td>
</tr>
<tr>
<td>• Drugs (e.g., corticosteroids)</td>
<td>• Mechanism of injury</td>
</tr>
<tr>
<td>• Inherited immune defects</td>
<td>• Degree of post-wound contamination</td>
</tr>
<tr>
<td></td>
<td>• Reduced perfusion</td>
</tr>
</tbody>
</table>

**FIGURE 1. THE BACTERIAL BURDEN: A CONTINUUM FROM CONTAMINATION TO INFECTION**
that begins small, such as a laceration, can ini-
tially become contaminated, colonized, critically 
colonized, then infected, producing systemic 
manifestations of infection. In the past, this was 
frequently associated with *Streptococcus group*
A, “flesh-eating bacteria,” or *Clostridium perfrin-
gens*. Recently, this necrotizing type of infection 
has been described with MRSA not in the hospi-
tal, but in the community and in normal hosts.1 
Outbreaks of fulminant infections have occurred 
cross the United States in athletes (ie, wrestlers, 
football players) who suffer small abrasions that rapidly become 
severely infected and occasionally develop necrotizing fasciitis, 
associated bacteremia, multiorgan failure, and occasionally death.7

An increased bacterial burden in the wound is extremely prob-
lematic, because objectively, the wound does not appear to be 
infected. In many wounds, mild erythema and hyperemia are present, 
which is normal in an area that is attempting to heal. The dilem-
ma is how to determine if the area beneath or surrounding the 
open wound is actually infected.5 Unfortunately, many clinicians 
continue to take swabs of wounds and send them to the microbiol-
ogy laboratory for culture. The concordance rate associated with 
swab cultures and true pathogens’ is less than 60%. Thus, the 
results of superficial cultures are frequently misleading and pro-
 mote the inappropriate use of systemic antimicrobials.

Wounds that are colonized but not infected still may not heal. 
Aside from removing foreign bodies and necrotic material, decreas-
ing the colony count is crucial to wound healing. The dilemma 
levels of 10^5 or greater are associated with impaired wound healing. 
This can be seen in acute traumatic wounds (eg, before a skin graft 
is placed over a burn or wound), in surgical wounds, and in chronic 
wounds where either colonization, contamination, or acute infection 
is considered to be present in the area.5,6

**MANIFESTATIONS OF WOUND INFECTION**

Typically, 4 classic signs or symptoms are present that differen-
tiate an acute wound infection from a chronic wound infec-
tion.5 Erythema, warmth, swelling, and pain are the 4 character-
istic findings commonly associated with acute wound infections. 
However, these signs are frequently not seen in chronic wound 
infec tions. Although all 4 are frequently found simultaneously, 
some individuals will not exhibit all of these signs or symptoms 
(Table 2). For instance, in the patient with diabetes mellitus who 
has severe peripheral neuropathy, pain (dolor) is not going to be 
present until the infection becomes severe and extends into the 
bone and nervous system. In addition, purulence and fever are 
symptoms that may not necessarily be present all of the time.

**TABLE 2. CLASSIC SIGNS AND SYMPTOMS OF INFECTION**

<table>
<thead>
<tr>
<th>Acute wound infection</th>
<th>Chronic wound infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Dolor (pain)</td>
<td>• Purulence</td>
</tr>
<tr>
<td>• Rubor (erythema)</td>
<td></td>
</tr>
<tr>
<td>• Calor (warmth)</td>
<td>• Fever</td>
</tr>
<tr>
<td>• Edema/swelling</td>
<td></td>
</tr>
</tbody>
</table>

Another problem is that what frequently looks like purulence is 
extruded produced from healthy granulation tissue. Physicians 
commonly mistake the presence of purulence for an infected 
wound and initiate systemic antibiotics, which again contributes 
to the production of resistant bacteria.

Secondary signs or symptoms, suggestive of a critically colo-
 nized wound with increased bacterial burden, include delayed wound healing; changes in color of the wound bed; friable gran-

**“...the results of superficial cultures are frequently misleading and promote the inappropriate use of systemic antimicrobials.”**

**ESTABLISHING COLONIZATION VERSUS INFECTION USING CLINICAL SKILLS**

Newman et al.9 evaluated the ability of physicians to identify 
patients with soft tissue infection versus those with underlying 
osteoarthritis in diabetic foot infections. The physicians who 
participated in this study were experienced in managing patients with 
diabetic foot infections. The study enrolled 35 patients with 41 
ulcers. While it was not a large study, it produced some important 
findings. Osteomyelitis was proven by bone biopsy in 28 out of the 
41 ulcers (approximately 68% of the patients). However, the diag-

nosis of osteomyelitis was made in only 9 out of 41 ulcers (32%). More importantly, 18 of the 28 patients (64%) with
underlying bone infection had no clinical evidence of inflammation and did not have an open or chronic wound.

This study illustrated that traditional signs and symptoms need not be present for local wound infection to be found in a chronic wound. It is common for clinicians to fail to establish and visually differentiate soft tissue infections from colonization or underlying osteomyelitis. Additionally, clinicians frequently underestimate the severity of the infection. In this study, quantitative tissue biopsy demonstrated that secondary signs or symptoms can occur in chronic wound infections and that a wound does not have to exhibit the classic manifestations of infection for it to be infected. No single sign or symptom is 100% sensitive. Increasing pain and wound breakdown should always be sufficient manifestations to consider a wound infected in patients who have an intact sensory system. These 2 manifestations are frequently absent in patients with diabetes or in paraplegic patients because they do not have an intact peripheral nervous system. For this reason, these patients frequently have undiagnosed severe wound infections.

In a separate study, wound swabs and deep tissue cultures were evaluated and compared in an attempt to establish their concordance rate. The study showed that if a wound swab alone is used as a guide for antibiotic selections, it will only be accurate approximately 62% of the time. Aside from the fact that a culture from a swab has low sensitivity, a routine wound swab cannot detect anaerobic bacteria, which may be present in these infections, specifically in pressure ulcers and diabetic foot infections. The study also evaluated the sensitivity of the needle aspirate, which was only slightly more effective than a wound swab, detecting approximately 69% of true pathogens. Use of a more invasive culture technique, such as deep ulcer-based curettage, improved culture sensitivity to approximately 75%. However, without obtaining true quantitative cultures from either deep tissue during debridement or from bone tissue, clinicians will still be using antibiotics incorrectly 25%–40% of the time. This inappropriate and empirical use of antimicrobials in turn leads to the development of broad-spectrum bacterial resistance.

### TABLE 3. SECONDARY SIGNS AND SYMPTOMS OF INFECTION

<table>
<thead>
<tr>
<th>Critically colonized</th>
<th>Bacterial burden</th>
<th>Local wound infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Delayed healing</td>
<td>• Change in color of wound bed</td>
<td>• Absent or abnormal granulation tissue</td>
</tr>
<tr>
<td>• Change in color of wound bed</td>
<td>• Friable granulation tissue</td>
<td>• Abnormal odor</td>
</tr>
<tr>
<td>• Friable granulation tissue</td>
<td>• Absent or abnormal granulation tissue</td>
<td>• Serous drainage</td>
</tr>
<tr>
<td>• Absent or abnor mal granulation tissue</td>
<td>• Abnormal odor</td>
<td>• Pain at wound site</td>
</tr>
<tr>
<td>• Abnormal odor</td>
<td>• Serous drainage</td>
<td>• Pain at wound site</td>
</tr>
</tbody>
</table>

### THE IMPACT OF ANTIMICROBIAL RESISTANCE IN WOUND MANAGEMENT

Antimicrobial resistance has become a problem not only in the hospital setting but also in the community because of the overuse and misuse of community provided antimicrobials. The greater the misuse of antibiotics in the community, the greater the resistance problem will be in the community.

The SCOPE study was a surveillance study across the United States that examined the distribution of blood-borne pathogens recovered from hospitalized patients (Figure 2). Approximately 60% of the isolates recovered were gram-positive cocci (coagulase-negative *Staphylococcus*, ~31%, *Staphylococcus aureus* (20%), and *Enterococcus* (9.5%). Over the past 5–10 years, *Candida* spp have become the fourth most commonly isolated species from the bloodstream, followed by gram-negative rods.

### FIGURE 2. IMPORTANT HOSPITAL PATHOGENS: MOST COMMON PATHOGENS IN NOSOCOMIAL BACTEREMIA 2003 (SCOPE STUDY)

- **Most Common Gram-Positive Pathogens Total 71%**
such as E coli, Klebsiella pneumonia, Pseudomonas aeruginosa, and Enterobacter spp. Gram-positive cocci are the most common cause of nosocomial infections in blood, the respiratory tract, and surgical sites. In the NNIS study, another surveillance study, investigators evaluated surgical site wounds and found Staphylococcus aureus and found patients treated as a nonvirulent organism and thought to be an “innocent bystander” in infection. Clinicians now know that Enterococcus is extremely important as a sole pathogen. Recent epidemiologic studies demonstrated that gram-positive cocci are the cause of approximately 50% of all skin and skin structure infections. Thus, the frequent use of parenteral lipopeptides in nosocomial wound infections leads to selective antimicrobial pressure and the generation of multidrug-resistant bacteria. An additional problem in clinical practice is the trend to provide sustained and prolonged use of systemic antibiotics until the wound is closed. It is important to re-educate practitioners and stress the importance of appropriate antimicrobial use and the fact that all open wounds do not require antimicrobials until they close.

WHY DOES ANTIMICROBIAL RESISTANCE DEVELOP?

Exposure to systemic antibiotics is the number 1 cause of antimicrobial resistance. Clinicians frequently overuse and abuse parenteral and orally administered antibiotics. Induction of resistance occurs due to prolonged exposure of microorganisms to antibiotics. All bacteria are capable of mutating and adapting to their surrounding milieu. Antimicrobial utilization practices must improve thorough education and practice-based medicine.

A recent study has shown that biofilm formation by certain bacteria has become an important virulence factor associated with the generation of secondary resistance. This occurs because antimicrobials are not able to penetrate the biofilm and completely eliminate the organisms living within the biofilm.

Another important mechanism of resistance is the transfer of genetic material from organism to organism. The best example of this is the development of several vancomycin-resistant S aureus strains, which acquired the vanA gene from a vancomycin-resistant enterococci.

A further means of eliciting antimicrobial resistance is by “selective pressure.” Whenever antimicrobials are used repeatedly in closed systems, such as hospitals, certain microorganisms that are intrinsically resistant to that selective antimicrobial frequently become common causes of nosocomial infections. For example, institutions that use fluoroquinolones, such as ciprofloxacin, tend to generate nosocomial infections due to MRSA. In addition, exclusive use of cephalosporins tends to breed nosocomial enterococcal infections. These bacteria can adapt and survive in this environment.

Prolonged hospitalization is also associated with nosocomial infections due to multidrug-resistant organisms. In patients admitted into the intensive care unit (ICU), after 1 week, 55% are colonized with the bacteria that colonize the ICU (ie, MRSA, Pseudomonas spp, and Candida spp); after a 2-week stay in the ICU, 75% of patients are colonized by the bacteria, and 92% are colonized after a 3-week length of stay (Table 4). Other interventions associated with increasing resistance include person-to-person spread,
immunosuppressive therapy, and HIV-positive status.

In 1989, resistance to fluoroquinolones was virtually nonexistent. However, the increase in quinolone use to treat nosocomial infections has produced an increase in the frequency of fluoroquinolone-resistant bacteria. This is evident not only in ICU patients but also in non-ICU patients. This is currently the case in many large tertiary care centers across the United States.

For many years, imipenem has been used to treat infections caused by multidrug-resistant organisms because of its efficacy and the lack of resistance to it. In 1988, the incidence of Pseudomonas resistance to imipenem was at approximately 5%. Over the last 5–10 years, resistance has risen to approximately 11%. In addition, in settings where it is used more frequently, such as ICUs, resistance has increased to 20%. A similar situation has been described with Klebsiella pneumonia, which initially was a susceptible organism and recently has acquired resistance from other gram-negative organisms.

The mnemonic “SPACE” is a term for the group of gram-negative bacteria that carry inducible beta-lactamases and thus have the ability to create havoc in hospitals across the country. In this situation, if the inappropriate beta-lactam antibiotic is initially used and it does not effectively kill the bacteria, the bacteria begin producing beta-lactamase and subsequently develop into multidrug-resistant organisms. The SPACE bacteria include 

- **Serratia marcescens**, **Pseudomonas aeruginosa**, **Acinetobacter**, which is surfacing at many VA institutions or facilities that treat veterans returning from the war in Iraq; **Citrobacter**; and **Enterobacter**. These bacteria have become a significant problem as a cause of nosocomial infections.

Extended spectrum beta-lactamases (ESBLs) are plasmid-mediated beta-lactamases initially reported in Germany in the 1980s and in the United States in the mid-1980s. In the 1990s, the spread of these enzymes became global. The ESBLs represent the ultimate result of the selective pressure process caused by the overuse of extended spectrum beta-lactam antibiotics (Table 5).

**TABLE 5. GRAM-NEGATIVE BACTERIA IN WHICH ESBLs ARE DESCRIBED**

- Citrobacter spp
- Enterobacter spp
- Acinetobacter spp
- Escherichia coli
- Klebsiella pneumonia
- Proteus spp
- Pseudomonas aeruginosa

Many of the gram-negative bacteria that have acquired the ESBLs are frequently found in ICUs and long-term care facilities. A study published in 1999 found that 64% of patients identified during a facility-wide outbreak in New York nursing home patients were a source of multidrug-resistant and ESBL producing E coli and Klebsiella. The risk factors that appeared to be associated with these multidrug-resistant infections included infected pressure ulcers, gastrostomy tube use, functional status, and prior exposure to either a fluoroquinolone or trimethoprim/sul-famethoxazole.

Beta-lactamases may be found in almost any microorganism. The ESBLs have been described in many gram-negative organisms including Enterobacter, Acinetobacter, Pseudomonas, Klebsiella, E coli, and indole-positive Proteus. These organisms are able to quickly adapt to the surrounding environment and survive. The obvious concern regarding these gram-negative organisms is that they have the intrinsic capability to produce beta-lactamase but can also acquire ESBLs from their surrounding environment, accepting the transference of these enzymes from other organisms.

The history of gram-positive bacteria resistance essentially parallels what has occurred over the past 15 years in gram-negative bacteria. Methicillin-resistant *S aureus* became endemic US hospitals during the 1980s. In 1989 and 1990, the incidence of MRSA was in the 20% to 30% range. Today, in most institutions across the United States, the incidence is between 50% and 60%. Although coagulase-negative *Staphylococci* (CoNS) have been methicillin resistant for many years, the incidence of resistance has also increased from 70% in 1989 to 90%–95% in 2001–2002. However, it was still susceptible to penicillin in the 1960s. These bacteria are almost 100% resistant to methicillin, meaning that few systemic antibiotics are available to treat CoNS infections. Thus, the combination of CoNS as the most frequent cause of nosocomial infections and the fact that vancomycin is the most
commonly used antibiotic to treat these infections is leading to vancomycin resistance emerging in gram-positive cocci, such as MRSA and VRSA.

For many years, researchers thought that once a strain of bacteria mutates and develops resistance, the organisms have lower virulence. This myth has now been dispelled by gram-negative bacilli and certainly by gram-positive cocci, especially MRSA and VRE. Recent epidemiological studies evaluating the outcome of patients infected with susceptible and resistant bacteria have in fact demonstrated the opposite, time after time. Studies comparing the cost and outcome of treatment for patients infected with either MRSA or methicillin-susceptible Staphylococcus aureus (MSSA) demonstrate a cost per patient per infection of approximately $65,000 and $24,500, respectively. In a separate study by Chaix et al., the investigators were able to show that the length of stay doubled from 12.5 days (MSSA) to approximately 21 days (MRSA). In addition, the mortality rate more than doubles from 22% to 56%. A multicenter evaluation of 296 ICU patients with either MRSA or MSSA showed that the length of stay increased from 7 to 14 days, and mortality rates increased from 24% to 35%. This is almost a 50% increase in mortality due to MRSA versus MSSA.14,26

In addition to MSSA and MRSA, there are 3 different strains of S. aureus. There are recent reports of bloodstream and wound infections caused by MRSA with reduced susceptibility to vancomycin (minimum inhibitory concentration [MIC] 8–16 μg/mL). These strains are currently known as vancomycin-intermediate S. aureus (VISA) or glycopeptide intermediate S. aureus (GISA) (vancomycin is only one of the glycopeptide antibiotics). The first GISA case was reported in Japan in a child with an open heart and a mediastinitis infection due to MRSA. Again, wound infections are frequently associated with the development of many of these types of resistance cases. Another more recent discovery is vancomycin-resistant S. aureus (VRSA). To date, 6 cases of VRSA have been reported worldwide. Four of these cases have been described in southeast Michigan hospitals. In June, 2002, the first case of VRSA was recovered from a catheter exit site. The normal vancomycin MIC is in the range of 0.25 to 1 μg/mL; in these multidrug-resistant organisms, the MIC is as high as 128 μg/mL. Using molecular genotyping studies on several VRSA isolates, investigators discovered the vanA gene, which was previously described in vancomycin-resistant enterococci. These patients initially start out with an enterococcal infection and frequently receive vancomycin. If the patient has an open wound, the wound is either colonized or infected with MRSA. The patients with the VRSA isolates generally have received several courses of parenteral vancomycin to treat the initial MRSA and/or enterococcal infection. Under the selective pressure of vancomycin, the enterococci found in the wound develop resistance to vancomycin (VRE). After an unknown time period, the VRE is able to transfer the vanA gene to MRSA and thus generate VRSA strains in the process. Thus, the VRE is able to transfer its genetic material into MRSA under the pressure of vancomycin. The combination of S. aureus and Enterococcus found simultaneously in a wound is common.

The third strain type of MRSA is known as HR-VISA or heteroresistant S. aureus. In certain MRSA strains, there appears to be a subpopulation with decreased susceptibility to vancomycin (4–6 μg/mL). With HR-VISA, heteroresistance is determined when a MIC or a susceptibility assay is performed and reveals a decreased susceptibility to vancomycin. Unfortunately, many VISA heteroresistance strains appear susceptible in routine laboratory evaluations.

Many major medical journals have been reporting on the increased incidence of “super bugs”—bacteria that have the capability to acquire multiple forms of resistance. Enterococcus is a super bug, because it has rapidly evolved from a susceptible organism to one that now has multiple mechanisms of resistance and is the possible cause of VRSA. In addition, enterococcal infections have been associated with mortality rates of up to 30%. Furthermore, in patients with underlying malignancy and an enterococcal infection, the mortality rates increase to 56%, while adding approximately 2 additional months to hospitalization time. Therefore, Enterococcus and MRSA in an open wound and the addition of vancomycin is a significant problem.

Although vancomycin has been the workhorse for gram-positive infections for many years, it still has some major limitations, and recently, problems with the development of resistance have emerged (Table 6). Overuse and abuse of vancomycin leads to the production of vancomycin-resistant gram-positive cocci, VRE and VISA. The HR-VISA populations previously mentioned may be only the tip of the resistance “iceberg.” Other limitations of vancomycin are the adverse events that have been associated with its use. Although not a very nephrotoxic drug, many patients are

<table>
<thead>
<tr>
<th>TABLE 6. VANCOMYCIN LIMITATIONS</th>
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<tbody>
<tr>
<td>• Slow bactericidal activity</td>
</tr>
<tr>
<td>• Poor tissue penetration</td>
</tr>
<tr>
<td>• Rising MICs against MRSA (MRSA/vancomycin “creep”)</td>
</tr>
<tr>
<td>• Insufficient dosing</td>
</tr>
<tr>
<td>• Nephrotoxicity when used in combination with other drugs</td>
</tr>
<tr>
<td>• Increasing VISA strains (MICs 4–8 μg/mL)</td>
</tr>
<tr>
<td>• VRSA strains (&gt; 32 μg/mL)</td>
</tr>
<tr>
<td>• Heteroresistance in MRSA (VISA disguised as MRSA)</td>
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</table>
unable to tolerate parenteral vancomycin, especially at the higher doses that are being used today. For many years, when given vancomycin, patients would develop infusion-related toxicity and reactions known as the "Redman syndrome." This "Redman syndrome" does not occur frequently today, but it still does on occasion. Finally, because of the prolonged use of vancomycin and through the advent of better in-vitro susceptibility assays, clinicians have become aware that vancomycin is slowly losing its potency, and resistance among many gram-positive cocci is gradually increasing.35,36

STRATEGIES TO IMPROVE CURRENT ANTIMICROBIAL RESISTANCE TRENDS

The ever constant trend of microbial resistance has challenged pharmaceutical companies to develop newer antibiotics to manage these multidrug-resistant bacteria.35 Unfortunately, every year, fewer companies are investing in the research and development of newer antimicrobial agents. It is imperative that steps be taken to prevent or slow the development of antimicrobial resistance (Table 7).

Hand washing, infection control, and antimicrobial use are all important components in preventing the development of resistance. Avoidance of systemic antimicrobial exposure, if possible, is also important in lowering resistance rates, whether it is resistance to vancomycin in the gram-positive organisms or to the ESBLs in the gram-negative organisms.

Use of a potent, "cidal" antibiotic that kills bacteria within a couple of hours, instead of a "static" antibiotic, may be beneficial to prevent resistance. Static antibiotics stop the organism from reproducing, but the organisms remain in the wound until they die. If antibiotic use is stopped before the bacteria have died, the bacteria may continue to multiply and reproduce. Another plausible method is the use of an appropriate antibiotic in shorter courses.35,36 It is no longer necessary to prescribe 2 to 3 weeks of antibiotics for many types of infections. In fact, in nosocomial pneumonias, 3 to 7 days may be all that is needed.36 Another possible recourse is antimicrobial heterogeneity to prevent constant and selective pressure of only certain antibiotics in a closed system (eg, hospital setting). Many hospitals have chosen a system that cycles antibiotics over a period of 4–6 months; thus, the same antibiotics are not used repeatedly over prolonged periods of time.35

Recent outcome studies have shown that a delay in the appropriate antibiotic increases morbidity and mortality. Increases in length of stay between 1 and 1.5 months and increases in cost have been associated with inappropriate antibiotic selection.35,36 This creates a burden not only to the patient but also to the hospital and the entire healthcare system. It is important to choose the correct antibiotic. Many organisms are ready for these antibiotics due to the development of multidrug resistance. The medical community needs to improve strategies to prevent antimicrobial resistance.

In many situations involving open wounds and wound infections there is no need for systemic (oral or IV) antibiotic use when there is no evidence of systemic infection or extension of the infection into surrounding tissues or into the bloodstream. In this situation, topical antibiotics should be considered. Clinicians need to decrease the use of broad-spectrum antimicrobials, such as cephalosporins, quinolones, beta lactams, and vancomycin, in these situations.

CONCLUSION

Recent data has shown the emerging resistance trends in many gram-negative bacilli including Pseudomonas, E coli, and Klebsiella as well as in the gram-positive cocci, such as MRSA and VRE. A more recent concern is that many cities across the United States are encountering an increasing incidence of CA-MRSA. Until recently, MRSA was specifically associated with hospital infections and was rarely identified in the community. The current rate of CA-MRSA appears to be between 16% and 50%. Better understanding of antimicrobial resistance mechanisms, whether it is selective pressure or improved selection of systemic antibiotics versus topical antibiotics, is imperative. Hopefully, the pharmaceutical industry will continue to produce antibiotics aimed at treating the organisms
that are becoming increasingly resistant. Also of importance is the rapid identification of resistant organisms. This process frequently takes 2 to 3 days for an organism to grow on selective media and another 48 to 72 hours to gauge that organism's susceptibility. In situations where patients are extremely ill, this time lapse may be too late.

**REFERENCES**


Trends in Management of Critical Colonization and Infection

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INTRODUCTION

The management of wound infection requires a global approach to the patient. The global approach is exemplified by the wound bed preparation algorithm (Figure 1), which includes 3 key components. First, the clinician must identify and ameliorate the underlying cause of the wound. Second, the clinician must address patient-centered concerns. If the patient's cultural sensitivities, wishes, desires, pain, and psychosocial aspects are not taken into consideration, he or she is unlikely to adhere to the wound care plan. The third component of the wound bed preparation algorithm is local wound care, which has 3 major components. The first is removal of nonviable tissue. The second is management of inflammation and infection — clinicians are beginning to realize that many wounds are inflamed but not infected and must distinguish between inflammation and infection. Finally, appropriate dressing selection will maintain moisture balance at the wound bed. If all components of the wound bed preparation algorithm are in place and the wound still is not closing, an edge effect may be the cause, and biological agents, skin grafts or substitutes, and adjunctive therapies should be considered.

This article will identify interventions to prevent and treat critical colonization and infection and discuss the mechanism of action, indications, and appropriate uses of nanocrystalline silver and cadexomer iodine.

FIGURE 1. PREPARING THE WOUND BED PARADIGM

BACTERIAL BALANCE CONTINUUM

In the bacterial balance continuum (Figure 2), a battle exists between the host and the invading bacteria. To treat the wound effectively, the clinician must consider the host's defenses as well as the bacterial number (colony counts) and virulence. Any wound that has been present for even a brief period of time will be contaminated with a small number of bacteria on the surface; the bacteria will be nonadherent and nonreplicating, and these ulcers will...
The host’s defenses are sufficient to manage the contaminating bacteria on the surface. As bacteria begin to replicate, they form colonies, which are adherent to the surface. Colorizing bacteria are usually not significantly invasive, and these ulcers often progress to healing. Host resistance is still great enough to overcome the number and virulence of the bacteria. However, a subtle point, critical colonization, occurs when the bacteria begin to overwhelm the host defenses. The bacteria are now beginning to invade, and subtle signs of infection and delayed wound healing become evident. Finally, the wound becomes clinically infected, and the bacteria are deeply invasive. The classic signs and symptoms of infection are usually present.

Clinical characteristics may aid in differentiating between critical colonization and infection (Figure 3). Increasing wound size, increasing exudate, friable, bright red granulation tissue, or increasing odor are signs of critical colonization. Critically colonized wounds often can be treated with a topical antimicrobial agent unless the patient is severely immunocompromised. Deep tissue infections, however, are characterized by erythema and edema extending more than 2 cm beyond the wound border, probing to bone, pain in a previously painless ulcer, tenderness where there was previously none, and new or satellite areas of breakdown. Systemic antibiotics are necessary to treat a deep compartment or deep tissue infection. Edema that may be present in this ulcer may prevent systemic antibiotics from reaching the wound surface and from reaching the organisms that may repopulate the deeper tissues. Under these circumstances, a topical antimicrobial to reduce surface bacterial burden in combination with systemic antibiotics to manage the deep tissue bacterial loads may be necessary.

PREVENTION

Prevention should be the clinician’s primary focus. Patient location is an important consideration because prevention strategies will differ between inpatient and outpatient treatment settings. The virulence of the organisms is also important. Populations of organisms tend to differ between inpatients and outpatients and tend to have different spectrums of activity. Again, a global assessment of the patient is necessary, and clinicians must be attuned to the immunocompromised patient whose host defenses may be decreased because of either the disease process or treatment. This group of patients may include those with collagen vascular disorders taking prednisone, those taking chemotherapeutic agents, such as methotrexate or the new immune modulating drugs, patients under active treatment for malignancy, immunocompromised HIV-positive patients, or transplant patients taking immunosuppressive drugs. All of these patients will require more aggressive prevention strategies. Environmental factors that have to be considered include the skill of the healthcare providers and availability of resources.
The most important vectors of infection are the hands of health-care providers. Clinicians should use gloves for all dressing changes and need to disinfect their hands frequently — at a minimum between patient visits.

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pathways in the bacteria. They have a specific activity against a specific range of microorganisms. The term antimicrobial agent encompasses both antiseptics and antibiotics.

Several basic principles should be considered when selecting a topical antimicrobial agent:

1. Avoid an agent that may be used systemically at a later point.
   Chronic use of topical agents often creates resistant surface flora in the wound, which may become systemic infecting organisms.

2. Avoid sensitizers. Many topical antibiotics are potent topical sensitizers that create a contact allergic dermatitis in as many as 30% to 40% of patients, particularly patients with venous leg ulcers.11

3. A topical antimicrobial agent should kill bacteria quickly to avoid the development of antimicrobial resistance.
   Common topical sensitizers include neomycin, framycetin, bacitracin zinc, and agents containing lanolin or perfumes.11 Metronidazole is an exception to the rule of avoiding topical use of systemic agents. Metronidazole is only effective against anaerobes, and minimal resistance to metronidazole has been reported.
   Unfortunately, many clinicians use metronidazole in ulcers that are growing staphylococcus or streptococcus and not growing anaerobic organisms. Mupirocin was initially effective against methicillin-resistant Staphylococcus aureus (MRSA), but there are now a number of MRSA strains that are resistant to mupirocin, particularly in some parts of Canada. It is not currently recommended for use in wounds. Silver sulfadiazine must be applied frequently to the wound bed and should be avoided in patients with sulfa allergies.
   It is, however, relatively inexpensive and often covered by drug benefit plans. The advent of various silver dressings has revolutionized topical management of bacterial burden in ulcers.

ANCIENT ANTISEPTIC USE

Antiseptics were used in ancient times and were reported in an Egyptian papyrus. The Egyptians used copper as an antiseptic, and the Greeks used silver to disinfect water. The Greeks also created dried powders called “enhemes” that contained copper, zinc, and aluminum compounds or wet formulations that contained vinegar, honey, copper, or aluminum. These compounds were either pastes or powders and were used on wounds, particularly on soldiers that had been injured in battle.12 Vinegar is reported in the Greek literature as preventing suppuration, and wine was a common antiseptic. Interestingly, the alcohol content in wine is too low to be effective; it is approximately 10% in modern wine. However, wine contains polyphenols, such as malvolside and oenoside, which work only in the acidic pH of wine. Most likely, these were the antiseptic components of the wine that were useful. Honey was widely used in ancient times. For many years, clinicians believed that it was useful because of its osmotic effect; honey is a hypertonic solution of sugar in water, which would have an osmotic effect causing bacteria to rupture. Honey becomes more effective as it is diluted due to the release of hydrogen peroxide. It also sequesters oxygen-free radicals. Like wine, honey might also contain phytochemicals; however, this has yet to be proven. Some lab work has identified increased lymphocytic and phagocytic activity when honey is present in the wound, but it is dependent on the source and how the honey is processed.13

MODERN ANTISEPTIC USE

The modern use of antiseptic agents can be traced to 1865 when Joseph Lister introduced carbolic acid or phenol use in surgery. Over the next century, people tried to develop other antiseptics, and many of them were halogen-containing compounds, such as sodium hypochlorite, chlorhexidine, and povidone iodine solution. The advent of various alcohols followed, as well as the acridine dyes and mercury-containing compounds, quaternary ammonium compounds, hydrogen peroxide, and silver. Other approaches to antisepsis included gamma irradiation, heat, ultraviolet light, and microwaves. In the 1990s, research indicated the toxicity of antiseptics to normal tissue, most of which was conducted in vitro with fibroblast migration on plates or in animal models.19 Almost all antiseptics were found to be toxic to fibroblasts in vitro. Additionally, the Agency for Healthcare Research and Quality (AHRQ) clinical practice guideline for pressure ulcer prevention9 indicated that antiseptics were harmful. Emerging expert opinion suggests that the toxicity observed in animal and in-vitro models may not be found in actual wounds. Toxicity may be a concentration effect, and when diluted, some antiseptics may have the benefit of disinfection without inducing tissue toxicity.

Sodium hypochlorite (ie, bleach) has a high pH and is a skin irritant. Examples of sodium hypochlorite are Dakin’s solution and Eusol. Eusol is buffered, but it often selects out gram-negative organisms. Hydrogen peroxide is a desloughing agent while active; when inactive, it is water. Hydrogen peroxide, particularly in high concentrations, harms healthy granulation tissue. Additionally, 2 studies reported air emboli formation when hydro-
and gram-positive organisms and has relatively low toxicity, but it is avoided in wound care. The quaternary ammonium compounds are effective detergents but should be reserved for cleaning hard surfaces. Chlorhexidine has good activity against gram-negative bacteria and is effective against pseudomonas but it often selects out Staphylococcus aureus. Additionally, patients do not like acetic acid because it stings. Povidone iodine has the broadest spectrum of activity. Unfortunately, its activity decreases in the presence of pus, and when used in large amounts over large surfaces for prolonged periods, it may be toxic.2

Antiseptics are finding their niche in chronic wound management in “maintenance wounds” — wounds that are not expected to heal but in which clinicians want to control the bacterial burden. Clinicians may also use topical antiseptics in a wound for brief periods when the bacterial burden in that wound is of greater concern than the healability at that point. Aqueous chlorhexidine and povidone iodine are the 2 most commonly used antiseptics. Iodine appears to be the ideal antiseptic because of its broad spectrum of activity. It works in many ways; it disrupts cell walls and cell nuclei, and it also facilitates oxidative killing of microorganisms and neutrophils.

**ANTIMICROBIAL DRESSINGS**

**Cadexomer iodine.** Cadexomer iodine is a novel delivery system in which the iodine is contained within a cadexomer starch bead that acts as a carrier and allows the slow release of iodine into the wound bed. The cadexomer starch is highly absorbent and forms a gel on contact with exudate. Wound exudate, pus, and debris enter the cadexomer bead and cause the cadexomer bead to swell. The cross linking in the bead then breaks apart. The openings become larger, which allows a slow, sustained release of the iodine molecules that are inside the bead. There is a gradient that exists between the beads and the wound bed, which keeps a steady state 0.9% iodine concentration at the wound bed. Iodine is brown, and iodide, which is the inactive form of iodine, is colorless. The dressing transforms from brown to colorless when the iodine has been used. It provides a controlled release for 72 hours, and it is indicated for healable wounds, because it is nontoxic to healthy tissue. Also, the gel formed by cadexomer starch supports autolytic debridement and desloughing of the wound bed, and because it is absorbent, it can help manage wound exudate. It will absorb approximately 6 times its weight in exudate.

**Nanocrystalline silver.** Silver is an antimicrobial that has a broad spectrum of activity against yeasts, molds, and bacteria, such as MRSA and vancomycin-resistant enterococcus (VRE). Silver kills by several different processes: inhibiting cellular respiration, denaturing nucleic acid, and altering cell membrane permeability. With 3 different routes of kill, mutation development is difficult but not impossible. Silver does not induce resistance if used at adequate levels, and mammalian cell toxicity for silver is low. The active species is the Ag+ ion. The kill rate for silver is directly proportional to the silver ion concentration — the higher the silver ion concentration, the higher the antimicrobial efficacy. However, silver is fairly reactive. It is bound by halide, such as chloride, inorganic anions, organic acids, and proteins, all of which are present in wound fluid. Individual silver crystals are only 20 nm in diameter. This means that an exceedingly high number of silver atoms in the silver metal are present on the surface rather than in the interior, resulting in a rapid and sustained release of silver into the wound. It is a release of silver metal, Ag0 and Ag+, that coexist in the wound fluid. Figure 4 shows a scanning electron micrograph of the nanocrystalline silver membrane, illustrating the large surface area that facilitates rapid release of silver into the wound bed. Silver is indicated as an antimicrobial barrier dressing. Once silver is on the outside of the wound, it will kill bacteria that attempt to migrate through the dressing into the wound bed. Silver dressings are indicated for partial- and full-thickness wounds and partial-thickness burns.

One acceptability and efficacy study of Acticoat moisture control (Smith & Nephew, Largo, Fla) or a silver foam dressing enrolled 10 patients; 9 completed the study.13 The investigators conducted 3
assessments over 14 days. Wounds were identified as being critically colonized or at risk of becoming critically colonized and were of mixed etiologies: venous ulcers (4), traumatic ulcers (2), stage 2 pressure ulcers (2), and mixed etiology (1). All received standardized care according to their particular etiology. Wound surface area was calculated using digitized acetate tracings on Day 0 and Day 14. Photographs were taken; patients rated pain on a 4-point scale; and clinicians rated acceptability of the dressing. In 2 weeks, 4 of the 9 wounds closed. The mean reduction in surface area was almost 60%, and 8 of 9 patients reported improved pain scores during the 2 weeks. Clinicians rated the dressing as “good” to “excellent” in terms of ease of application and conformability. Figure 5 shows each of the wounds and the relative change in the surface area. Only 1 patient, patient number 6, had an increase in wound size.

CASE REPORTS

Case 1. A 55-year-old man with type 2 diabetes for 15 years, severe peripheral neuropathy, normal vascular supply, and a plantar ulcer was referred to the author’s clinic for treatment. On the night prior to his clinic visit, the patient soaked his feet. With his peripheral neuropathy, he managed to soak his feet in scalding hot water and developed a second-degree burn over most of the forefoot. Treatment included twice-weekly dressing changes, once with home care and once at the author’s clinic. The ulcer was sharp debrided to remove nonviable tissue and pressure was offloaded with a pneumatic walker. The patient was treated for 10 days with broad-spectrum oral antibiotics, and his ulcer and burns were covered with a nanocrystalline silver dressing. The patient was managed adequately as an outpatient. The ulcer did not develop an infection, and the wounds had 80% reepithelized in 3 weeks. The neuropathic ulcer on the plantar surface of the foot healed within a 5-week period. Figure 6 shows the patient’s foot at presentation. The plantar ulcer for which he presented is visible on the left. Figure 7 shows the foot wrapped in nanocrystalline silver, the Acticoat burn dressing (Smith & Nephew), 1 week after presentation. The dressing was easy to apply and made reasonable contact with the area. Figure 8 shows the foot 2 weeks after presentation, and Figure 9 shows the foot healed at 5 weeks.
Case 2. A 55-year-old man with a normal ankle brachial pressure index and a previous ankle fracture presented to the author’s clinic with an ulcer of 1 year’s duration. The patient had been self-treating the recurrent ulcer. The wound was diagnosed as a venous stasis ulcer. A review of the literature shows that compression therapy is the treatment of choice for venous stasis disease; thus, no progress could be made with the patient’s ulcer until compression therapy was initiated. However, the patient-centered concerns had to be addressed first. Since he had been treating the ulcer by himself for a year, it was evident that he was reluctant to seek treatment from medical professionals. Thus, his psychosocial issues had to be addressed, not the least of which was pain. It became necessary to convince the patient that if the swelling in his leg reduced, the pain would reduce as well. Every part of treatment had to be fully explained to the patient in order to convince him of what needed to be done. There was nonviable tissue in the wound bed, so the ulcer was debrided with a method that did not increase pain. Considering the duration of the ulcer, it was assumed that it had at least a superficial infection if not a deep infection. Maceration was visible, indicating that the wound was highly exuding. Absorbent dressings were necessary to control the exudate. In this particular case, cadexomer iodine supported autolytic debridement, provided bacterial balance at the wound bed, and absorbed wound exudate. Additionally, cadexomer iodine is useful under compression therapy.

Case 3. A 35-year-old man with type 1 diabetes for 10 years presented to the author’s clinic. The patient worked as a non-skilled laborer. His glycemic control was somewhat variable. The patient unknowingly stepped on an insulin needle. He had peripheral neuropathy, so he was not aware that he stepped on the needle. The patient walked on the embedded needle for several days, perhaps a week, prior to presentation. He also had a second ulcer. The needle embedded between the first and second toes, creating a large sinus. Nonviable tissue that was impeding wound healing was removed; his wounds were surgically debrided; and the sinus between the first and second toes was deroofed as well (Figure 10). The wound beds still contained slough and required further debridement.

While the wound was not heavily exuding, the intact wound edge required protection. Cadexomer iodine was selected as the preventative approach to keep the wound bed surface free of bacteria in order to prevent deep tissue infection. It also supported autolytic debridement and absorbed some exudate. Cadexomer iodine was used in this case rather than silver dressings because silver dressings tend to suppress the inflammatory response. On the other hand, the iodine tends to be pro-inflammatory, and this is beneficial in the person with diabetes whose inflammatory response may be suppressed by glucose levels. Figure 11 shows the outcome.

Case 4. An 80-year-old bedridden woman who had a stroke, a poor appetite, and bowel and bladder incontinence presented to the author’s clinic with several ulcers that resulted from shearing caused by inappropriate transfers and from the patient sliding down in the bed. This particular issue required the help and support of an occupational therapist to develop good positioning strategies to keep the patient off the ulcers and to prevent the friction and shear that initially caused the problem. Since the patient had multiple comorbid conditions and was considered palliative by her family, her ulcers were not managed aggressively. Eschar and slough were present in 1 ulcer, and since she was incontinent of bowel and bladder, the focus of treatment was cleaning the wounds, reducing exudate, reducing the frequency of dressing changes, and preventing ulcer contamination. Cadexomer iodine was applied under an adhesive dressing to prevent contamination and reduce the frequency of dressing changes to twice weekly as long as the dressing did not lift or leak. She subsequently died of her multiple medical conditions, but remarkably, her pressure ulcers were completely closed at the time of death.

FIGURE 10.

FIGURE 11.
CONCLUSION

Cadexomer iodine has historically been a useful, nontoxic antiseptic for the management of chronic wounds. It has 3 key properties: it supports autolytic debridement; helps maintain bacterial balance in the wound; and helps maintain moisture control by absorbing exudate. Other dressings that have been useful are antiseptic dressings containing various forms of nanocrystalline silver. Silver dressings are indicated for critically colonized wounds or as septic dressings containing various forms of nanocrystalline silver.

REFERENCES


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