The Centers for Disease Control and Prevention reports that 103,000 deaths in 2000 were linked to hospital-acquired infections. Hospital-acquired infections now rank as the fourth-leading cause of death in the United States. The American Hospital Association blames unprecedented cost-cutting, financial instability, and physicians' lack of adherence to infection-control policies for this statistic. The Centers for Disease Control and Prevention states that many deaths were caused by unsanitary facilities, germ-laden instruments, and unwashed hands. These conditions could have been avoided with appropriate use of disinfectants and antiseptics.

Simon reported that approximately 10 million patients with traumatic wounds are treated in US emergency departments annually. These traumatic wounds may be classified, using the system provided by Holmes, as incised wounds, lacerations, and burns. According to White et al., traumatic wounds are more likely to have higher infection rates owing to devitalized tissue, debris, and contamination with microorganisms. Regardless of the type of traumatic wound, management must center around two paramount practices to avoid infection: meticulous irrigation and wound cleansing. Some confusion may exist between these two practices. Lawrence states that wound irrigation is the practice of washing with a stream of water or other fluid, whereas wound cleansing may range from vigorous washing to surgical toilet and debridement. The practice of wound cleansing or antiseptic management has a dichotomous history anchored in tradition and science.

The purpose of this article is to critically evaluate the potential harm to patient outcome by the use of antiseptics on acute wounds. First, animal and cell culture data that describe the effects of topical antiseptics on wound healing are offered. Second, human case studies are presented to illustrate the potential harm of the indiscriminate use of antiseptics. Finally, data from previously published reviews are presented and evaluated for clinically based evidence to justify the current practice of antiseptic use in acute traumatic wounds.

Antiseptic Properties

Ryan defines antiseptics as disinfectants used on body surfaces to reduce the number of normal flora.
and pathogenic contaminants. Antiseptics can be considered nonselective dilute disinfectants and, therefore, can be toxic to host tissues.5

Unlike antibiotics, which selectively act on a specific target, antiseptics have multiple targets. They function as nonspecific broad-spectrum microbial inhibitors without a specific cellular target site.11 Russell12 reviews the antimicrobial mechanisms of antiseptics and disinfectants, highlighting the relationship between phenolics and bacterial proteins. White et al3 found that antiseptic solutions must be concentrated to have their desired short-term effect on open wounds. An ideal antiseptic has the following attributes: a broad spectrum of activity, a low potential for resistance, rapid activity, nonirritant or nonsensitizing, effective in the presence of cellular debris, and, most important, nontoxic.13

Hippocrates realized that cleanliness was important to wound healing. He taught that wounds could be prepared for healing by first being irrigated with known antiseptics of the time: vinegar and wine.14 An antiseptic’s use and its resulting physiologic effects on exposed tissue rather than its chemical action on bacteria is the central focus of Alexander Fleming’s Hunterian Lecture.15 Lawrence7 further emphasizes this concept when he suggests that the choice of an antiseptic is based on the balance between its bactericidal or bacteriostatic effectiveness and the degree of damage it might cause to healthy human tissue. Brennan and Leaper16 advise balancing potential antimicrobial benefits with potential cellular toxicity of healing tissues before selecting an antiseptic. Sussman17 regards the use of topical antiseptics in acute wounds as warranted because traumatic wounds have a very high risk of infection from contamination at the time of wounding.

**Antiseptic Availability**

Several antiseptic categories exist, including alcohols, anilides, biguanides, bisphenols, chloride compounds, iodine compounds, silver compounds, per-oxygens, and quaternary ammonium compounds. Antiseptic uses and indications vary. Alcohol, boric acid, chlorhexidine, hypochlorite, aluminum salts, gentian violet, hydrogen peroxide, iodine salts, and acetic acid are freely marketed and readily available as inexpensive over-the-counter products in pharmacies, groceries, and gas stations. They are indiscriminately marketed to the public as “cure-alls” by the press, radio advertisements, and television commercials. On the other hand, sterile saline is a prescription product regulated by federal and state governments. This enigma is disturbing. If wound-care experts cannot agree on the potential harm of these products, how can individuals who are fed media publicity select the right product for a particular traumatic acute wound?

**Laboratory Studies**

Rodeheaver18 presented the controversies surrounding topical wound management as a guest editor in the premier issue of *Wounds: A Compendium of Clinical Research and Practice*. The stated purpose of his editorial was to describe the dangers of the indiscriminate use of antiseptic products on wounds. Rodeheaver et al19 previously advocated that it is the force of pressure used to clean a wound and not the choice of antiseptic that dictates whether contamination is removed. Whittington20 aims to dispel the myth of cleaning or packing wounds with antiseptics. She defends her position by citing literature evidence that this practice is harmful to white blood cells. However, Whittington’s use of evidence from the Agency for Healthcare Research and Quality21 is inappropriate because it is based on chronic wounds rather than acute wounds.

Mertz et al22 carried out evaluations comparing single applications of 70% alcohol and povidone-iodine on nine young Yorkshire pigs. These animals were wounded with partial-thickness wounds inoculated with *Staphylococcus aureus*. They concluded that a single application of both agents had limited efficacy for the treatment of superficial wounds. One salient point from the work of Mertz et al is the recognition of the need for a model that can closely duplicate the real-life situation of antiseptic use.

Gruber et al23 applied 0.25% acetic acid, 3% hydrogen peroxide, and povidone-iodine solutions to experimental wounds on rats and to human donor sites to test the effects on wound healing. Their study revealed that acetic acid and povidone-iodine solutions had no significant gross or microscopic effects on the wounds. On the other hand, hydrogen peroxide caused bullae formation and ulceration, prompting the authors’ recommendation to avoid this product.

Brennan and Leaper16 studied the effects of several antiseptic agents on granulation tissue using rabbit ear chambers as models. They compared different strengths of hypochlorite solutions with saline, hydrogen peroxide, and various povidone-iodine strengths applied to the ear chambers and measured microcirculatory local perfusion with a laser Doppler flowmeter. They concluded that hypochlorite solutions might be sufficiently toxic to negate their clinical value because of adverse effects on the local wound environment.
Subsequently, hypochlorite solutions were thoroughly investigated in animal and cell culture models. Cotter et al advocated that sodium hypochlorite as a dilute solution may be an attractive topical agent. Lineaweaver and colleagues used human fibroblasts from newborn foreskin to research the effects of 1% povidone-iodine, 0.25% acetic acid, 3% hydrogen peroxide, and 0.5% sodium hypochlorite applied directly to the cells. All four antiseptics were 100% cytotoxic. Retardation of wound epithelialization was observed with the use of povidone-iodine and acetic acid. Significant epithelialization retardation was observed with the use of sodium hypochlorite for up to 16 days. However, there was no significant difference in reepithelialization or wound tensile strength at 8 days among any of the antiseptic agents tested and no significant difference in reepithelialization among any of the agents by day 12 after the incision.

Kozol et al investigated an in vitro model of neutrophil migration and concluded that no safe concentration of sodium hypochlorite existed for use on wounds. A further investigation by Heggers et al concluded that tissue toxicity was observed in vitro and in vivo at a concentration of 0.25% but not at a concentration of 0.025%. Therefore, 0.025% modified Dakin solution was therapeutically efficacious.

Cooper et al evaluated the cytotoxicity of human dermal fibroblasts and epidermal keratinocytes as a result of the application of topical antimicrobial agents. Only Neosporin GU Irritant (neomycin sulfate—polymyxin B; Monarch Pharmaceuticals, Bristol, Tennessee) showed no significant cytotoxicity. Smoot et al evaluated cultured human keratinocytes in relation to cytotoxicity and cellular migration in relation to the application of topical antiseptics. These authors concluded that their findings are unique because they can be directly extrapolated to a clinical setting. The experiments by Lineaweaver and colleagues can be extrapolated to a clinical setting; therefore, the findings by Smoot et al are only unique to the type of cell line they selected.

Given that neutrophils appear in a wound 6 hours after the wounding event, only the in vitro model of neutrophil migration by Kozol et al and the cytotoxicity and cellular migration model by Smoot et al can be used as content validity tools. Their findings directly apply to the use of antiseptics within 6 to 8 hours and the subsequent detrimental effects on wound healing. The conclusion of Kirsner et al that acute wound fluid is generally stimulatory to cell movement and proliferation emphasizes the detrimental effects of antiseptics. The other studies have more elements of validity—criterion related, content, concurrent, construct, and face validity—for chronic wound-healing models because they demonstrate toxic effects on fibroblasts and angiogenesis. Their data may have some merit for acute wound healing that has not yet been discovered.

Using the cell stick method, Viljanto and Vilkki demonstrated significant inhibition of migration, fibroblast activity, and wound cellularity during the first 24 hours of wound healing when surgical wounds were exposed to a 5% povidone-iodine solution. Furthermore, the findings of Viljanto and Vilkki demonstrated that there was little difference between wounds exposed to a 1% povidone-iodine solution and a 5% povidone-iodine solution by 72 hours. They also showed that there was no significant difference in migration, fibroblast activity, and wound cellularity between 1% povidone-iodine solution and normal saline.

**Human Cases**

Wound healing in humans is a complex and dynamic process. Owing to this complexity, no correlation has been established between results gained from using static in vitro or in vivo methods and the human experience. Mayer and Tsapogas in their critical review of povidone-iodine and wound healing, conclude that the results of human and animal studies indicate that exposure to povidone-iodine solutions for skin preparation does not adversely affect tissue repair. They further offer that, based on their review, povidone-iodine solution is relatively benign to tissues when used correctly.

It has been reported that topical therapy is attractive because it is free of the risk of systemic drug exposure. However, the first case studies documenting the potential harm from using antiseptics may be found in the pediatric literature. During the 1950s and 1960s, bathing neonates with topical hexachlorophene to prevent S aureus epidemics proved to be more harmful than beneficial. The occurrence of seizures and death associated with vacuolar encephalopathy prompted the medical community to discontinue this practice. Howard warns that pediatricians should limit the use of isopropyl alcohol for umbilical care because premature infants are at a greater risk of toxic effects and older siblings are at risk for accidental ingestion and poisoning. The indiscriminate use of chlorhexidine has been implicated in the development of a resistant strain of Serratia marcescens in a pediatric oncology unit.

Adverse effects from the use of hydrogen peroxide and povidone-iodine have been reported in children and adults. Subcutaneous gas from the adminis-
tation of hydrogen peroxide under pressure has been reported in two children. The mechanism of hydrogen peroxide liberation of free oxygen is secondary to its contact with the blood enzyme catalase. A case of pulmonary edema after hydrogen peroxide irrigation was reported in a Sarajevo soldier by Saisyy et al. They concluded that hydrogen peroxide passed into the venous bloodstream before being decomposed by tissue catalase, thus causing cytotoxic effects.

Perturbation of the production of neonatal thyroid hormone and hypothyroidism have been attributed to the use of povidone-iodine in neonates. Thyrotoxicosis has been reported in a 72-year-old man from the application of povidone-iodine to pressure ulcers. Some authors have disputed that the excess iodine available from povidone-iodine causes hypothyroidism in infants. Percutaneous absorption of excess iodine may be due to an immature skin barrier or the high surface-weight ratio. Regarding elderly skin, Kanj and Phillips identify slow replacement of neutral lipids as the reason for adverse barrier function. This may explain the excessive absorption of nonionized, topically applied iodine in the elderly. Niedner defends the use of povidone-iodine with his conclusion that in vitro experiments showing cytotoxicity are not easily transferred to in vivo circumstances. The Purdue Frederick Company reported povidone-iodine solution as the cause of injury to patients, more specifically, chemical contact dermatitis when povidone-iodine solution remains in contact with intact skin.

Andrews published a commentary in 1994 entitled “The Perils of Povidone-Iodine Use.” The central themes were that “research has demonstrated the harmful effects of the use of povidone-iodine in wound care and nursing practice related to wound care needs to be evaluated.” Andrews’ commentary prompted a flurry of correspondence from people who sought to explain and defend the use of povidone-iodine in wound care. The commentary by Welch revisits clinical studies that defend the use of povidone-iodine in wound care. The correspondence by Rodeheaver defends Andrews’ position and directs the reader to the differences in Andrews’ and Welch’s observations. Andrews treated a full-thickness wound, whereas Welch cited results obtained from superficial wounds. The position of Rodeheaver can be summarized with the following salient point: “until results have been obtained in controlled human trials on full thickness wounds, the repeated use of topical povidone iodine solution in full thickness wounds should be avoided.” In his correspondence, Mayer recognized that iodine absorption and toxicity can be significant with the indiscriminate use of povidone-iodine in humans. He states that high anion gap metabolic acidosis, cardiovascular instability, renal insufficiency, and even death have been linked to high serum iodine concentrations that result from povidone-iodine use. However, Mayer offers a common denominator in most of these adverse events: either continuous irrigation or the application of povidone-iodine to extensive wounds involving 25% or more of the body surface area. Mayer concludes his correspondence with the position that products containing povidone-iodine pose no significant hazard to wound healing. Finally, Welch reports that the use of Betadine Microbicides (povidone-iodine; Purdue Frederick Co, Stamford, Connecticut) in either infected or noninfected human volunteers has no effect on wound healing.

Howell and Chisholm conducted a national survey to examine outpatient wound preparation and care in US emergency departments. They determined that antiseptics used to clean traumatic wounds varied among practitioners. The results indicated that 13% still used hydrogen peroxide, whereas 11% used povidone-iodine solutions and 25% scrubbed with chlorhexidine. A reason for these results may be found in the practice directive by Dearden et al. It explains that research on antiseptic therapy for traumatic wounds is not sufficient to direct practice. Although antiseptics should not be used routinely, certain solutions may be used on a one-time basis. The use of antiseptics on wounds is currently being viewed with skepticism.

The early observations of Fleming on the effects of antiseptics on open wounds form the foundation for clinicians who argue against the use of antiseptics on open wounds. Fleming observed that antiseptics are not as effective against bacteria that reside in wounds as they are against bacteria in vitro. On the other hand, Mertz et al conducted bacterial studies demonstrating that antiseptics can decrease bacterial counts in open wounds.

The second argument against the use of antiseptics is perhaps the strongest among clinicians. Antiseptics have been found, primarily using in vitro models, to be cytotoxic to cells essential to the wound-healing process, such as fibroblasts, keratinocytes, and leukocytes. The results of human studies have failed to confirm the pronounced cytotoxicity found in the in vitro reports. Most clinical trials have found that antiseptics seem to be safe and not detrimental to wound healing. Further randomized controlled studies to evaluate the effect of each antiseptic on all types of wounds are indicated to provide greater evidence regarding the benefits of antiseptic use on wounds.

Singer et al explain, by citing the investigation by
that many irrigation fluids have been studied but that saline remains the most readily available, economic, and effective. Gouin and Patel compared saline with chlorhexidine (2%) and povidone-iodine (10%) on minor wounds (abrasions, bites, and lacerations) and found that sterile saline is the least toxic solution for wound irrigation. Therefore, sterile saline may be considered the “gold standard” of irrigating solutions.

Lawrence stated that the merits of irrigation fluids have received little scientific study. This author presented objective animal and cell culture data that describe the effects of topical antiseptics on wound healing in an attempt to clarify the use of antiseptics on traumatic, acute wounds. Siwek et al defined levels of clinically based evidence on a scale from A to D: level A-rated evidence involves high-quality randomized controlled trials with or without meta-analysis; level B ratings include nonrandomized clinical trials, clinical cohorts, case-control studies, historical controls, and epidemiologic studies; level C defines research consistent with consensus and expert opinion; and level D-rated research involves anecdotal evidence and in vitro or animal studies. Most studies that involve the use of antiseptics in acute traumatic wounds are rated level D. The recommendations to avoid the use of 0.25% acetic acid, 3% hydrogen peroxide, and 0.5% sodium hypochlorite because of the potential for cell damage are grounded in level D clinically based evidence. The adverse events reported as a result of these agents have been translated as anecdotal evidence, expert opinion, and consensus, elevating the clinical evidence to a level C rating. The evaluation and observations by Mayer and Tsapogas on povidone-iodine use in wounds are grounded in level B clinical work. The clinically based evidence reveals that povidone-iodine, when used appropriately, poses no significant hazard to wound healing.

**Conclusion**

This review was intended to critically evaluate the potential harm to patient outcome of the use of antiseptics on acute wounds. Animal and cell culture data that describe the effects of topical antiseptics on wound healing were presented. Human case studies that document the potential harm of the indiscriminate use of antiseptics were offered. Finally, data from previously published reviews were presented and evaluated for clinically based evidence to justify the current practice of antiseptic use in acute traumatic wounds.

The podiatric physician must remember that wound healing in humans is a complex and dynamic process. Because of this complexity, no correlation has been clearly established between results obtained in laboratory in vitro models and clinical human observations. Antiseptics have been found, primarily using in vitro models, to be cytotoxic to fibroblasts, keratinocytes, and leukocytes. The results of human studies have not confirmed the pronounced cytotoxicity found in the in vitro reports. Most clinical trials have found that antiseptics seem to be safe and not detrimental to wound healing. Specifically, povidone-iodine poses no significant hazard to wound healing.

Controversy still surrounds the use of other antiseptic agents because of the lack of a sufficient number of human studies to be accepted as clinically based evidence. Until this evidence becomes available, the indiscriminate use of acetic acid, hydrogen peroxide, and sodium hypochlorite should be carefully evaluated by the podiatric physician when treating acute traumatic wounds.

**References**

1. **ASSOCIATED PRESS**: 103,000 die from hospital infections, Daytona News Journal, July 22, 2002, p 1A.