

wound healing perspectives[®]

A CLINICAL PATHWAY TO SUCCESS

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➔ INFECTION AND CHRONIC WOUNDS

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Treatment and challenges of chronic wounds

The skin provides an all-important barrier to the outside world. From a wound healing perspective, skin is the first line of defense from invading organisms. Breaks in this barrier—from microscopic alterations associated with dermatophyte infections, to widespread acute skin loss due to burns or drug reactions (e.g., toxic epidermal necrolysis)—have been associated with invasion of microorganisms. One of the major goals of healing is to restore the functional integrity of the skin, in part to prevent opportunities for microorganisms to gain a substantial foothold.

In this issue of Wound Healing Perspectives, we focus on infections and microbiology important to wound care providers. Specifically this issue will address the cardinal signs of recognizing wound infection and cellulitis, the importance of dermatophyte (fungal) infections, the emerging role of biofilms in wound care, and the crisis of resistance of bacteria to antibiotic therapy, especially *Staphylococcus* and *Pseudomonas* infections.

We hope you find this issue of WHP informative and useful in your practice.

Sincerely,



Robert Kirsner, MD, PhD
Medical Advisory Board

Infection and chronic wounds

Wounds that fail to heal are often linked to the interaction of a complicated series of abnormalities in the wound bed and the host's responses to tissue injury. According to an article by Warriner and Burrell [2005], factors such as infection, any condition that produces abnormal blood flow and hypoxia, cellular failure, and trauma can contribute to a chronic wound not healing.

The majority of chronic wounds—even clean surgical wounds—are contaminated and colonized by bacteria. Although not necessarily a problem, it is often difficult to tell when the bacterial load is acceptable or if the healing of the wound may become impaired due to an undesirable shift in the bacterial balance [Warriner et al, 2005]. Since bacteria are present in all chronic wounds, a balance must be maintained between host resistance and the quantity and virulence of bacteria for wound healing to occur.

According to Warriner et al [2005], an increased bacterial bioburden on the wound's surface and in wounded tissue increases the metabolic requirements of the wound



TRADITIONAL SIGNS AND SYMPTOMS NEED NOT BE PRESENT FOR A CHRONIC WOUND TO HAVE A LOCAL INFECTION.

and of the host's response to that bacterial load, often causing healing failure. It also can affect tissue oxygen availability, favoring bacterial growth.

Individuals with diabetes have an increased risk of infection, due, in part, to compromised neutrophil function, impaired chemotaxis and mobility, impaired

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The role of silver in wound bed preparation



Silver is a broad-spectrum antimicrobial agent that controls yeast, mold, and bacteria, including methicillin-resistant *S. aureus* (MRSA) and vancomycin-resistant enterococci (VRE)—when provided at an appropriate concentration. As a result, silver-based wound dressings are often used to prepare the wound for healing. Silver kills microbes on contact by inhibiting cellular respiration, denaturing nucleic acids, and altering cellular membrane permeability. Silver also has low mammalian cell toxicity and is now known to have potent anti-inflammatory properties. It also may be used to maintain a microbe-free, moist wound healing environment. ■

SOURCE: WARRINER ET AL, 2005

adherence, and impaired phagocytosis [Warriner et al, 2005]. Diabetics also have more depressed antioxidant systems and humoral immunity to some extent.

Virulence factors that may favor bacteria (and thus impair healing) include adhesins, cell capsules, biofilms, and antibiotic resistance, states Warriner et al [2005].

When identifying and evaluating an infection, therefore, identifying the number of organisms alone is not always as important as identifying the type of pathogen present. Since wounds are polymicrobial, infections in acute and chronic wounds generally involve mixed populations of aerobic and anaerobic bacteria. In fact, results from multiple studies suggest that anaerobic bacteria are present in 38 percent of non-infected wounds and 48 percent of infected wounds [Warriner et al, 2005].

Chronic wounds do not always behave like acute wounds, especially when an increased bacterial burden is present. In fact, traditional signs and symptoms need not be present for a chronic wound to have a local infection [Warriner et al, 2005]. According to a study by Gardener et al [2001] where 36 chronic wounds were assessed for signs and symptoms of wound infection, investigators found that the positive correlation between the presence of the culture-demonstrated infection were friable granulation tissue, an increase in odor or abnormal color, increased pain at the wound site, and wound breakdown.

Properly diagnosing the infection by taking a tissue culture from the wound or a blood culture in patients where there is systemic involvement is recommended. Most studies indicate that a tissue biopsy is the best way to determine the amount of the causative

organisms of a wound infection. However, diagnosis is practically made by clinical examination of the wound's physical and clinical characteristics and treatment is determined by a swab culture or biopsy [Warriner et al, 2005].

Wound bed preparation also is key to reducing the bacterial burden of the wound. Necrotic tissue, which harbors bacteria and serves as a physical barrier to wound healing, should be removed. Saline is often recommended to cleanse the wound surface. Antiseptic agents, however, are not routinely recommended (slow-release antiseptics such as slow-release iodine are appropriate in cases where controlling the bacterial burden is top priority) and are considered controversial (see page 6 for article). Also, systemic antibiotics may not be useful in heavily contaminated or infected wounds. ■

METHICILLIN-RESISTANT *S. AUREUS* (MRSA)

Methicillin-resistant *S. aureus* (MRSA) is a type of staphylococcal infection. In fact, approximately 33 percent of the population is colonized with MRSA, reports Edmunds [2005]. Staphylococcus is a

common organism carried on the skin, nares, and perineum of healthy individuals and usually causes superficial skin infections that are treatable with appropriate antibiotics and skin care. Over time, however, it

has become resistant to beta-lactam inhibitors such as methicillin and was later identified as a nosocomial infection, or health-care-associated MRSA (HA-MRSA) [Romero et al, 2006]. ■

Challenges of MRSA infection

MRSA can be transmitted by direct contact (contaminated hands or droplet transmission) or indirectly by sharing items that have the organism. Types of nosocomial infections include wound infections, surgical incisions, catheters, prior antibiotic use, an immunocompromised state, or intravenous drug use. MRSA also can result in devastating blood-borne infections, which few antibiotics can now treat [Romero et al].

Those at greatest risk for acquiring HA-MRSA include individuals in hospitals or long-term treatment facilities, as well as individuals who undergo surgery, dialysis, or implantation of invasive devices, and those who have had a previous diagnosis of MRSA [Edmunds, 2005].

Preventing the spread of MRSA into the community has been an ongoing issue since the 1990s when the first cases of MRSA in the community were reported. A 2003 study stated that 12 percent of clinical MRSA are community-associated and the rates of CA-MRSA are rising [Romero et al, 2006].

When compared to HA-MRSA, CA-MRSA cases are unique demographically, clinically, and microbiologically. CA-MRSA and HA-MRSA

come from different strains. CA-MRSA is unique due to the Pantone-Valentine leukocidin, a powerful toxin that can lead to tissue necrosis. It also carries the type IV staphylococcal cassette chromosome mec. A 2002 study by Okuma et al stated that multiple methicillin-resistant *S. aureus* (MRSA) clones carrying mec, identified in the CA-MRSA strains of both the United States and Australia, seem to multiply much faster than health-care-associated MRSA and were resistant to fewer non-beta-lactam antibiotics. What's more, CA-MRSA cases seem to have been derived from more diverse *S. aureus* populations than health-care-associated MRSA strains. In addition, CA-MRSA and HA-MRSA have different pulsed-field gel electrophoresis patterns, which reveal that they come from different *S. aureus* strains [Romero et al].

Diagnosis

Since HA-MRSA is a type of methicillin-resistant *S. aureus* infection, much of diagnosis, treatment, and care of infection are the same as for *S. aureus*. Definitive diagnosis of *S. aureus* infection is made by obtaining a culture from the area of suspected infection. Suspect diagnosis is based on patient symptoms and the healthcare provider's evaluation [Minnesota

Department of Health website, 2006].

CA-MRSA infections are usually skin or soft tissue infections that are accompanied by fever, swelling, pain, purulent drainage, or warmth. Furthermore, CA-MRSA should be included in the differential diagnosis of all patients with skin infections, reports Romero et al [2006], especially those who live or have lived in a group setting. Differential diagnosis should look for the presentation of skin infections, as well as non-MRSA staph infections, streptococcal infections, erysipelas, contact dermatitis, impetigo, herpes, insect bites, foreign body reactions, lymphedema, and deep vein thrombosis. In more severe cases, the differential diagnosis may include sepsis syndrome, osteomyelitis, necrotizing pneumonia, septic arthritis, and necrotizing fasciitis.

According to the CDC, a diagnosis of CA-MRSA does not require a past history of MRSA or colonization and requires no history of the risk factors associated with HA-MRSA. In addition to methicillin resistance on laboratory susceptibility testing, MRSA infections are diagnosed by aerobic bacterial cultures [Romero et al, 2006]. ■

Transmitting CA-MRSA



CA-MRSA is transmitted from person to person via contaminated hands, sharing towels or clothing, using others' personal hygiene items or sports equipment, contact sports, food-borne outbreaks, and intravenous syringes, reports Romero et al [2006]. Outbreaks also have been linked to poor hygiene in group settings.

Studies have shown that CA-MRSA is often found in the following populations: intravenous drug users; aboriginals in Canada, New Zealand, and Australia; Native Americans; Pacific Islanders; children; prisoners; sports participants/athletes; men who have sex with men; group home residents; and military recruits [Romero et al, 2006]. ■

Cellulitis: An overview

Precautions to prevent the spread of MRSA

Since the most significant reservoirs of MRSA are infected or colonized patients in hospitals, healthcare personnel have been identified as a link for transmission. As a result, healthcare professionals must take these precautions to prevent the spread of MRSA:

- Washing hands
- Wearing gloves
- Wearing masks and eye protection
- Wearing gowns
- Handling devices appropriately
- Handling, transporting, and processing laundry appropriately
- Using contact precautions (e.g., placing patient in private room, etc.)
- Culturing of personnel (those who are implicated in MRSA transmission based on epidemiologic data)
- Outbreak control (when outbreak occurs, an epidemiologic assessment should be initiated to identify risk factors for MRSA) ■

Cellulitis is an acute, spreading bacterial infection of the skin and tissues just beneath the skin. This infection may follow damage to the skin, such as a bite or a wound or after injuries that have occurred in water or dirt. However, it can also occur in skin that is not overtly injured [Merck Manual Home Edition, 2003].

Cellulitis may be caused by many different bacteria, but most commonly by group A streptococcus. Streptococci spread rapidly in the skin because they produce enzymes that hinder the ability of the tissue to confine the infection. Staphylococcus bacteria can also cause cellulitis, as do many other bacteria. Although uncommon, fungal infections also may cause cellulitis [Merck Manual Home Edition, 2003].

As the cellulitis spreads, a patient may produce a fever, erythema, develop enlarged lymph nodes (lymphadenitis), skin abscesses, or in some cases the infection could spread through the blood (sepsis) [Merck Manual Home Edition, 2003]. What's more, when cellulitis affects the same site repeatedly—such as the legs—lymphatic vessels may be damaged, causing permanent swelling of the affected tissue. Cellulitis

of the lower extremity, according to an article published by Lippincott, Williams and Wilkins [2003], is more likely to develop into thrombophlebitis in an older patient.

Diagnosis

Cellulitis is usually diagnosed by its appearance and symptoms. The classic signs of cellulitis include erythema and edema due to inflammatory response, pain at the site and possibly in surrounding areas, as well as fever and warmth. Laboratory testing can be used to identify the bacteria from blood, pus, or tissue specimens, but these are not usually required and only necessary if the person is seriously ill. Since the symptoms of this and deep vein thrombosis are very similar, some doctors perform tests to confirm the diagnosis [Merck Manual Home Edition, 2003].

Treatment

According to Merck Manual Home Edition [2003], cellulitis should be treated promptly with antibiotics (especially those that are effective against both streptococci and staphylococci such as dicloxacillin or cephalexin). Such prompt treatment can help prevent the infection from spreading to the blood or organs. Individuals with



SYMPTOMS OF CELLULITIS USUALLY DISAPPEAR AFTER A FEW DAYS OF ANTIBIOTIC THERAPY.

mild cellulitis can take antibiotics orally, while those with more serious spreading infection and high fever can receive antibiotics intravenously. Other forms of treatment include, antifungal medications (if necessary), warm soaks to the site to help relieve pain and discomfort, pain medication as needed, elevation of infected extremity, and cool wet dressing to the infected area to relieve discomfort. Symptoms of cellulitis usually disappear after a few days of antibiotic therapy. ■

Pseudomonas infections

A pseudomonas infection is caused by a bacterium known as *Pseudomonas aeruginosa*. Although the infection can affect any part of the body, according to website healthAtoZ.com, it generally strikes people who are very ill and/or hospitalized. The onset of *P. aeruginosa* can be sudden and severe or slow with little associated pain, and symptoms vary depending on the type of infection.

P. aeruginosa is an opportunistic pathogen; it rarely causes disease in healthy people but typically infects those who are severely ill, hospitalized, taking broad-spectrum antibiotics, or immuno-

What's more, the bacteria associated with this infection are very resistant to certain antibiotics, which make them very difficult to treat. Infections can occur in the heart and blood, bones and joints, central nervous system, eye and ear, urinary tract, lungs, as well as skin and soft tissue.

Diagnosis

Since *P. aeruginosa* is commonly found in hospitals, many patients carry the bacterium without having a full-blown infection. Cultures can be performed, and results are typically ready in two to three days. Depending on the location of the infection, certain body

damaged tissue and can be used for brain abscesses, eye infections, bone and joint infections, ear infections, heart infections, and wound infections.

Prevention

Many hospitals have programs in place to prevent nosocomial infections such as this. Patients with cystic fibrosis may be given periodic doses of antibiotics to prevent episodes of pseudomonas pneumonia, for example. Minor skin infections can be prevented by avoiding use of dirty hot tubs and swimming pools at the end of the day when they are at their dirtiest. Other preventive measures

THE ONSET OF P. AERUGINOSA CAN BE SUDDEN AND SEVERE OR SLOW WITH LITTLE ASSOCIATED PAIN, AND SYMPTOMS VARY DEPENDING ON THE TYPE OF INFECTION.

compromised. For example, people with AIDS have an increased risk of developing serious pseudomonas infections, and those who are being treated with broad-spectrum antibiotics. When patients have chronic wounds, their skin, the primary defense against infection, is compromised, putting them at increased risk of *P. aeruginosa*. These infections are a very serious problem in hospitals since critically ill patients could die if they contract a pseudomonas infection.

fluids can be tested for *P. aeruginosa* such as blood, urine, cerebrospinal fluid, sputum, pus, and drainage from an infected ear or eye. If deep organs are suspected, X-rays or other imaging techniques can be performed.

Treatment

Since *P. aeruginosa* is often resistant to antibiotics, infections are treated with two antibiotics at once. Antibiotic eye drops are used if the infection is in the eye. Surgery is sometimes used to remove the infected and

include bathing after using a hot tub or pool, cleaning hot tub filters every six weeks, and using appropriate amounts of chlorine in the water. ■

Diagnostic tests to confirm Cellulitis



- White blood cell count
- Erythrocyte sedimentation rate
- Gram stain and culture of fluid from abscesses and bulla
- Culture of primary lesion by biopsy or aspiration
- Touch preparation-skin lesion specimen touched to microscopic slide; application of KOH; examination for yeast and mycelial forms of fungus ■

SOURCE: LIPPINCOTT WILLIAMS AND WILKINS, ANATOMICAL CHART COMPANY, ATLAS OF PATHOPHYSIOLOGY, 2003.

Antiseptics: Proceed with caution

Hydrogen peroxide and its role in wound care



Hydrogen peroxide appears not to negatively influence wound healing, but it is also ineffective in reducing the bacterial count. It may be useful as a chemical debriding agent. The American Medical Association concluded that the effervescence of hydrogen peroxide might provide some mechanical benefit in loosening debris and necrotic tissue in the wound. ■

The use of antiseptics—substances that destroy or inhibit the growth and development of microorganisms in or on living tissue—has been under scrutiny lately. Safety is the main concern for clinicians considering applying a topical agent, such as an antiseptic, on an open wound. Agents that are cytotoxic, or cause delay in wound healing, should be used with reservation. In addition, antiseptics are not typically used on open wounds because they are not as effective against bacteria that live in wounds as they are against bacteria *in vitro*.

Although controversial, the use of antiseptics should not be omitted altogether. For those patients and wound types with high risk of infection, antiseptics may be used to prevent wound infection that would have deleterious effects on wound healing. In fact, there are many advantages to using antiseptics. For one, antiseptics do not cause the emergence of drug-resistant bacteria such as topical antibiotics and have broader antimicrobial spectrum and lower sensitization rates [Drosou, Falabella, and Kirsner, 2003].

Antiseptic uses and indications vary. Several antiseptic agents focus primarily on cleansing intact skin. Such agents are used for prepping

patients preoperatively and prior to intramuscular injections or venous punctures, pre- and postoperative scrubbing in the operating room, and hand washing by medical personnel [Drosou et al, 2003]. There are some antiseptics that contain detergents and therefore should not be used on nonintact skin. In fact, according to Drosou et al [2003], the use of antiseptics as prophylactic anti-infective agents for open wounds, such as abrasions, burns, chronic ulcers, and lacerations, has been an area of intense controversy for many years.

Both the FDA and the U.S. Department of Health and Human Services have offered guidelines recently about antiseptic use on wounds. Povidone iodine has been approved by the FDA for short-term treatment of superficial and acute wounds, although the FDA statement cites that povidone iodine has not been found to either promote or inhibit wound healing. Guidelines for the treatment of pressure ulcers by the U.S. Department of Health and Human Services strongly discourage the use of antiseptics and promote the use of normal saline for cleansing pressure ulcers [Drosou et al, 2003].

In clinical practice, however, antiseptics are

broadly used for both intact skin and wounds, although concerns have been raised on both sides. Some strongly disapprove of the use of antiseptics in open wounds while others believe antiseptics have a role in wound care. The main reason antiseptics are used on open wounds is to prevent and treat infection by reducing the bacterial load of a wound, thus helping speed up the wound's healing process [Drosou et al, 2003].

Following is a review (based on animal and human studies) by Drosou et al (2003) on the most common antiseptics used today and their appropriateness for wound care.

Iodine Compounds

Iodine and its compounds have been broadly used for prevention of infection and treatment of wounds. Molecular iodine, however, can be very toxic for tissues, so formulations composed by combining iodine with a carrier that decreases iodine availability were developed. Povidone iodine (PVP-I) results from the combination of molecular iodine and polyvinylpyrrolidone and is available in several forms (solution, cream, ointment, scrub). Several animal studies have examined the effects of povidone iodine on the bacterial load of wounds. These results have not

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BOTH THE FDA AND THE U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES HAVE OFFERED GUIDELINES RECENTLY ABOUT ANTISEPTIC USE ON WOUNDS.

Cadexomer Iodine

Antiseptics: Proceed with caution *(continued from page 6)*

proven the efficacy of povidone iodine; however, the results of numerous clinical trials show that it is effective in reducing the bacterial load of wounds.

Chlorhexidine

Chlorhexidine has been commonly used in disinfectant and antiseptic solutions and is used mainly in urology, gynecology, dentistry, and in the treatment of wounds. It is highly bactericidal and appears to be relatively safe with little effect on the wound healing

process, and its use may favor healing of open wounds in risk for infection. Study results are insufficient to draw conclusions about the use of chlorhexidine on open wounds.

Silver Compounds

Silver compounds have widely been used as wound antiseptics, primarily in burns. Silver sulfadiazine (SSD) and silver nitrate (AgNO₃) are among the most commonly used. Silver sulfadiazine is the most broadly used treatment

for the prevention of infection in patients with burn wounds. Also, it appears that silver compounds do not have a negative effect on wounds and may accelerate wound healing clinically. ■



Cadexomer iodine gel is used to treat heavily draining wounds, or wounds that produce a large amount of liquid exudate due to bacteria. It is appropriate for wounds that are heavily contaminated, and for second-degree burns. Cadexomer iodine gel promotes autolytic debridement, and may assist in managing bacterial contamination in the wound. It is also helpful in reducing the foul odor that may be present in heavily contaminated wounds. Cadexomer iodine gel is available as a sheet, a gel, and a spray. It is used to help control drainage and protect the skin around the wound from maceration. ■

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Working with a Wound Healing Center specializing in infected wounds

Staffed by dedicated, skilled physicians trained specifically in the identification, diagnosis, and treatment of chronic infected wounds, Wound Healing Centers are expertly equipped to work with patients afflicted with such non-healing wounds. Not only are the clinicians at the Centers ready to administer the proper therapies, they also offer follow-up education for primary care physicians and their patients to ensure

optimal healing. The knowledge gained by tracking outcomes consistently is applied to each treatment plan to speed healing and improve each patient's quality of life.

There are other benefits as well. By partnering with a Wound Healing Center your practice can offer state-of-the-art treatment modalities as well as avoid upfront costs for advanced products, avoid storage



problems, provide access to clinicians with experience dealing with an extensive wound population, ensure follow-up patient education, and stay informed about healing progress with regular reports from our Outcomes Disease Management System. ■

CONTACT YOUR LOCAL WOUND HEALING CENTER IF:

- Your patient has a wound that persists for more than 30 days with standard wound treatment
- Your patient has a chronic wound and hypothermia
- Your patient has a chronic wound and has myocardial ischemia/hypoxia
- Your patient has a chronic wound and is deficient in vitamins A, B, C, D, or K, as well as zinc, copper, or magnesium
- Your patient has a chronic wound and has a disease of the liver or kidney, heart failure, or diabetes
- Your patient has a chronic wound and has an immunodeficiency such as HIV
- Your patient has a chronic wound and is taking corticosteroids or nonsteroidals, anti-inflammatory drugs, or chemotherapeutic agents
- Your patient has a chronic wound that has necrotic material or foreign debris such as sutures
- Your patient has a chronic wound and a remote infection
- Your patient has a chronic wound and is a smoker or uses tobacco products



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