Approach to infected skin ulcers

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ABSTRACT

OBJECTIVE To review the diagnosis and management of infected chronic skin ulcers.

SOURCES OF INFORMATION Cochrane database, MEDLINE, and Google were searched for clinical practice guidelines (CPGs) for wound care. Most recommendations found in the CPGs had level II or III evidence. Expert and consensus opinion from the Canadian Chronic Wound Advisory Board and the International Wound Bed Preparation Advisory Board were also used.

MAIN MESSAGE Bacteria in skin ulcers act along a continuum from contamination through colonization and critical colonization to infection. Critical colonization is not always associated with overt signs of infection but can result in failure to heal, poor-quality granulation tissue, increased wound friability, and increased drainage. Good-quality swab samples should be an adjunct to clinical acumen, not a primary strategy for diagnosis. Iodine and silver-based dressings, topical antibiotics, and systemic antibiotics can be helpful.

CONCLUSION Diagnosis of chronic wound infection is based on clinical signs and a holistic approach to patients. More research into assessment and treatment of skin ulcer infection is needed.

RÉSUMÉ

OBJECTIF Faire le point sur le diagnostic et le traitement des ulcères cutanés chroniques infectés.

SOURCES DE L’INFORMATION On a consulté la base de donnée Cochrane, MEDLINE et Google à la recherche des guides de pratique clinique (GPC) pour le traitement des plaies. La plupart des recommandations provenant des GPC reposaient sur des preuves de niveau I ou II. On a également utilisé l'opinion d'experts et l'opinion consensuelle du Conseil consultatif canadien sur les blessures chroniques et de l’International Wound Bed Preparation Advisory Board.

PRINCIPAL MESSAGE L’action des bactéries dans les ulcères cutanés évolue progressivement de la contamination à la colonisation, à la colonisation critique et à l’infection. La colonisation critique ne s’accompagne pas toujours de signes évidents d’infection mais elle peut entraîner un défaut de guérison, un tissu de granulation de mauvaise qualité, des blessures plus friables et un exsudat plus abondant. Le prélèvement par écouvillonnage d’échantillons de bonne qualité devrait s’ajouter aux connaissances médicales et non constituer une stratégie primaire pour le diagnostic. Les pansements à base d’iode ou d’argent et les antibiotiques locaux ou systémiques peuvent aussi être utiles.

CONCLUSION Le diagnostic des plaies chroniques infectées repose sur des signes cliniques et sur une approche holistique du patient. L’évaluation et le traitement des ulcères cutanés infectés devra faire l’objet de recherches additionnelles.
Case history
Mr J.S., an 80-year old man, had had bilateral painful venous ulcers above his malleoli for 2 years. He had a normal ankle-brachial index (ABI) and had been treated with high-compression dressings (Profore) for 4 months without evidence of ulcer healing. His ulcer was increasingly painful and produced copious exudate. He was taking hydromorphone (1 mg every 4 hours as needed) for pain and sublingual fentanyl before dressing changes.

Other medical problems included dementia and a remote bypass graft of a coronary artery. He had been coping poorly in the community and was living in a long-term care facility, after hospitalization for his leg ulcers and his declining cognitive function.

He had multiple ulcers with dusky friable granulation tissue at the base. There was evidence of hyperkeratosis and dermatitis on the surrounding skin.

Skin ulcers are normally managed by family physicians. A recent survey found that Canadian family physicians are not confident in their abilities to manage skin ulcers. This might be particularly true of managing ulcer infections, as infected ulcers can be difficult to diagnose and assess. Optimal strategies for prevention and treatment are unclear.

Management of skin ulcers was discussed in a recent issue of Canadian Family Physician. Diagnosis and treatment of infections in non-surgical skin ulcers will be reviewed in this article.

Sources of information
The Cochrane database, MEDLINE, and Google were searched for articles related to skin ulcer infections. There is little high-level evidence in this area, and expert and consensus opinions from the Canadian Chronic Wound Advisory Board and the International Wound Bed Preparation Advisory Board were used for this paper. Guidelines and best practice documents from the Registered Nurses Association of Ontario, the Canadian Association of Wound Care, and the US Agency for Health Care Policy and Research were also used because they were practical and applicable to patients in a variety of Canadian clinical settings. Most clinical practice guidelines rated the quality of evidence used in developing the guidelines; where possible, the quality is reported in this paper. Most recommendations cited have level II or III evidence.

Main messages
Prevention. Optimizing the wound-healing environment involves treating underlying factors, such as malnutrition and ischemia. Improving the healing environment might decrease infection rates but has not been formally studied. Good wound cleaning using saline has not been studied for infection prevention, but is recommended by most authorities (level III evidence). Use of cytotoxic agents, oral antibiotics, and topical antibiotics, is not recommended for preventing colonization (level II evidence). Cytotoxic agents, such as povidone iodine and chlorhexidine, might be considered in specific circumstances to decrease bacterial burden when risk of cellular injury is less than risk of infection. This is most likely in wounds that are unlikely to heal (eg, palliative patient, ischemic ulcer) and when the cytotoxic agent is to be used for a short period.

Necrotic material provides a good medium for bacterial growth and colonization, and surgical

Levels of evidence
Level I: At least one properly conducted randomized controlled trial, systematic review, or meta-analysis
Level II: Other comparison trials, non-randomized, cohort, case-control, or epidemiologic studies, and preferably more than one study
Level III: Expert opinion or consensus statements

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Débridement can reduce risk and can help treat acute infection. When eschar is present on infected ulcers, surgical débridement should be done unless otherwise contraindicated (eg, due to severe arterial insufficiency) (level III evidence).³

**Diagnosis.** Acute ulcers, such as surgical wounds, heal in relatively predictable phases. Inflammation precedes granulation and is followed by re-epithelialization and remodeling. Inflammation is mediated by well-understood pathways, and is manifest by pain, erythema, swelling, and warmth. Chronic ulcers, on the other hand, often appear to be in a prolonged inflammatory phase.² Given the overlap in symptoms and signs, the interaction between the inflammatory process and pathogens is important to consider in diagnosis of skin ulcer infection.

Bacteria in ulcers usually act along a continuum from contamination through colonization to critical colonization and finally to infection.⁷ All wounds become contaminated, regardless of prevention strategies. Sources of contamination include the local environment (which is particularly relevant for hospitalized patients), the surrounding skin, and endogenous patient sources. Gastrointestinal or oral pathogens can establish large colonies, particularly with large or slowly healing ulcers. Unfortunately, health care providers remain an important vector for wound contamination.⁸

The role of colonization in delaying wound healing is uncertain, but is most commonly ascribed to aerobic or facultative species, such as *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and beta-hemolytic streptococci. The reported role of anaerobic species could be related more to the omission of anaerobic culture strategies in studies than to lack of virulence. Anaerobic organisms are more difficult to culture and identify but have been found to represent 30% of total microbial isolates in wounds.²⁹¹⁰ Over time, the nature of bacterial colonization changes. In wounds less than 1 month old, cutaneous and Gram-positive organisms tend to predominate. As ulcer healing becomes prolonged, a broader spectrum of organisms can colonize the wound, including Gram-negative organisms such as coliforms, anaerobes, and *Pseudomonas* species.¹¹

Critical colonization is also referred to as increased bacterial burden or covert infection. Substantial colonization might or might not cause the obvious signs of inflammation but will likely affect wound healing, with failure to heal or slowing of progression. Signs of critical colonization are atrophy or deterioration of granulation tissue, discoloration of granulation tissue to deep red or gray, increased wound friability, and increased drainage. Bacteria sometimes produce a biofilm to protect themselves on the wound bed.⁷ This should be considered if wounds fail to improve or degenerate despite a healthy appearance.

Infection occurs when bacterial activities overcome the host’s immune response and host injury occurs. Infection risk is determined by the type and number of organisms colonized, and by host factors affecting resistance, such as nutrition, oxygenation or tissue perfusion, and medical conditions (such as diabetes). Chronic wounds often display the typical findings of infection, including warmth, purulent drainage, and advancing erythema. These can be absent, however; findings such as increased pain, change in exudate, increased friability, exuberant and bright red granulation tissue, breakdown of wound surface, or new areas of skin breakdown and foul odour¹² should raise the suspicion of infection.¹³⁻¹⁵ Deep infections can cause erythema and warmth beyond wound margins. Wound size or satellite ulceration can increase and can extend to involve bone. Osteomyelitis is particularly common among patients with diabetes and deep ulcers of long duration.¹⁶

Laboratory investigations can be used to aid the clinical diagnosis. The Agency for Health Care Policy and Research guidelines suggest use of complete blood count, erythrocyte sedimentation rate, and plain films for initial evaluation of possible osteomyelitis (level III evidence).⁵ The erythrocyte sedimentation rate and C-reactive protein levels can also be useful for monitoring the response of deep wound infections to antibiotic treatment.²

The use of microbiology swabs should be viewed as an adjunct to clinical acumen rather than a primary strategy for diagnosis of infection (level III evidence).³⁻⁵ Swabs can provide relevant information about wounds that fail to progress or
show evidence of critical colonization. Culture can indicate the predominant flora in such wounds, can identify resistant organisms, and can target systemic treatment for infected wounds.

The techniques for swabbing ulcers are controversial, but some basic principles are important to consider (level III evidence). Dead tissue and foreign matter should be excised from the ulcer bed and the wound cleaned with saline. Cotton, rayon, or alginate-tipped swabs may be used. The swab tip should be rolled on its side for one full rotation over the area of granulation tissue with the most obvious evidence of infection. Areas of surface pus, debris, or slough should be avoided. Using a zigzag pattern or swabbing more than one area should be considered for larger ulcers (>5 cm²). Culturing tissue from deep débridement or fluid from aspirates can provide relevant information also.

**Topical treatment**

**Iodine and silver preparations:** Several new formulations of older topical agents should be considered to treat nonhealing wounds with or without evidence of clinical infection (level II evidence). Iodine, while toxic in high concentrations to tissue in vitro, can be beneficial at low doses. Cadexomer iodine releases low levels slowly into wounds and has been shown to be safe and effective at decreasing bacterial burden in the superficial compartment. Cadexomer iodine is available as an ointment and as an impregnated gauze dressing.

### Table 1. Topical iodine and silver-based treatments

<table>
<thead>
<tr>
<th>Dressing</th>
<th>Dressing Characteristics</th>
<th>Spectrum of antibacterial activity</th>
<th>Wound characteristics and clinical use</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cadexomer iodine</td>
<td>- Sterile beads formed from a three-dimensional network of cadexomer (chemically modified starch) containing elemental iodine</td>
<td>*Staphylococcus aureus, MRSA, Streptococcus, Pseudomonas, anaerobes</td>
<td>• For moderate exudation</td>
<td>• Thought to increase inflammation</td>
</tr>
<tr>
<td>(Iodosorb) tube</td>
<td>- Beads absorb exudate, swell, and slowly release iodine</td>
<td></td>
<td>• Has débridement and antibacterial activity</td>
<td>• Contraindicated with Hashimoto thyroiditis, non-toxic nodular goitre, and iodine sensitivity, and for children and pregnant or lactating women</td>
</tr>
<tr>
<td>10 g $13</td>
<td></td>
<td></td>
<td>• Change dressing when colour changes from brown to white or gray (up to 5-7 days)</td>
<td>• Use in renal failure; relative contraindication with other thyroid disorders</td>
</tr>
<tr>
<td>paste (8X6 cm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nanocrystalline silver</td>
<td>Fine silver-coated mesh consisting of crystals less than 20-nm diameter in lattice structure</td>
<td>*S. aureus, MRSA, Streptococcus, Pseudomonas, anaerobes</td>
<td>• Change every 5-7 days; might need to change secondary dressing depending on amount of exudate</td>
<td>• Believed to reduce inflammation</td>
</tr>
<tr>
<td>(Acticoat 7) 10X10 cm $12</td>
<td></td>
<td></td>
<td>• Acticoat absorbent for heavily draining wounds (change every 5-7 days)</td>
<td>• Contraindicated in patients with known hypersensitivity to silver or other dressing components</td>
</tr>
<tr>
<td>Sodium carboxymethyl cellulose with 1.2% ionic silver</td>
<td>10X10 cm $11</td>
<td>*Pseudomonas, S. aureus, MRSA, and vancomycin-resistant enterococcus</td>
<td>• Good exudate-absorbing capacity</td>
<td>• Argyria (blue-black discoloration of the skin as a result of silver deposits in the dermis) can occur</td>
</tr>
<tr>
<td>Silver sulfadiazine</td>
<td>10X10 cm $11</td>
<td>• Silver stays in dressing and very little is deposited into wound base</td>
<td>• No débridement activity</td>
<td>Forms gel, locking exudate into dressing when saturated</td>
</tr>
<tr>
<td>cream (Flamazine)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>tube (50 g) $12</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**MRSA**—methicillin-resistant *Staphylococcus aureus.*
Silver preparations have been used on ulcers for many years. Nanocrystalline silver (crystals <20 nm) can deliver topical concentrations to the superficial compartment that are effective against a range of organisms, including yeast.\textsuperscript{18,19} Use of iodine and silver-containing preparations is summarized in Table 1.

**Topical antibiotics:** Topical antibiotics should be considered to treat critical colonization or compartment infection. Choice of topical agent depends on the bacteria identified by culture or by clinical assessment, and on the risk of topical sensitization. Agents such as neomycin, bacitracin, and lanolin-containing preparations (eg, Fucidin ointment) can increase the inflammatory response and are potential sensitizers. Topical aminoglycosides, such as gentamicin, can increase the risk of microbial resistance. A summary of topical antibiotic choices is found in Table 2.

The role of topical antibiotics in treatment of wounds that are not healing or continue to have serious exudation after 2 to 4 weeks of optimal management has been studied. A 2-week trial of topical antibiotics with Gram-negative, Gram-positive, and anaerobic coverage should be used in these circumstances, even with no other evidence of critical colonization or infection (level I evidence).\textsuperscript{3}

**Systemic antibiotics.** Oral or parenteral antibiotics should be used for specific indications rather than for all wound infections, to minimize the risk of developing drug resistance. A Cochrane review on the use of antibiotics and antiseptics for venous ulcers is expected to be published in 2005 and might clarify the uncertain evidence for antibiotic use.

Systemic antibiotics for treatment of sepsis or bacteremia from wound infections, for cellulitis, and for osteomyelitis have level I evidence of effectiveness.\textsuperscript{3} Infections in the deep compartment might not respond to topical treatments, and infections in the superficial compartment that are not responding to topical agents might require oral or parenteral antibiotics. When signs of infection spread beyond the ulcer margins or when the ulcer is enlarging or developing satellite ulceration, systemic antibiotics are indicated. A surgical probe should be used to explore the wound base and edges of deep ulcers, particularly those with evidence of infection.\textsuperscript{16} Contacting underlying bone with the probe has reasonable sensitivity and specificity for osteomyelitis. Magnetic resonance imaging is the most accurate investigation if osteomyelitis is suspected, but plain films or nuclear scanning can still be helpful if magnetic resonance imaging is unavailable.

<table>
<thead>
<tr>
<th>Table 2. Topical antibiotics for infected skin ulcers</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AGENT</strong></td>
</tr>
<tr>
<td>Mupirocin (Bactroban)</td>
</tr>
<tr>
<td>Fusidic acid (eg, Fucidin)</td>
</tr>
<tr>
<td>Neomycin sulfate</td>
</tr>
<tr>
<td>Gentamicin (eg, Garamycin)</td>
</tr>
<tr>
<td>Bacitracin (eg, Baciguent)</td>
</tr>
<tr>
<td>Bacitracin, polymyxin B, and gramicidin (Polysporin Triple Antibiotic)</td>
</tr>
<tr>
<td>Metronidazole</td>
</tr>
</tbody>
</table>

*Hospital acquisition cost in 2004.
Antibiotic agents can be chosen by culture and by clinical evidence. There are no guidelines for use of oral agents, although local hospitals’ handbooks often provide suggestions (Table 320,21). White or creamy pus can indicate Staphylococcus aureus; Pseudomonas infection can cause blue or green discoloration, and anaerobic infection can have a marked odour. Swab samples can identify resistant organisms, particularly among hospitalized patients. The duration of antibiotic therapy is controversial, with risk of treatment failure balanced against risk of microbial resistance. Most authors recommend 2 to 4 weeks of treatment with oral agents24 (level III evidence).

### Table 3. Antimicrobial coverage of commonly used antibiotics

<table>
<thead>
<tr>
<th>ANTIBIOTIC</th>
<th>DAILY COST* ($</th>
<th>MICROBIAL COVERAGE</th>
<th>GRAM-NEGATIVE ENTERICS</th>
<th>COMMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral cephalosporins</td>
<td></td>
<td>STAPHYLOCOCCUS</td>
<td>STREPTOCCUS</td>
<td>PSEUDOMONAS</td>
</tr>
<tr>
<td>- Cefalexin</td>
<td>0.64</td>
<td>Excellent</td>
<td>Excellent</td>
<td>Inactive</td>
</tr>
<tr>
<td>- Cefuroxime</td>
<td>0.64</td>
<td>Good</td>
<td>Excellent</td>
<td>Inactive</td>
</tr>
<tr>
<td>Intravenous cephalosporins</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Cefazolin</td>
<td>3.75</td>
<td>Excellent</td>
<td>Excellent</td>
<td>Inactive</td>
</tr>
<tr>
<td>- Ceftriaxone</td>
<td>34.00</td>
<td>Moderate</td>
<td>Excellent</td>
<td>Inactive</td>
</tr>
<tr>
<td>- Ceftazidime</td>
<td>17.46</td>
<td>Poor</td>
<td>Excellent</td>
<td>Inactive</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>5.02</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Excellent</td>
</tr>
<tr>
<td>Amoxicillin–davulanate potassium (Clavulin)</td>
<td></td>
<td>Excellent</td>
<td>Inactive</td>
<td>Good</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cloxacillin</td>
<td>0.28</td>
<td>Excellent</td>
<td>Moderate</td>
<td>Inactive</td>
</tr>
<tr>
<td>Intravenous vancomycin</td>
<td>12.54</td>
<td>Excellent</td>
<td>Inactive</td>
<td>Inactive</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>- Oral 0.08</td>
<td>Inactive</td>
<td>Inactive</td>
<td>Excellent</td>
</tr>
<tr>
<td></td>
<td>- Intravenous</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.46</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clindamycin</td>
<td>- Oral 2.76</td>
<td>Excellent</td>
<td>Inactive</td>
<td>Excellent</td>
</tr>
<tr>
<td></td>
<td>- Intravenous</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>7.08</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trimethoprim-sulfamethoxazole</td>
<td>0.16</td>
<td>Excellent</td>
<td>Variable (not active against Group A Streptococcus)</td>
<td>Inactive</td>
</tr>
</tbody>
</table>

UTI—urinary tract infection.

*Hospital acquisition cost in 2003.

Adapted with permission from Dr R. Pennie.20,21

Case resolution

Given his failure to improve despite criterion-standard treatment with compression therapy, Mr J.S. was treated for 2 weeks with topical antimicrobials (nanocrystalline silver dressing). When rate of healing did not improve, swab samples were taken; they were positive for numerous S aureus. He was treated with clindamycin (300 mg three times daily for 2 weeks) and with compression bandaging. His pain and drainage improved dramatically, and his wound healed within 2 months.

Conclusion

Treatment of infected skin ulcers is controversial and various treatments lack good-quality evidence...
of effectiveness. Chronic wounds are always colonized by bacteria, and critical colonization and infection can present with a variety of clinical signs. Treatment for 2 weeks with topical antimicrobials should be considered for wounds that are not healing despite optimal treatment. Good-quality swab samples should be used to identify resistant organisms and to guide antibiotic treatment. A 2- to 4-week course of oral antibiotics should be used for infections spreading beyond the wound margins or involving the deep space of the wound. Figure 1 summarizes

Figure 1. Basic management of infected skin ulcers

- Wound healing “stalled,” possibly with increased exudate, pain, friability
- Overt signs of infection

### YES

- Cellulitis or deep space infection

### NO

- 2-week course of topical antibiotic, or silver-based or iodine-containing product

### NO

- No improvement

### YES

- ≥14-day course of systemic antibiotics

- Good-quality swab

- 2- to 4-week course of systemic antibiotics
- Monitor for clinical improvement after antibiotic course
- Consider repeat swab if no improvement (to identify resistant organisms)
a general approach to managing infected skin ulcers.

Competing interests
None declared

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References

EDITOR’S KEY POINTS
• All chronic wounds are contaminated with bacteria, and some progress along a continuum from colonization to critical colonization and to overt infection when the host immune system is overcome.
• Chronic wounds often present with the usual signs and symptoms of warmth, redness, and exudate, but increased pain, friability, enlarging size of ulcer, and foul odour might be the only symptoms.
• Consider osteomyelitis in chronic, deep wounds, and use x-ray examinations, bone scans, or magnetic resonance imaging to diagnose it. Complete blood count results, erythrocyte sedimentation rate, and C-reactive protein levels are also useful markers.
• Topical antimicrobials (cadexomer iodine, nanocrystalline silver) or topical antibiotics should be tried first, but when they fail, oral antibiotics (after swabs for culture and sensitivities) should be used.

POI NTS DE REPÈRE DU RÉDACTEUR
• Toutes les plaies chroniques sont contaminées par des bactéries et certaines évoluent progressivement de la colonisation à la colonisation critique et à l’infection franche lorsque les défenses immunitoires de l’hôte sont dépassées.
• Les plaies chroniques ont comme premières manifestations les signes et symptômes habituels de chaleur, rougeur et exsudat, mais parfois, une augmentation de la douleur, une friabilité, un agrandissement de l’ulcère ou une odeur nauséabonde constituent les seuls symptômes.
• Penser à l’ostéomyélite devant une plaie chronique profonde et vérifier le diagnostic à l’aide de radiologie, tomodensitométrie osseuse ou résonance magnétique. Numération globulaire complète, vitesse de sédimentation globulaire et taux de protéine C-réactive sont aussi des marqueurs utiles.
• Antimicrobiens topiques (cadexomer d’iode, argent nanocristallin) ou antibiotiques topiques devraient être essayés initialement, mais en cas d’échec, il faut recourir aux antibiotiques oraux (après écouvillonnage pour culture et antibiogramme).