Abstract: Introduction. Topical application of acids, such as citric acid, acetic acid, ascorbic acid, boric acid, and algic acid, to wounds to control infection and to promote healing has been reported in various earlier studies. The present review summarizes the role of surface pH and acidic environment in the process of wound healing, and attempts to cover recent developments in wound healing with special reference to acidic environment and its physiological effects on the wound healing process. Methods. A literature search was performed in PubMed using appropriate keywords, as well as a manual search using references cited in original publications and relevant review articles. Out of 115 articles found, 45 of the most relevant articles were evaluated and analyzed, and relevant data were included. Results. The studies show that an acidic environment created by use of acid helps in wound healing by controlling wound infection, increasing antimicrobial activity, altering protease activity, releasing oxygen, reducing toxicity of bacterial end products, and enhancing epithelization and angiogenesis. Conclusion. The current review of the literature indicates the acidic environment plays an important role in the promotion of wound healing.

Key words: acidic environment, surface pH, wound healing
toxicity. Therefore, pH value affects the regular cellular events in wound healing. It has also been observed that wounds with a high alkaline pH have a lower healing rate in both acute and chronic wounds as compared to wounds with a pH closer to neutral. Wound healing progression decreases when pH is elevated to alkaline condition. The environment of acute as well as chronic wounds progresses from an alkaline state to a neutral state and then to an acidic state when healing begins.5-9

This literature search on chronic wounds shows that the complex process of healing an infected wound can be affected by surface pH. This review highlights the importance of an acidic environment and its physiological effects on the wound healing process.

Methods
A literature search was performed using PubMed, as well as a manual search using references cited in original publications and relevant review articles. For the search of the PubMed database, the key words used were “acetic acid,” “ascorbic acid,” “boric acid,” “citric acid,” “acid environment,” and “surface pH.” All studies commenting on the role of acid in wound healing were included in the present review. A large number of papers reporting use of acetic and citric acids for treatment of infected wounds, and showing primitive and similar types of results were excluded. A few papers reporting use of other acids with primitive and inconclusive findings were also excluded. A total of 115 articles were found, out of which 45 of the most relevant articles were included in the present review. All included studies were evaluated and analyzed, and all relevant data were included.

Results
Using the previously listed key words, a total of 115 articles pertaining to acidic environment and wound healing were found. After reading the title and abstracts, 70 articles out of the 115 were excluded because of repetitive or similar findings. The findings of 45 different studies were analyzed and evaluated, and the detailed results of these studies are presented in Tables 1 and 2.

These studies show that an acidic environment created by use of acids, such as acetic acid, boric acid, ascorbic acid, alginic acid, and hyaluronic acid, help in wound healing by controlling wound infection, increasing antimicrobial activity, altering protease activity, releasing oxygen, reducing toxicity of bacterial end products, and enhancing epithelization and angiogenesis.

Discussion
Use of acids for treatment of wounds. The use of various acids, such as acetic acid, boric acid, ascorbic acid, and hyaluronic acid, has been reported for the treatment of skin and soft tissue infections, and burn wound infections in various earlier studies. For the past 19 years, the authors have used citric acid in their practice for the effective treatment of chronic wound infections caused by a variety of bacterial pathogens, and for the treatment of chronic wounds that are not responding to conventional injectable or oral antibiotic therapy and local wound care management. Efforts to decrease wound surface pH using topical agents have had varying degrees of efficacy. Dilute acetic acid has been successfully used for the treatment of skin and soft tissue infections, and burn wound infections caused by Pseudomonas aeruginosa. Acetic acid in 1% and 5% concentrations has been widely used in an attempt to reduce pH. Application of sterile gauze swabs soaked in 1%-5% concentrations to ulcers and burn wounds has been used in different studies.10-14 Topical application of acetic acid in a concentration of 5% to burn and soft tissue wounds has been found to be an effective treatment for P. aeruginosa infec-

Keypoints
- The pH value within the wound milieu directly and indirectly influences all biochemical reactions taking place in the process of wound healing.4
- The environment of acute as well as chronic wounds progresses from an alkaline state to a neutral state and then to an acidic state, when healing begins.5-9

Keypoints
- A literature search was performed in PubMed, using key words “acetic acid,” “ascorbic acid,” “boric acid,” “citric acid,” “acid environment,” and “surface pH.”
- A manual search using references cited in original publications and relevant review articles was also completed.
- A total of 115 articles pertaining to acidic environment and wound healing were found; 70 were excluded because of repetitive or similar findings.
- The findings of 45 different studies were analyzed and evaluated, and the detailed results of these studies are presented in Tables 1 and 2.
Keypoints

- Irrigation of wounds with acetic acid solution,\textsuperscript{15} 3% percent boric acid,\textsuperscript{16} and 2% ascorbic acid\textsuperscript{17} have proved to be effective in clearing \textit{P. aeruginosa} from various wound types.
- Hyaluronic acid to wounds was found significantly more effective and safe in the treatment of leg ulcers of venous or mixed origin.\textsuperscript{18}
- Based on these studies, the authors initiated the successful use of citric acid in a concentration of 2%-3% for the treatment of pseudomonal wound infections.\textsuperscript{19,21}

Role of Acid in Wound Healing

The application of acid significantly contributes to the wound healing process in the following ways.

Infection control. Infection is one of the most prevalent causes for nonhealing and chronicity of wounds.\textsuperscript{31,32} Chronicity begins with bacteria. The presence of bacteria and bacterial products, such as endotoxins and metalloproteinases, can cause disturbances in the orderly scheme of wound healing, thereby affecting each of the phases of healing.\textsuperscript{31,32} Thus, infection is a common reason for poor wound healing, especially in chronic wounds, so significant reduction in the number of bacteria is important in the management of chronic wounds. Most of the pathogenic bacteria associated with infected wounds in humans need a pH value > 6; their growth is inhibited by lower pH values.\textsuperscript{33-35} Applying acids to the wound surface lowers the pH of the infected surfaces and makes an environment unsuitable for the growth and multiplication of the bacteria. This has been proved by microbiological studies and the rapid clearing up of infected surfaces.\textsuperscript{36} Thus, application of acid is effective in clearing bacterial pathogens from contaminated or infected wound beds by creating an acidic environment unfavorable for the growth of bacterial pathogens present on the wound surface (Table 1).

Increase in antimicrobial activity. Various acids have been shown to increase the antimicrobial activity of topical antimicrobials such as iodine and silver that are incorporated into wound dressings.\textsuperscript{37,38} The bioavailability of active free metal ions in a wound is affected by numerous factors including the metal ion solubility which is known to increase with a decrease in pH.\textsuperscript{39,40} It has been experimentally proven that pH affects the activity of silver-containing wound dressings on antibiotic-resistant bacteria.\textsuperscript{38} It has been found that a decrease in pH from 8.5 to 5.5 enhances the activity of silver dressings against both gram-positive and gram-negative bacteria.\textsuperscript{38} These findings substantiate that pH of the wound surface plays an important role in antimicrobial activity and enhances the performance of silver.\textsuperscript{41} It has been shown that the use of 2% ascorbic acid to create an acidic medium in tropical climates, where the warm weather and alkalinity of the medium renders 0.1% silver sulfadiazine less effective, potentiates the effect of silver sulfadiazine, thereby making it more effective.\textsuperscript{17} The alginate wound dressings contain-
ing alginic acid make the wound environment slightly more acidic, which helps to enhance the performance and bioavailability of ionic silver present in alginate wound dressings. By ensuring maximum antimicrobial performance of a wound dressing, it could be possible to achieve positive clinical outcomes. The silver alginate dressing demonstrated a broad spectrum of antimicrobial barrier activity within the dressing against all wound isolates including *Candida albicans* and a vancomycin-resistant *Enterococcus* strain at a pH of 5.5 compared with a pH of 7.

**Alteration of protease activity.** Proteases are enzymes with the ability to cleave proteins. They are produced by the wound itself as well as by bacteria. The enzymatic activity of proteases is dependent on the amount of proteases and presence of protease inhibitors. Every protease enzyme shows optimum and maximum enzyme activity at a certain pH value, at which the protein is broken down more rapidly than at other pH values. For example, the enzymes elastase and plasmin show optimum enzymatic activity at a pH of 8, neutrophil elastase is maximally active at a pH of 8.3, and the enzyme urease, produced by bacteria, is more active in alkaline conditions. It appears proteases are more active in alkaline conditions and their end products are toxic to wound tissues. The lowering of pH to a more acidic environment may reduce the activity of these enzymes, thereby reducing the formation and toxicity of their end products.

**Release of oxygen.** Oxygen is the basic requirement for survival of cells in the human body and oxygenation of wounds is of vital significance in the wound healing process. It has been observed that a lower degree of oxygenation impairs immunity and the process of wound repair. The majority of the oxygen is required for oxidant-radical production (ie, for killing bacteria). This is a mainstay of immunity to bacterial infection caused by staphylococci, *E. coli*, *Klebsiella*, and other bacteria commonly involved in wound infections. Oxygen is also required for collagen synthesis and epithelization. The release of oxygen is influenced by the acidic environment. A low pH value leads to the Bohr-effect (ie, an increase of the amount of available oxygen of cells). The delivery of oxygen to damaged tissue, especially in chronic wounds, depends on perfusion as well as diffusion. Improvement in tissue oxygenation increases resistance to infection and promotes healing. A lowering of pH by 0.6 units releases 50% more oxygen and a shift of pH by 0.9 units causes 5-fold increase in release of oxygen. The local tissue oxygen partial pressure (PO2) is needed to force oxygen into injured and healing tissues. The process of wound healing, especially in chronic wounds, is comparatively higher if PO2 is > 40 mm Hg; however, the healing process is impaired when a PO2 is < 20 mm Hg. It has been observed that any factor that could cause even a small change in pH of the wound may appreciably alter the available supply of oxygen to the tissues and impair the process of

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<th>Table 1. Effect of acids against various bacterial pathogens.</th>
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Note: A = Strong; B = Moderate; C = Average

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wound healing. The PO$_2$ also affects replication of fibroblasts that occurs optimally at a PO$_2$ of about 40-60 mm Hg. Epithelial cells are also affected by PO$_2$, and it has been demonstrated that epithelization occurs better in well-oxygenated tissues. This also explains the effectiveness of hyperbaric oxygen therapy.

Reduction of toxicity of bacterial end products. Lowering the pH and creating a more acidic environment also reduces the toxicity of bacterial end products such as ammonia, which is liberated from urea by the action of the enzyme urease. Ammonia is toxic to wound tissue and also leads to an alkaline environment, which is not suitable for the wound healing process.

Epithelization and angiogenesis. The acidic environment also promotes epithelization and angiogenesis. In a histopathological study on chronic wound infections, use of citric acid was shown to enhance epithelization and found to actuate the wound healing process by boosting fibroblastic growth and neovascularization, which increases microcirculation of wounds that enables the formation of healthy granulation tissue, thereby leading to faster healing of wounds. One of the important reasons for promotion of epithelization is increased oxygenation of local tissue because of the acidic environment.

Other effects. In addition to the effects on protease activity and oxygen release, the acidic environment also enhances the destruction of abnormal collagen in the ulcer bed, increases macrophage and fibroblast activity, and controls activities of various enzymes participating in the wound healing process (Table 2).

### Conclusion

The results of different studies on the use of various acids for the treatment of wounds show the acidic environment helps in wound healing by controlling wound infections, increasing antimicrobial activity, altering protease activity, releasing oxygen, reducing toxicity of bacterial end products, and enhancing epithelization and angiogenesis. The results of this literature review also suggest that monitoring wound pH may help in the evaluation of treatment progress. The authors conclude that creating an acidic environment in a wound bed has an additional benefit that positively influences the wound healing process.

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