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**A Symposium:
Wound Infection and Occlusion—
Separating Fact from Fiction**

GUEST EDITOR:

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Wound Infection and Occlusion— Separating Fact from Fiction

Proceedings of a round table discussion sponsored by Hahnemann University, Philadelphia, Pennsylvania held at the Great Ormond Street Hospital, London, England, October 2-5, 1992. This publication is designed for use as a vehicle for continuing medical education. Upon successful completion of the *quiz and evaluation*, physicians will be awarded Continuing Medical Education credit from the Hahnemann University Office of Continuing Education.

EDUCATIONAL OBJECTIVES

After reading this monograph, you will be able to:

- differentiate between wound contamination and infection;
- compare infection rates and identify risk factors for pressure, venous, diabetic ulcers, burns, donor sites;
- review the effect of occlusive and non-occlusive dressings on wound healing and infection;
- apply techniques to reduce airborne microorganisms in the clinic;
- discuss the interaction between patient immune defenses and wound infection.

ACCREDITATION

As an organization accredited by the Accreditation Council for Medical Education (ACCME) to sponsor continuing medical education for physicians, Hahnemann University designates this continuing medical education activity for 4.5 credit hours in Category 1 of the Physicians's Recognition Award of the American Medical Association.

This program is eligible for 4.5 credit hours in Category 2A of the American Osteopathic Association.

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Overview of Wound Healing in a Moist Environment

Charles K. Field, MD, Morris D. Kerstein, MD, Philadelphia, Pennsylvania

Maintaining a moist wound environment facilitates the wound-healing process. The beneficial effects of a moist versus a dry wound environment include: prevention of tissue dehydration and cell death, accelerated angiogenesis, increased breakdown of dead tissue and fibrin, i.e., pericapillary fibrin cuffs, and potentiating the interaction of growth factors with their target cells. In addition, pain is significantly reduced when wounds are covered with an occlusive dressing. Concerns that moisture in wounds would increase the risk of clinical infection over traditional therapies are unfounded. The use of hydrocolloid occlusive dressings in maintaining a moist wound environment has proved to be a useful adjunct in facilitating wound healing.

Moisture is no longer the enemy of effective, efficient wound healing. Winter's 1962 study [1], which demonstrated enhanced wound reepithelialization under occlusive dressings, signaled the beginning of the so-called dressing revolution. The use of moisture-retentive dressings (i.e., dressings capable of maintaining a warm, moist environment) has been shown to provide an optimal environment that accelerates healing and promotes tissue growth. This overview serves to summarize the beneficial effects of moist environment on wound healing.

OXYGEN TENSION, ANGIOGENESIS, AND DRESSINGS

Oxygen tension at the wound site influences different aspects of the tissue repair process. In the past, there has been evidence that increased rates of epithelialization and collagen production (two integral components of wound healing) are dependent on increased concentrations of ambient oxygen in the wound [2]. Recent evidence supports the exact opposite hypothesis; i.e., wound healing is stimulated and facilitated by a relatively hypoxic wound environment [3]. In vitro trials have demonstrated that optimal growth of fibroblasts in tissue culture occurs at low partial pressures of oxygen (5–10 mm Hg), and epidermal cell growth is inhibited at oxygen levels higher than that in surrounding air [3,4].

Knighton et al [5] identified chronic tissue hypoxia as a potent stimulator of capillary proliferation. Using a modified Clark rabbit ear chamber model, they noted that vessel growth in healing wounds follows energy and oxygen gradients [5,6]. Oxygen gradients between the wound edge and center stimulate capillary ingrowth toward the relatively hypoxic center of the wound. Capillary ingrowth and the overall wound repair process continue until hypoxia is abolished. In the experimental model, the premature reversal of this oxygen gradient stopped all capillary growth [5]. Hypoxic promotion of angiogenesis may be mediated by the macrophage, a cell common to all healing wounds. Macrophages may be stimulated by local hypoxic wound conditions to release growth factors. As the wound heals and hypoxic conditions subside, the macrophage is "turned off" and release of growth factors is terminated [5].

Clinically, it has been shown that hydrocolloid dressings are capable of maintaining low oxygen tension, independent of the underlying disease process [3]. To quantitate the effect of oxygen tension on the process of angiogenesis further, Lydon and colleagues [7] conducted an in vivo study, comparing the effects of occlusive hydrocolloid, semipermeable film, and conventional gauze dressings. Using immunohistochemical staining techniques, they were able to show significantly greater

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angiogenesis under the hydrocolloid (DuoDERM; ConvaTec, Skillman, NJ) versus the gauze dressings 3–12 days after wounding, while the film-dressed wounds exhibited a similar but less pronounced increase during days 6–9, compared to control. The immunohistochemical findings were confirmed by laser Doppler flowmetry measurement of vascular perfusion, which increased significantly ($p < 0.025$) in hydrocolloid- versus gauze-dressed wounds starting on the third day after wounding. [7].

NECROTIC TISSUE AND FIBRINOLYSIS

Fibrinolysis, i.e., the dissolution of fibrin, occurs naturally in wounds through the action of local plasminogen-activator or other enzymes. Dead or inflamed tissue contains fibrin that needs to be removed before healing can occur. In addition, capillary hyperpermeability secondary to venous hypertension has been found to lead to leakage of fibrinogen into the pericapillary space. The resulting fibrin deposits often surround capillaries near ulcers [8]. These “fibrin cuffs” may contribute to reduced diffusion of oxygen and exchange of nutrients and metabolic waste through affected vessels, and they may prevent growth factors and other stimulatory substances for tissue repair from reaching the wound [9,10]. At first, it was thought that occlusive dressings were capable of facilitating autolytic debridement because they retain the enzymes and water required to help dissolve dead tissues [11,12]. However, recent *in vitro* and *in vivo* research has shown that wound fluid from occluded wounds also contains proteinase [13,14]. In addition, the *in vitro* observation that one hydrocolloid dressing is able to lyse fibrin has recently been confirmed in the clinic where it was shown that after 1 week of treatment, venous ulcers treated with the DuoDERM dressing were significantly more likely to exhibit a decrease in the number of pericapillary fibrin cuffs, compared with the control ulcers treated with the same compression plus Unna's boot, but without the fibrinolytic dressing [7,15]. In addition to the benefit of obtaining a clean, possibly better perfused, wound, fibrinolysis may have a secondary benefit to the wound healing process, for it is thought that fibrin degradation products may exert a chemotactic effect on macrophages and the subsequent secretion of many of the macrophage-derived growth factors [7].

MOISTURE RETENTIVE DRESSINGS AND GROWTH FACTORS

The variety and number of growth factors—i.e., peptides that serve to recruit and stimulate different cell types during the wound healing process—continue to grow [11]. Following wounding, platelet-derived growth factor (PDGF) and transforming growth factor-beta (TGF- β) are considered to be among the first growth factors to be released, for the purpose of stimulating fibroblast proliferation and as chemoattractants for macrophages, neutrophils, and smooth muscle cells. Fibroblasts synthesize and extrude the collagen matrix framework for granulation tissue formation. To avoid

abnormal scarring, fibroblasts differentiate to their quiescent form after producing enough collagen for normal remodeling [11]. Macrophages, specialized white blood cells present in the wound bed during the inflammatory and repair process, also secrete growth factors (including epidermal growth factor [EGF], fibroblast growth factor [FGF] PDGF, TGF- β , and interleukin-1 [IL-1]). Among others, these growth factors act on epidermal cells or keratinocytes as they differentiate to form the outer stratum corneum and help the process of angiogenesis by providing a stable collagen matrix [11].

The two cell types involved in angiogenesis are the endothelial cell and the pericyte. The latter is the microvascular equivalent of smooth muscle cells and may inhibit the growth of endothelial cells by a contact-dependent mechanism. Capillary quiescence is mediated by the interaction of endothelial cell and pericyte. FGF overcomes the inhibitory effect of the pericyte, allowing endothelial cell proliferation and, thus, capillary growth [16].

Dressings may play an important role in facilitating the release and complex interactions between the cell types and their respective growth factors involved (Figure 1). Moisture-retentive dressings will not only keep cells viable, enabling them to release growth factors while maintaining contact between them and the healing tissues, but may also modulate or stimulate their proliferation [17]. Specifically, PDGF, FGF, and EGF have been found in the fluid beneath occlusive dressings, and fluid from human blister wounds covered with a film dressing has been reported to stimulate *in vitro* fibroblast and endothelial cell growth, whereas fluid from burn wounds covered with DuoDERM dressings was found to stimulate keratinocyte proliferation [7,13,18–20]. Ongoing research in this area suggests that during the healing cycle, numerous growth factors are released, depending on the needs of the wound [21]. Until such time as we are able to identify which combination of growth factors is needed and when, we can at least provide a wound environment that has been shown to retain those provided by nature.

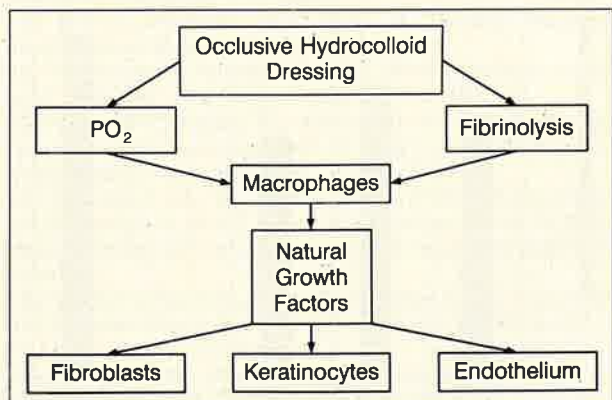


Figure 1. Occlusive dressings help create a permissive environment for growth factor–target cell interaction. PO₂ = partial oxygen tension.

MOISTURE VAPOR TRANSMISSION AND DRESSINGS

Keeping the wound surface hydrated is not only important for the reasons outlined previously, but it also allows for rapid delivery of topical medication and, in case of enzymatic debridement, provides the moisture necessary for these water-dependent enzyme systems [11].

Many dressings and ointments (for instance, petrolatum) will provide a more or less occlusive dressing and possibly moist wound environment. In an attempt to quantify the capacity of dressings to maintain a moist wound environment, Bolton and colleagues [11,22] measured the moisture vapor transmission rate (MVTR) of a variety of dressings. They found that a MVTR of <35 g of water vapor transmitted per square meter of dressing per hour is low enough to maintain a moist wound surface and that MVTR values range from 68 ± 2 for gauze to 57 ± 4 for impregnated gauze and 8 ± 0.08 for DuoDERM CGF dressings. Interestingly, MVTR values also differed significantly among the various occlusive dressings available today [11,22].

MOISTURE RETENTIVE DRESSINGS AND RATE OF HEALING

Clinically, the effects of dressings discussed can have a profound impact on the rate of healing (Figure 2). Compared with conventional gauze-dressed wounds, acute, partial-thickness wounds covered with a moisture-retentive dressing can be expected to heal an average of 3–4 days faster [18,23–26]. Similar trends have been observed in other controlled clinical studies. For instance, when comparing the healing rates of shave biopsies, after 2 weeks 100% of those dressed with a hydrocolloid compared to 63% of wounds dressed with a topical antimicrobial and gauze were healed [27]. The

effect of these dressings on deeper wounds is similar, albeit the difference in the number of days involved is usually larger. In vivo, the healing time difference between gauze control and film or hydrocolloid dressings is 7–9 days [28,29]. Clinically, the reported median time to healing deep facial excisions was 20 days for film-dressed compared with 26 days for antimicrobial ointment and gauze-dressed wounds [30]. Studies in chronic wounds, such as leg and pressure ulcers, tend to be plagued by patient and wound variables unrelated to the treatment modality studied; however, the overall results obtained confirm the findings reported on acute wounds. In the majority of controlled clinical studies, hydrocolloid-dressed ulcers are more likely to heal and during a shorter period of time, compared with conventional gauze control-dressed ulcers [31–34].

DRESSINGS AND PAIN

Madden and colleagues [18] found that patients with mirror-image donor sites covered with DuoDERM had less pain at rest than those whose wounds were covered with fine mesh gauze. This difference in pain perception became highly significant with ambulation ($p < 0.001$) [18]. Numerous studies describe the decrease in wound pain associated with hydrocolloid occlusive dressings [23–27,32–34]. This added benefit has been attributed to the moist dressing/wound interface that protects nerve endings from drying and exposure and limits damage to the wound surface during dressing changes.

MOISTURE RETENTIVE DRESSINGS AND INFECTION

Hydrocolloid dressings can protect wounds against penetration of bacteria from the outside. Dunn and Wilson [35] have used hydrocolloid dressings to prevent

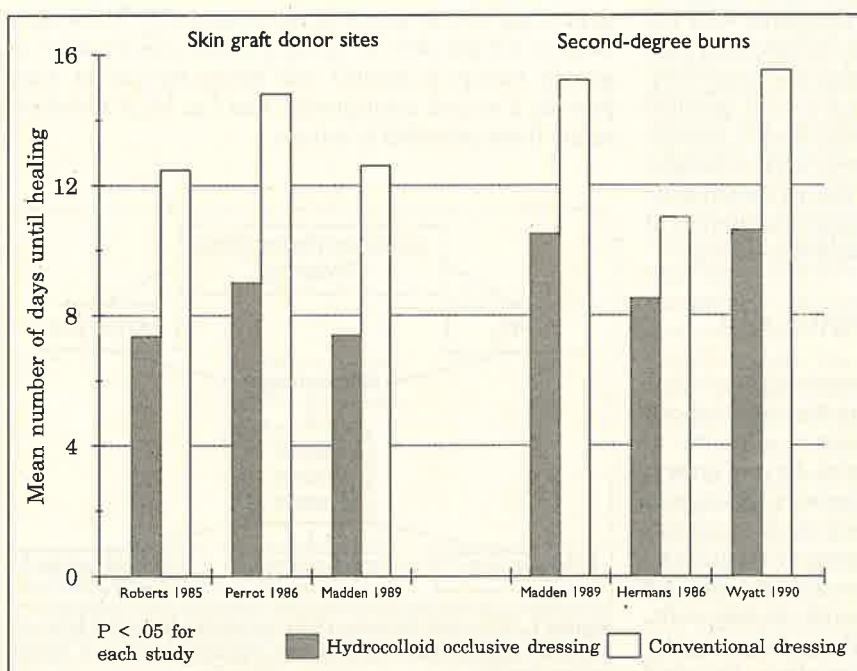


Figure 2. Reported number of days until healing of skin graft donor sites and second-degree burn wounds.

the spread of methicillin-resistant *Staphylococcus aureus* (MRSA) in colonized chronic venous ulcers in hospitalized patients. In vitro testing of several different brands of hydrocolloid dressings disclosed a high incidence of single-site penetration at a mean of 8.5 days [35]. Penetration was more likely by antibiotic-sensitive strains of *Staphylococcus* than by resistant strains; nonetheless, the authors suggest that hydrocolloid dressings used to control the spread of MRSA should be changed every 7 days. Covering a wound colonized with MRSA with an occlusive dressing has been suggested as an alternative to long-term isolation maneuvers to prevent spread of MRSA [35]. The warm, moist environment provided by occlusive dressings would seem to favor the growth of pathogenic microorganisms leading to clinical infection. This early concern among proponents of occlusive dressings appeared groundless.

The presence of bacteria in conjunction with such clinical signs as local pain, cellulitis, lymphangitis, heat, erythema, and edema leads to a diagnosis of infection. However, a distinction needs to be made between colonization and infection. The presence of microorganisms alone (colonization) does not indicate infection. Placement of an occlusive dressing may change the bacterial flora of the wound but does not predispose to infection. Hutchinson and McGuckin [36] reviewed 75 studies investigating the incidence of infection under occlusive dressings (sample size: 3,047 wounds) and 36 studies comparing infection rates under occlusive dressings using conventional gauze or impregnated gauze dressings as controls. Overall infection rates were 2.6% for occlusive dressings and 7.1% for nonocclusive dressings ($p < 0.001$).

In vitro studies, occlusive dressings provided an environment that allows the host's phagocytic mechanisms, mediated by polymorphonuclear leukocytes (PMNs), to function [3]. This confirms earlier clinical observations that viable PMNs, macrophages, lymphocytes, and monocytes have been found in the fluid that accumulates underneath these dressings [38]. Saymen and colleagues [37] also demonstrated that PMNs are more likely to infiltrate a moist occluded wound than a desiccated wound. Examination of fluid from occluded wounds has confirmed that wound PMN activity is equal to PMN activity in circulating blood [39]. Several researchers have shown that an acid environment develops under hydrocolloid dressings [3,35,40,41].

Pseudomonas aeruginosa and *S. aureus* are capable of causing clinically evident infection in colonized wounds. Lilly [39] was able to show in vitro that extracts (aqueous suspensions) of hydrocolloid dressings were both acidic and capable of inhibiting growth of *S. aureus* and *P. aeruginosa*. The acidification of wounds under hydrocolloid dressings may lead to lower infection rates.

CONCLUSION

Moisture helps wounds heal. A moist wound/dressing environment facilitates recruitment of vital host defenses and the necessary cell population, such as the

macrophage, that helps promote wound healing. These cells elaborate an amazing number of growth factors, creating a milieu characterized by accelerated angiogenesis, increased fibrinolysis, and an accelerated rate of healing. Early concerns that occluding a wound would lead to infection are unfounded. The immediate application of an occlusive dressing does not increase the incidence of clinical infection. An added benefit of moist wounds is decreased pain at rest, during ambulation, and during dressing changes. Although much remains to be investigated, our increased knowledge of wound healing in general, and the effect of dressings on this process in particular, will help us implement up-to-date patient-care practices.

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DISCUSSION

P. Thomson: The polymorphonuclear leukocyte (PMN) triggers the macrophage to initiate the wound repair process. Did I hear you say that completely blocking the PMN might not be a good idea?

M. Kerstein: In fact, we should facilitate the viability of the PMN. When it sticks to endothelium and bacteria, I think that ultimately inhibits wound healing.

P. Thomson: To get the macrophage turned on, does not one have to endure some of that damage?

M. Kerstein: It is not damage but rather an aspect of the process.

C. Baxter: What is the role of topical antibiotics? If I put them on wounds, within an hour they are all gone. I use silver sulfadiazine encapsulated in liposomes, and the concentration of antimicrobial stays up for 2-3 days. For example, 0.1% silver sulfadiazine administered this way can prevent as much infection in burns as 1% silver sulfadiazine [1].

M. Kerstein: The bacteria colony count on the surface is not a measure of infection; rather it is contamination. The moisture, not the antibiotic, may be the helper. The encapsulated liposome is not the same as a topical ointment. Does the same rule apply for bacitracin, Neosporin, polymyxin, and all the other topical antibiotics?

C. Baxter: It does. The liposomes function as more than an antibody.

P. Thomson: There is a distinction between antimicrobial and antibacterial or antibiotic activity. Do the liposomes work for all of them?

C. Baxter: Yes, regardless of whether it is an antibiotic or an antimicrobial [2-4].

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