INTRODUCTION

Wound infection has a significant impact on wound healing potential and patient outcomes. In the clinical battle of managing an infected wound, the first step is to determine if it is an acute or chronic wound infection.

Acute wound infection can be devastating and is often an underappreciated clinical condition that has been reported to increase the cost of care by up to 70%.[1] Chronic wound infections are associated with an increased risk of complications such as delayed wound healing, tissue and structure infections, gangrene, amputation, sepsis, and even death.

Chronic wounds are microbiologically, immunologically, and clinically distinct from acute wound infections and require a different treatment strategy. Understanding the differences between acute and chronic wound infections, including the clinical manifestations, microbial involvement, proper clinical assessment, and strategies to optimize management, will ultimately improve healing outcomes and support antibiotic stewardship efforts in wound care.

THE IMPACT OF WOUND INFECTIONS

Wound infections carry heavy financial and human costs with the potential for negative patient outcomes.

A recent United Kingdom study found the incidence of diabetic foot ulcers is on the rise in outpatient centers. The study also reported that infected diabetic foot ulcers were less likely to heal within 12 months, and when they did heal, they took longer than non-infected diabetic foot ulcers, incurring additional costs throughout.[2] Individuals with an infected diabetic foot ulcer have shown a 155-fold increased risk for amputation compared to diabetics without an ulcer.[3] Two additional studies indicate surgical site infections are the most expensive surgical complications and accrue an average of $5,968 in increased Medicare costs per patient.[4] These two wound etiologies illustrate the adverse patient impact wound infections cause across the wound care spectrum.

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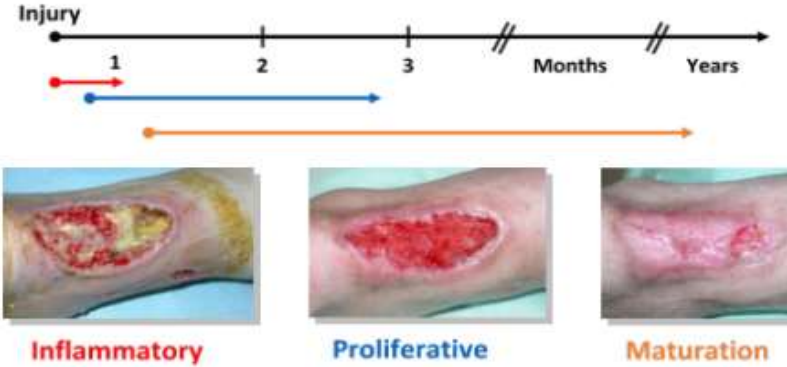
The wound healing process is as systematic as it is complex. Interruptions in the normal cascade of wound healing can easily occur due to intrinsic and extrinsic factors. Intrinsic factors such as obesity, multiple comorbidities, increased age, and nutritional and health status can impact wound healing, as can extrinsic factors of the wound environment including mechanical force, chemical stress, smoking, and wound infection. Understanding the process of wound healing will support clinical understanding of the involvement of factors that impede or delay wound healing.

THE PROCESS OF WOUND HEALING

1. **Hemostasis (within 15 minutes following injury).** Hemostasis is the first phase of the natural wound healing process that occurs by clot formation, initiating the wound healing cascade. Hemostasis begins within the first 15 minutes of tissue injury of the epidermis into the dermis. The injury to blood vessels triggers the coagulation activation processes involving platelet aggregation, which seals the blood vessel wall. Fibrinous threads bind together in the process of coagulation, reinforcing the platelet seal. This process is followed by fibrinolysis or clot breakdown, which releases growth factors and is advanced by vasoconstriction.[5,6]

2. **Inflammatory (1 to 5 days following injury).** Normal physiological changes may be seen during the inflammatory phase of wound healing including localized edema, warmth, erythema, and pain. Blood vessels leak transudate comprised of water, salt, and protein. As the fluid builds up, it allows healing and repair cells to move into the wound bed. Physiological changes such as increased pain, warmth, redness, and swelling are due to cellular activity from the presence of white blood cells, neutrophils, growth factors, and enzymes that support wound healing progression. A prolonged inflammatory stage of healing may result in a chronic wound.[5]

Normal Wound Healing Cascade of Events

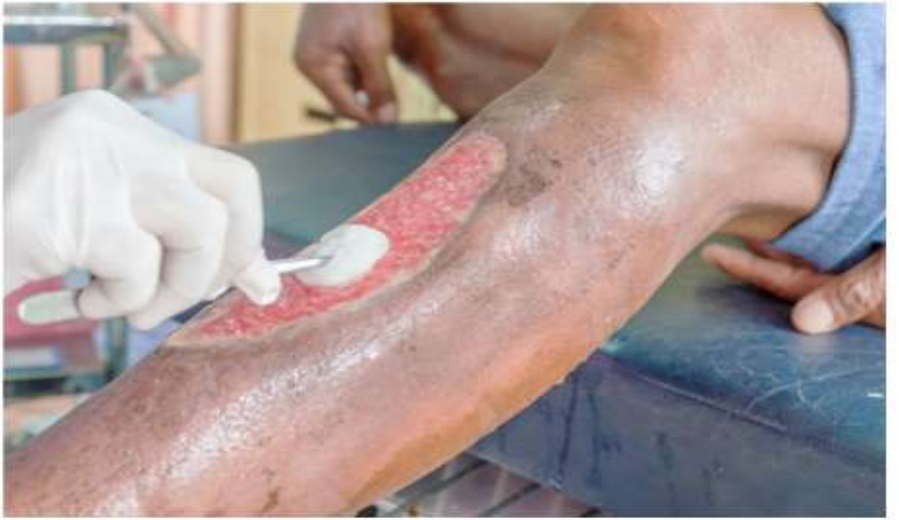


3. **Proliferative (5 to 25 days following injury).** This phase of wound healing only involves full-thickness wounds, such as stage 3 and 4 pressure injuries/ulcers. As new tissue comprised of collagen and extracellular matrix forms in the wound bed, the wound edges contract. This phase of healing involves the formation of *granulation tissue*. Healthy granulation tissue is characterized by a pink or red appearance, with an uneven mounded texture. Granulation tissue that is dark and dusky in color is a sign of infection, ischemia, and/or poor perfusion. This phase of healing is complete when myofibroblasts help contract the wound, and epithelial cell resurfacing begins to take place across the wound bed.[5]

4. **Maturation ("Remodeling"; 21 days to 24 months following injury).** Maturation is the final phase in the wound healing cascade for full-thickness wounds. Collagen continues to remodel in the wound bed until full wound closure. Collagen reduces scar tissue and strengthens the wound tissue following injury; however, the tensile strength of scar tissue will only reach 80% compared to the original tissue.[5]

WOUND INFECTIONS DEFINED

When the wound healing cascade is interrupted, a wound infection may be present. Wound infection-related research defines a wound infection as a host inflammatory response to interfering microorganisms that either directly or indirectly damage viable host tissue, hence preventing wound healing. This research points to the fact that there are clearly two types of wound infections: acute and chronic.[7-11]



Both types of wound infections involve an inflammatory response that prevents healing, but in an acute infection, the inflammation is in response to pathogen invasion. The host inflammatory processes are able to destroy the pathogens, with the acute infection typically resolving within a few days.

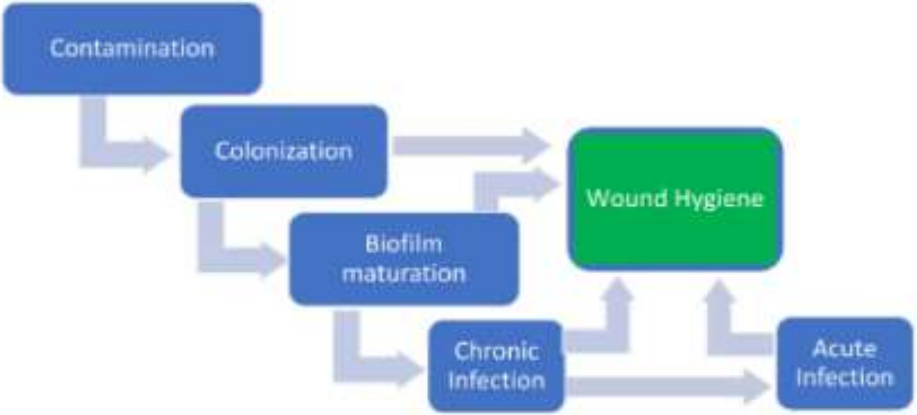
In a chronic wound infection, the main culprit is biofilm, and the host inflammatory phase processes are ineffective against pathogens protected by biofilm. Wounds unable to effectively respond to this pathogenic attack become stalled in the inflammatory phase of wound healing.

Because of the clinical, microbiological, and immunological distinctions between acute and chronic wound infections, both types of infection require different management strategies that incorporate antibiotic stewardship principles.

ASSESSING AND TREATING CHRONIC AND ACUTE WOUNDS

Determining whether a wound has a chronic or acute infection begins with wound assessment. Clinical suspicion of acute infection is driven by presence of overt, classic signs of inflammation.[12] The overt signs of an acutely infected wound include warmth (calor), pain (dolor), swelling (tumor), redness (rubor), and loss of function.

Infection Continuum



Inflammation is a complex defensive vascular response to harmful stimuli, making acute infection sometimes difficult to distinguish from other causes, such as irritants, cell damage, and pathogen invasion. Infection is just one cause of overt signs of inflammation. As the clinical signs of acute inflammation can present similarly to other conditions like venous stasis dermatitis or cellulitis, these conditions must be ruled out before acute infection diagnosis can be made. Dermatitis caused by a topical irritant is most easily and effectively treated by removing the irritant.

In cases involving cellulitis, a bacterial infection of the skin resulting from invading pathogens, systemic antibiotics can be useful in resolving the infection, allowing the patient's immune system to regain control over the pathogenic invasion.

Venous stasis dermatitis is an inflammation related to chronically elevated pressure in the venous system, damaging capillaries by pushing leukocytes from the circulation into the tissues and resulting in recruitment of proteases and vasoactive compounds. Although venous stasis dermatitis can look similar to cellulitis, managing this type of inflammation requires compression and elevation — not antibiotics.

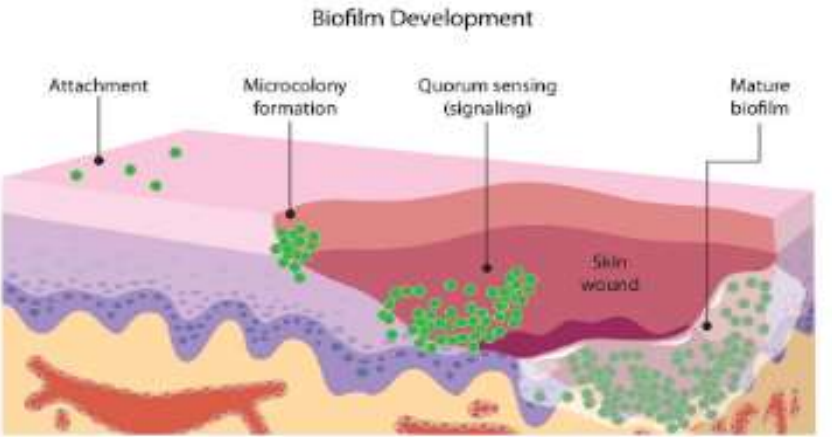
Unlike with acute wound infections, clinical suspicion of chronic wound infection is driven by the presence of covert, less obvious signs of inflammation[7,11] such as delayed healing, discolored or friable hypergranulation, breakdown of granulation tissue, serous exudate, and pain without signs and symptoms of acute infection. The signs of chronic wound infection reflect damage to wound bed tissues caused by a persistent, low-grade inflammatory response attempting to clear the wound of a parasitic biofilm.

THE INFECTION CONTINUUM

In 1998, Davis described the theoretical stages of increasing wound bacterial load, first involving contamination, which happens almost immediately upon injury, then colonization as bacteria begin to grow and multiply on a wound surface, and finally critical colonization.[3] Gardner et al. subsequently found that in infected chronic wounds, the signs specific to secondary wound infection, i.e., increasing pain, friable granulation tissue, wound breakdown, and foul odor, are expressed more frequently than the classic signs and symptoms of infection.[9]

Both researchers noticed these wounds were characterized not only by the absence of signs of acute infection, but also a noticeable delay in healing, with increased exudate and unhealthy-appearing granulation tissue, all of which are related to the body's stalled effort to eradicate a biofilm. The international wound community now concurs with Wolcott that this "critical colonization" phase should be more accurately referred to as biofilm maturation.

The development of biofilm as part of the infection continuum is important to understand when evaluating the microbiology of acute and chronic wounds. An acute wound infection involves invasion of viable wound tissue by metabolically active planktonic microorganisms that trigger a host inflammatory response,[12] such as a direct host response to virulence expression and tissue invasion by the pathogens involved.



A chronic wound infection typically manifests as an unclear and prolonged (covert) condition, in which biofilm is the root cause of the problem,[7] establishing another fundamental difference from acute wounds, which typically do not have biofilm present.

BIOFILM LIFE CYCLE AND CLINICAL CHALLENGES

Understanding the treatment of acute versus chronic wound infections requires an understanding of biofilm. In the life cycle of biofilm, planktonic or free-floating organisms attach to a surface, then begin to produce a sticky, protective extracellular polymeric substance (EPS).[14-15] They continue to mature into a tertiary structure which can become macroscopic but difficult to isolate in a wound containing other substances. Next, the organisms disperse from the EPS to attach to adjacent sites, thus proliferating the biofilm.

Within the wound bed, planktonic microbes promote acute infection, depending on how effective the topical wound care is and how adept the host immune system is at killing off the microbes before they can invade and begin multiplying in host tissue.[16,20]

The treatment of biofilm and free-floating planktonic bacteria (prior to forming a biofilm) differ. The microorganisms within the protection of biofilm are not susceptible to antimicrobial agents and host inflammatory cells, while free-floating, planktonic microorganisms are susceptible to antimicrobial agents like antibiotics and topical antiseptic dressings. This tolerance to antimicrobial action underscores the clinical challenge biofilm presents in wound care.

Biofilm is tenacious and difficult to remove by physical or antimicrobial strategies. It presents recurrent and persistent infections, a poor response to antibiotics and antiseptics, and causes chronic infections[21] such as otitis media, catheter-associated urinary tract infections, and infections associated with cystic fibrosis. The tolerance of organisms within a biofilm results from the fact that they exist in the protective EPS, but also because they present in a reduced metabolic state. Therefore, antibiotics — which typically attack the metabolic processes of microorganisms, such as respiration — cannot kill the bacteria as effectively at standard dosing. For example, *Candida auris* in biofilm is 20 times less susceptible to amphotericin B than in its planktonic state. The side effect profile of antibiotics is well established. In many cases, antibiotic concentrations adequate to achieve antimicrobial efficacy against biofilm bacteria would risk toxicity to the host.[21]

THE ROLE OF ANTIBIOTICS IN MANAGING WOUND INFECTIONS

Wound experts agree that diagnosis of infection can be one of the most challenging aspects of wound management. Underdiagnosis of wound infection can result in morbidity and even mortality. Overdiagnosis, or failing to recognize the signs of a chronic infection driven by the presence of biofilm, can expose the patient to unnecessary treatment and cost, as well as increased risk for antibiotic resistance.

Antimicrobial resistance is one of the biggest public health challenges of our time. Each year in the United States, at least 2.8 million people acquire an antibiotic-resistant infection, and more than 35,000 people die as a result. Antimicrobial resistance is associated with $20 billion in healthcare expenditures. Treating a clinically diagnosed infection should be the main reason providers prescribe antibiotics. Instead, the top three reasons they do so are a fear of poor clinical outcomes, patient demands, and uncertainty of infection presence.[22]

Bacterial infections unsuccessfully treated because of antimicrobial resistance claim at least 700,000 lives per year worldwide and are projected to be associated with the deaths of 10 million people per year by 2050, at a cost of $100 trillion to the global economy through loss of productivity.[22]

Because of the potential for antimicrobial resistance and the implicated dangers, it is important to determine the presence of infection before prescribing antibiotics for an acute infection. There are several methods for determining the presence of infection. Tissue biopsies for quantitative analysis are considered the gold standard, yet many providers collect a swab for semi-quantitative analysis.

Serena[23] et al. found that almost half of swab analyses were inaccurate in diagnosing wound infection. Additionally, in his review of more than 30 years of literature, Kallstrom[24] found only a 25 to 39 percent correlation between tissue biopsy and clinical signs of infection, leading to a recommendation that laboratory data not replace clinical assessment. A large post hoc analysis of 350 wounds in different wound centers found antibiotic prescribing patterns did not correlate with either clinical signs/symptoms or bacterial load, leading to a haphazard use of antimicrobials.[25]

THE WOUND HYGIENE PROTOCOL: FOUR SIMPLE STEPS

In 2020, an international panel of wound experts released a consensus document recommending the Wound Hygiene[14] protocol for chronically infected hard-to-heal wounds.[14] This four-step protocol should be carried out regularly and repetitively to promote healing in hard-to-heal wounds:

- Cleansing the wound and surrounding skin using a non-cytotoxic antiseptic wound cleanser. The wound and surrounding skin should be scrubbed as tolerated by the patient.
- Debridement of the wound (sharp or mechanical), including maintenance debridement, if necessary, to disrupt biofilm formation and to remove devitalized tissue.
- Refashioning or opening of the wound edge.
- Dressing, using an appropriate antimicrobial dressing to extend the therapeutic window between dressing changes. The dressing should address any residual bioburden and prevent contamination and recolonization. It should also manage exudate effectively to promote wound healing.

Biofilm is responsible for at least 78 percent of microbial healthcare infections.[27] Even with debridement, wound biofilm is difficult to manage, so it requires regular wound hygiene to reduce sustained host inflammatory response and keep wounds on a healing pathway. This protocol should be completed for each dressing change.[14]

AN ADVANCED DRESSING TECHNOLOGY SOLUTION

The fourth step of the Wound Hygiene protocol calls for the use of an appropriate antimicrobial dressing. With the addition of two components to engage synergistically with the ionic silver (MORE THAN SILVER™ technology), AQUACEL® Ag Advantage (Convatec) is the world's first wound dressing technologically designed specifically to manage biofilm within the dressing.* The dressing design manages biofilm within the dressing by using two safe, powerful technologies in synergy: Hydrofiber™ technology, which forms a cohesive gel that absorbs and effectively retains exudate and microorganisms, and MORE THAN SILVER™ technology. The MORE THAN SILVER™ technology formulation includes:

- **Benzethonium Chloride (BEC):** A surfactant that reduces surface tension.
- **Ethylenediaminetetraacetic Acid (EDTA):** A metal-chelating agent that weakens biofilm structure.
- **Ionic Silver:** A broad-spectrum antimicrobial that accumulates at microbial cell membranes and destroys multiple cellular processes.

AQUACEL® Ag Advantage offers differentiated performance compared to other silver dressings. One study shows a demonstrated reduction in the quantity and viability of microorganisms in biofilm, which it effectively captures compared to the other silver-based dressings used in the study.[27] Based on internationally recognized standard biofilm tests, AQUACEL® Ag Advantage further shows differentiation in dressing performance compared to standard silver dressings. In this study, complex three-species biofilms were cultured for 72 hours and exposed to different silver-containing gelling fiber dressings for 72 hours. AQUACEL® Ag Advantage was the only dressing in the test that demonstrated reduction of microorganisms to undetectable levels. The other silver gelling fibers included in the study contained just silver, and all of these had a negligible effect compared with the untreated controls.[28,29]

The efficacy of these dressings and formulations is supported by strong laboratory[27,28] and clinical evidence. One study showed that when using AQUACEL® Ag Advantage, there was a 90% reduction in the size of the wound within an average of 5.4 weeks.[29] This study and several more published since then suggest that MORE THAN SILVER™ Technology in AQUACEL® Ag Advantage effectively manages biofilm within the dressing.* This enables a majority of hard-to-heal wounds to progress toward healing as part of an overall Wound Hygiene strategy.

CONCLUSION

Acute and chronic wound infections differ significantly from immunological, microbiological, and clinical perspectives. As a result, acute and chronic wound infections must be approached differently to achieve wound healing. While an acute infection can be addressed by evaluating risk factors, managing local wound concerns, and implementing antibiotics when clinically indicated, alternative strategies are required to address the different factors involved with a chronic wound infection.

Chronic wound infections benefit from the regular and repeated utilization of the Wound Hygiene protocol to support improved patient outcomes. The Wound Hygiene protocol includes four steps: cleansing the wound, debridement, refashioning of the wound edges, and selecting an appropriate wound dressing. In addition to promoting healing in chronic wound infections, the Wound Hygiene protocol also achieves antibiotic stewardship goals as it addresses the root cause of the chronic wound infection at the local level, impacting biofilm.

AQUACEL® Ag Advantage dressings can be used within the Wound Hygiene protocol to support optimization of the wound healing environment by addressing barriers associated with biofilm present in chronically infected wounds. In winning the battle against wound infections, consider these strategies to successfully impact the unique clinical challenges of acute and chronic wounds and to support antimicrobial stewardship goals.