A Rational Approach to the Use of Topical Antiseptics

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The proper application of antiseptics to the open wound is controversial. With the goal of creating an optimal environment for wound repair, consideration of a topical antiseptic includes both its bactericidal activity and its potential cytotoxicity when applied to the healing wound in varying concentrations. This discussion reviews the events of wound healing, including the key cells that mediate this process, the significance of bacteria in the wound bed, and the impact of infection. Specific antiseptics including povidone-iodine, hydrogen peroxide, acetic acid, and Dakin's Solution are reviewed, emphasizing bacterial potential and their cytotoxic properties. (J WOCN 1994; 21:224-31)

The appropriate use of antiseptics continues to be one of the most controversial issues in the field of wound care: For years, topical therapy of chronic wounds revolved around prevention and management of infection[1]; wound care thus typically involved liberal use of antiseptics, along with wet-to-dry dressings and exposure to air. As our understanding of wound healing and wound management evolved, the focus in topical therapy shifted from the "prevention of infection" to "creation of an optimal environment for the repair process". Reports that commonly used antiseptics could be toxic to the cells of the repair process led many practitioners to totally eliminate the use of antiseptics in wound management. In deed, the axiom "Do not put anything in a wound that you would not put into your eye" became the governing principle[2]; povidone-iodine solutions, hypochlorite solutions, acetic acid, and hydrogen peroxide came to represent the "unenlightened" approach to wound care.

Although such "all or none" approaches to antiseptic use simplify the decision-making process, they fail to address the complexities of optimal wound management for the various wounds encountered in clinical practice. Some wounds are infected, whereas others are merely contaminated; some patients have intact immune systems, whereas others are immunosuppressed. Current studies indicate that selected antiseptics at specific concentrations may be effective in reducing bacterial contamination without trauma to the cells critical to wound repair. [3-7] Today, optimal wound management requires the clinician to consider the bacterial status of the wound, the immune function of the host, the

phase of wound healing, and the effects of various topical agents, both on bacteria and on the cells responsible for wound repair. This article includes a brief review of the wound healing process, the critical cells mediating the repair process, the impact of infection on wound healing, the bacterial spectrum of various antiseptics, and the impact of various antiseptics (in varying concentrations) on the cell governing the wound repair.

Wound Repair

Partial-thickness wounds involve loss of the epidermal layer and may extend into but not through the dermis. The primary component of partial thickness repair is epithelial proliferation and migration, which provides "resurfacing"; any accompanying dermal loss is repaired by collagen synthesis. [8,9] The primary mediator for partial-thickness repair is the epithelial cell, or keratinocyte; solutions that are toxic to keratinocytes would therefore be expected to delay the repair process and thus contraindicated.

Full-thickness wounds involve total loss of the skin layers; they extend into the subcutaneous tissue and may involve muscle or bone. Full-thickness wound healing involves a well-synchronized cascade of events that is commonly divided into three major phases. The first phase is the *defensive*, or *inflammatory*, phase. The key events in this first phase are hemostasis, which prevents excessive blood loss and causes the release of growth factors, and inflammation, which provides phagocytosis of invading bacteria and breakdown of necrotic material. The primary cells mediating the inflammatory response are the polymorphonuclear leukocytes and the macrophages.[8, 9] It is relevant to note that the inflammatory phase is prolonged by necrosis and wound infection; antiseptics could therefore theoretically enhance the host's ability to move through this phase by eliminating necrosis and reducing bacterial counts. The toxic effects of various antiseptics on leukocytes and macrophages, however, must be considered, along with the bactericidal spectrum of activity.

The second phase in full-thickness wound repair is the *proliferation* phase.   In open wounds healing by secondary intention, this phase involves granulation tissue formation, wound contraction, and finally epitheliazation. The key cells in the proliferative phase are the fibroblasts, which are responsible for synthesis of connective tissue, the endothelial cells, which are critical to neoangiogenesis, and the keratinocytes, which provide epitheliialization.[8, 9] Wounds in the proliferative phase of wound repair are typically clean and uninfected; antiseptics are therefore less likely to be needed, and any antiseptic used for proliferating wounds should be carefully evaluated in terms of toxic effects on the fibroblasts, endothelial cells, and keratinocytes.

The final phase of full-thickness wound repair is the *maturation* phase; this phase involves "remodeling" of the scar tissue through the concurrent processes of

collagen synthesis and collagen breakdown.[8, 9] The wound is closed at the surface; topical agents therefore have no role in this phase of wound repair.

Infection Versus Colonization: Impact on Wound Healing

It is well established that all open wounds are contaminated with bacteria; there is considerable evidence, however, that contamination is not deleterious to wound healing. Open, granulating wounds are generally considered to be resistant to infection, despite bacterial contamination. Indeed, the presence of bacteria in the wound may even support autolysis and the activation of the body's own defense systems.[10] Wound infection occurs when bacterial proliferation overwhelms the host defense mechanisms, permitting pathogens to invade the viable tissue; the standard laboratory indicator of wound infection is usually considered to be a colony count of 10^5 or higher.[10]

Most clinicians depend heavily on clinical evaluation (the presence of edema, erythema, and purulent drainage) to determine infection[11]; immunosuppressed patients may not have the typical inflammatory response, however, and in these patients laboratory values are a more accurate indicator. The negative impact of infection on wound healing is well known; infection is known to cause wound dehiscence, to inhibit the "take" of skin grafts, and to delay granulation tissue formatin.[10, 12, 13]

It is therefore clear that prevention or elimination of infection is a critical concern in promotion of wound healing; what is less clear is the impact of various topical agents on bacterial counts and on the viability of the leukocytes that are critical to the body's own defensive responses. The ideal agent for an infected wound (or a heavily contaminated wound in an immunosuppressed patient) would be bactericidal to a wide range of commonly encountered pathogens and noncytotoxic to leukocytes.

ANTISEPTICS: BACTERICIDAL SPECTRUM AND CYTOTOXICITY DATA

 Available data are conflicting regarding the effects of various antiseptics on the wound repair process. It is important when reviewing studies to differentiate between in vitro laboratory data, and in vivo clinical data. Many of the currently available studies have been done with cultured fibroblasts or keratinocytes in a laboratory setting.[5] These data should not be freely extrapolated to clinical situations because the wound environment contains many elements not found in the culture medium used for laboratory studies; these elements alter the

interactions among the antiseptic, the bacteria, and the cells mediating wound repair.[4] The in vivo data must also be reviewed carefully; much of these data are based on animal studies, and it is not yet clear how directly applicable these animal models are to the human repair process.[5] Finally, it is important to scrutinize the *form* and *concentration* of the antiseptic being studied with respect to the forms and concentrations commonly used clinically (Table 1).

Table 1.
Properties of topical antimicrobials

Antiseptic	Bactericidal spectrum	Cytotoxicity data*	"Safe" concentrations
Povidone-iodine solution, cream, or ointment	Staphylococcus aureus (0.001%)	Variable (dependent on concentrations)	Scrub: always contraindicated in open wounds Solution: 1% (1:10 dilution) or 0.001% (.1:1000 dilution) Ointment: 10% Cream: 5%
Sodium hypochlorite (Dakin's solution)	0.005% S. aureus P.aeruginosa E. Coli Group D Enterococcus B. fragilis 0.025% P. mirabilis S. marcescens E. cloacae K. pneumoniae S. epidermidis S. mitis	Variable (dependent on concentration)	0.025%(1:10 dilution) or 0.005% (1:200 dilution)

Acetic acid	S. aureus (inhibition with 0.25%) P. aeruginosa (partial inhibition with 0.0025%)	Variable (dependent on concentration)	No "safe" concentration with bactericidal activity
Hydrogen peroxide	S. aureus (3%)	Toxic	No "safe" concentration with bactericidal activity

MRSA Methicillin-resistant S. aureus.

*Toxic, nontoxic, or variable

Povidone-Iodine Products

 Povidone-iodine is one of the most widely used antiseptics in wound care; it may also be the most misunderstood and therefore misused antiseptic currently available. The misunderstanding arises from the availability of four different povidone-iodine compounds, all of which have different ingredients and differing impacts on the wound repair process. Povidone-iodine scrub is a detergent compound that is not recommended for wound care; this product is intended for preoperative preparation of intact skin, and the company that makes Betadine compounds acknowledges that the detergent component of the scrub is cytotoxic to the cells mediating wound repair.[5, 14] The results of studies with Betadine scrub cannot and should not be considered indicative of the properties of all povidone-iodine products. Specifically, studies with Betadine *scrub* should not be considered when analyzing the effects of Betadine soulution.[15]

As manufactured, povidone-iodine solution contains 10% polyvinylpyrrolidone iodine, a water-soluble complex containing elemental iodine bound to polyvinylpyrrolidone, a synthetic polymer. Polyvinylpyrrolidone iodine is designed to provide gradual liberation of free iodine, which is the bactericidal component of the compound; the actual concentration of free iodine is usually 1 ppm.[2, 16] Studies on free iodine have shown that this low concentration kills most bacteria in 60 seconds; the free iodine can be neutralized by protein, however, and some investigators have reported inactivation in the presence of purulent drainage and

necrotic tissue.[2, 16]

The dilution of povidone-iodine solution actually increases the liberation of free iodine because povidone-iodine is a water soluble compound.[14, 16] The beneficial effects of dilute concentrations of povidone-iodine thus may relate to an increased availability of free iodine. Povidone-iodine is also available as a water-soluble ointment and as a cream; the ointment provides a 10% concentration of polyvinylpyrrolidone iodine in a polyethylene glycol base, and the cream provides a 5% concentration of polyvinylpyrrolidone in a cream vehicle.[5]

Iodine has a broad antimicrobial spectrum, with reported effectiveness against gram-positive and gram-negative bacteria, viruses, fungi, and protozoa.[5, 16] In vitro studies substantiate its effectiveness against *Staphylococcus aureus;* [1, 7] however, in vitro tests of a 0.001% povidone-iodine (0.1 ml 10% solution per 1000 ml saline solution) failed to substantiate effectiveness against other organisms commonly encountered in open wounds: *Pseudomonas, Escherichia coli*, group D *Enterococcus,* and *Bacteroides.* This concentration was chosen because it had been found by Lineaweaver to be noncytotoxic to fibroblasts.[7]

Data regarding the cytotoxicity of povidone-iodine are conflicting; some studies indicate cytotoxicity and impairment of wound healing, whereas others reflect improved wound healing with the use of these compounds. In vitro studies typically involve tests of fibroblast and leukocyte viability after exposure to various concentrations of povidone-iodine in the laboratory setting. Lineaweaver and coworkers[1, 3] found that 1% povidone-iodine solutions were toxic to fibroblasts but a 1:1000 dilution of the 1% solution (0.001%) caused no fibroblast toxicity and was still bactericidal to *S. aureus.*[1, 3]

 Studies of McKenna and colleagues[7] essentially confirmed these findings. Cooper and associates[4] reported toxicity to both fibroblasts and kerantinocytes with a 0.5% povidone-iodine solution; this toxicity persisted even with further dilutions. The solution had been altered to a pH of 7.7, however, in an attempt to eliminate any toxic effects related to a nonphysiologic pH. This alteration may have affected the chemical balance of the iodine compound and may have increased its toxic effects; the normal pH of povidone-iodine compounds is about 5.0.[4, 17] Povidone-iodine toxicity to fibroblasts has been confirmed by the in vitro studies of other investigators.[18, 19]

 Although in vitro studies generally demonstrate fibroblast toxicity, in vivo studies of povidone-iodine performed in animal models provide conflicting data. Of seven studies reviewed by Mayer and Tsapogas, [5] five found no differences between animals whose wounds were treated with povidone-iodine and those whose wounds were treated with saline solution (evaluation parameters included blood flow, granulation tissue formation, time for wound healing, and tensile strength). The concentration of solution varied from 1% to 10%. Two studies indicated adverse responses to use of povidone-iodine. One, involving use of

1% povidone-iodine in rats, showed a delay in epithelialization and reduced tensile strength. In the second, involving evaluation of granulation tissue formation in a rabbit ear chamber, a 5% solution caused damage to small and midsized vessels, whereas a 1% solution caused no change in blood flow or cellular viability.[5]

Cameron and Leaper[18] evaluated the impact of 5% and 1% povidone-iodine on granulation tissue in a rabbit ear chamber; the 5% solution caused some damage to the blood vessels and an inflammatory response but the 1% solution had no impact on the blood vessels or the cells. Archer and colleagues[13] compared full thickness wound healing in pigs treated with antiseptics, sugar paste, and semipermeable film (OpSite; Smith & Nephew United, Inc. Largo, Fla.) In this study, treatment with a 0.8% solution of povidone-iodine caused delay in collagen maturation and in epithelialization. In addition, there was no reduction in bacterial growth compared with the sounds treated with OpSite or sugar paste.

 In vivo data involving human subjects are limited but obviously the most relevant. Mayer and Tsapogas[5] reported on two studies involving povidone-iodine solution. One involved surgical wounds managed with 5% and 1% povidone-iodine solution. The 5% solution caused diminished cell migration and fibroblast activity during the first 24 hours, whereas the 1% solution caused no adverse effects and was comparable to saline solution. At 72 hours, there was little difference between the wounds treated with 1% and the wounds treated with 5% solution.

The second study involved donor sites for split-thickness skin grafts: this showed no difference in wound healing between patients treated with saline solution and those treated with povidone-iodine solution. In contrast, Rodeheaver[2] reported on in vivo studies involving surgical wounds in human beings in which preclosure treatment with polyvinylpyrrolidone significantly increased the infection rate. Limited studies in human beings with povidone-iodine cream and ointment have demonstrated equal or accelerated healing compared with control subjects; the group with accelerated healing was treated with both the cream and a polyethylene oxide gel dressing.[5]

In addition to issues related to cytotoxicity, the clinician must be aware of the potential for systemic iodine toxicity when large, open wound are packed with povidone-iodine solutions. Particular caution is indicated when these agents are used for patients with preexisting thyroid or renal disease. [14, 20]

It is obvious that more data is needed to determine the impact of povidone-iodine on wound healing. Its bactericidal properties at various concentrations need to be further validated, as does its effect on the cell modulating wound repair. Data regarding the cytotoxicity to neutrophils and macrophages are particularly relevant because these are the cells that mediate the inflammatory phase of wound repair.

Sodium Hypochlorite Solutions

Sodium hypochlorite (Dakin's solution), first introduced as an antiseptic in 1915, was used extensively in the management of war wounds.[6] it is currently being used with increasing frequency in the management of chronic wounds such as pressure ulcers, especially those with necrotic tissue and clinical infection. Sodium hypochlorite can be prepared by diluting bleach (5.25% NaOCI, or Chlorox) 0.5:10 in distilled water. This provide a 0.25% solution which can then be further diluted.[6]

Clinical studies have confirmed that Dakin's solution is bactericidal to the organisms commonly encountered in open wounds. Lineaweaver and associates[3] found a 0.005concentraton to be effective against *S. aureus*[3;] McKenna and colleagues[7] found a 0.005%conventation also bactericidal to *Pseudomonas aeruginosa. E. coli,* group D *Enterococcus,* and *Bacteroides fragilis.* McKenna and colleagues[7] also found that a 0.005solution maintains its bactericidal effectiveness for at least 4 days when kept in a closed container at room temperature. Heggers and colleagues[6] tested a 0.025% concentration of Dakin's solution against all organisms tested included methicillin-resistant *S. aureus, Streptococcus mitis, Staphylococcus epidermidis, Klebsiella pneumoniae, Enterobacter cloacae, Serratia marcescens,* and *Proteus mirabilis.*

The cytotoxicity data on Dakin's solution are conflicting; some investigators have reported severe cellular damage, whereas others have reported "safe" concentrations. Most of the data are derived from in vitro studies. Kozol and associates[21] evaluated the effect of Dakin's solution on the viability of fibroblasts and migration of neutrophils (derived from rabbit skin and from bovine pulmonary arties). The concentration of test solutions ranged from 0.025% to 0.00025%. They found significant inhibition of neutrophil maintained viability but failed to migrate in response to chemoattractants. These studies also revealed marked cellular damage to fibroblast and endothelial cell at all concentrations of Dakin's solution.

Heggers and associates[6] used mouse fibroblast to evaluate the cytotoxicity of various concentrations of Dakin's solution. Their studies shoed that a buffered 0.25% solution caused fibroblast dealth; when the solution was diluted to a 0.025% concentration, the fibroblasts sloughed by maintained viability. When the solution was further diluted to a 0.0125% concentration, the fibroblasts were completely unaffected. Lineaweaver and coworkers[3] used cultured human fibroblasts in their in vitro studies; they found that a 0.5% concentration killed fibroblast, but dilution to a 0.005% concentration resulted in a nontoxic solution. Cooper and associates[4] used cultured human fibroblast and keratinocytes for their cytotoxicity studies. They found that a 0.125% solution was cytotoxic to both fibroblast and keratinocytes, but a 0.0125% solution caused no damage.[4]

Cameron and Leaper[18] conducted in vivo studies with an animal model; they evaluated the effects of a 1% hypochlorite solution (Chloroamine T) on blood flow in a rabbit ear chamber. This solution caused complete capillary shutdown, with cellular exudation into the pericapillary spaces. Cameron and Leaper[18] also conducted in vitro studies with hamster kidney fibroblasts and a 2% hypochlorite solution; this solution was found to be cytotoxic to the firbroblast.[18]

The bactericidal effectiveness of Dakin's solution, even at dilute concentrations, has been documented. Further studies are needed regarding its cytotoxicity, however, especially in relation to leukocytes (which are the critical cells during the inflammatory phase of wound repair).

Acetic Acid

Acetic acid is a commonly used antiseptic. If is often used for control of *Pseudomonas.* The typical concentration is 0.25%

Acetic acid is reported to be effective against a variety of gram-negative and gram-positive organisms. Clinical data, however, reveal that acetic acid has limited effectiveness as a bactericidal agent. Lineaweaver and colleagues[1, 3] tested 0.25% acetic acid for its ability to kill *S. aureus*; 78% of the bacteria survived 24 hours of exposure to acetic acid. McKenna and coworkers[7] tested a 0.0025% solution (the concentration found to be noncytotoxic to fibroblasts) for effectiveness against *S. aureus, P. aeruginosa, E. coli,* group D *Enterococcus,* and *B. fragilis.* The acetic acid showed slight inhibition of staphylococcal growth and moderate inhibition of *Pseudomonas* but was not found to be bactericidal to either of these organisms. The other organisms tested were unaffected by the 0.0025% concentration of acetic acid.

Limited studies are available on the cytotoxicity of acetic acid, but those available indicate that its cytotoxicity surpassed its bactericidal effects. Lineaweaver and coworker[3] studies cultured human fibroblast in vitro and found that 0.25% acetic acid caused total cell death; dilution to 0.025% significantly reduced toxicity, and dilution to 0.0025% totally eliminated toxicity.[3] Cooper and associates[4] evaluated various concentrations of acetic acid for toxic effects on cultured human fibroblasts and keratinocytes. The 0.25% concentration was toxic to both fibroblasts and keratinocytes, but dilution to 0.125% significantly reduces the toxicity, and further dilution 0.025% almost completely eliminated the cytotoxic

effects.

Current data suggest that acetic acid is an inappropriate wound antiseptic. Concentrations that provide weak bactericidal effects also cause cellular toxicity, and solutions that are nontoxic (according to in vitro studies) are also nonbactericidal. Dakin's solution and povidone-iodine both demonstrate greater bactericidal effectiveness and less cytotoxicity than acetic acid. [3, 4, 7]

Hydrogen Peroxide

Hydrogen peroxide is commonly used as a wound cleanser; it provides an effervescent cleansing action through its release of oxygen. It is commonly used as a 3% solution.

Studies available indicate that hydrogen peroxide has limited bactericidal effectiveness. Lineaweaver and coworkers[3] studied various concentrations of hydrogen peroxide for effectiveness against *S. aureus.* They found the 3% solution to be bactericidal; however, all further dilutions failed to provide any inhibition of this organism.[3] McKenna and associates studies a 0.003% concentration of hydrogen peroxide for bactericidal effectiveness against *S. aureus, P. aeruginosa, E. coli,* group D *Enterococcus,* and *B. fragilis*; they chose this concentration because it was the dilution found to be noncytotoxic in the studies of Lineaweaver and coworkers.[3] In the studies of McKenna and associates, [7] hydrogen peroxide failed to cause inhibition of growth for any of the bacteria tested.

The limited studies available indicate that hydrogen peroxide is cytotoxic at normal concentrations (3%). Lineaweaver and colleagues[3] evaluated the effect of hydrogen peroxide on cultured human fibroblasts and found 100% toxicity at both 3% and a 0.3% concentrations. The 0.3% concentration also provided no inhibition of *S. aureus.* A 0.03% solution remained moderately toxic, and absence of toxic effect was not demonstrated until the peroxide had been diluted 1:1000 (0.003%). Studies by Burkey and associated[19] substantiated the 1; 1000 dilution required to eliminate cytotoxicity and found that toxic effects on fibroblasts and red blood cells were demonstrated by four of five testing methods.

Current data indicate that hydrogen peroxide in inappropriate for use as an antiseptic. Its cytotoxicity outweighs its limited bactericidal effects.

CLINICAL IMPLICATIONS

It is evident that we have incomplete data regarding the various wound antiseptics; however, we must base our clinical practice on available knowledge and modify our practice as indicated by new findings. Current clinical

implications are as follows:

1. Antiseptics are indicated primarily for wounds in the inflammatory phase of wound repair, especially those heavily contaminated or clinically infected. Wounds in the proliferative phase of repair do not usually need antiseptics, and data indicate the cells mediating the proliferative phase (e.g., fibroblasts) may be adversely affected by wound antiseptics. Use of antiseptics in proliferating wounds should therefore be limited to selected cases (e.g., immunosuppressed patients) and should involve noncytotoxic concentrations of the selected antiseptic.

2. More research is needed on the effects of antiseptics on leukocytes, which are the critical cells during the inflammatory phase of wound repair. Most cytotoxicity studies currently available involve fibroblasts.

3. Current data indicate that Dakin's solution has the broadest bactericidal spectrum and that 0.025% (1:10 dilution) [6] and 0.005% (1:200 dilutions) [3] concentrations are noncytotoxic.

4. More data are needed on povidone-iodine solutions. Povidone-iodine appears to be less effective as a bactericidal agent than Dakin's solution. If used, it should be diluted to at least 1% solution (1:10 dilution) [5] or possibly a 0.001% solution (0.1:1000 dilution). [3]

SUMMARY

Appropriate use of antiseptics in wound management remains ambiguous. Optimal wound management requires the clinician to consider the wound characteristics, the host's immune response, and current data regarding topical agents to select the most appropriate treatment regimen. More research regarding specific antiseptics is needed; by my interpretation of the data currently available, dilute Dakin's solution is the antiseptic of choice for infected wounds.

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