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A Review on Antimicrobial Silver Absorbent Wound Dressings Applied to Exuding Wounds

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Abstract

Exuding often occurs in the inflammatory stage both for acute wounds and chronic wounds. Absorbent wound dressings are specially developed and used in exuding wounds. In order to reduce bacteria and risk of infection, many absorbent dressings are impregnated with silver ions or particles which are the most widely used substance to obtain antimicrobial effects and therefore this review focuses on the antimicrobial absorbent dressings treated with silver ions or silver particles. The methods of dispersing silver in dressings include coating or spraying silver-containing solution on the wound dressing surface, padding the wetted dressing with pressure, embedding silver nanoparticles in non-woven fibers. When silver dressings absorb exudate from wounds, the antimicrobial silver will be activated and then breaks down the bacterial cell wall to kill the bacterium. Silver foam dressings and silver alginate dressings are the most popular antimicrobial absorbent dressings, which have been developed and produced by many health care companies.

Keywords: Wound dressing; Absorbent dressing; Antimicrobial dressing; Exuding wound

Introduction

Skin is the largest organ in the human body, which plays a crucial role as a protective barrier to the external environment, preventing external noxious agents such as bacteria and viruses and maintaining the internal environment through the regulation of water and electrolyte balance and thermoregulation. It is crucial to keep its integrity, as these functions are no longer adequately performed when this barrier is disrupted and damaged due to any cause (mechanical injuries, ulcers, burns, neoplasm or surgical trauma) [1,2].

Since the principles of maintaining a moist wound environment have evolved into a science, the wet environment created by great amounts of wound exudate becomes favorable to the wound healing process. Absorbent wound dressings are designed to quickly absorb exudate from the wound and retain these fluids inside their space zone to offer a moist environment to the wound. However, the moist and warm dressing may give large chances to bacteria proliferation. Bacteria and other organisms in the exudate have an adverse effect on wound healing process which may prolong inflammatory stage and cause infection, even lead to acute wounds convert to hard-to-heal chronic wounds. As silver is one of the most commonly used antimicrobial agent, considerable absorbent dressings including foams and alginates have been impregnated or embedded with silver to reduce both the dressing and wound microbial bioburden [3].

Wounds and Wound Healing Process

Types of wounds

A wound is defined as a defect or a breakdown in the protective function of the skin [4]; the injury in the epithelial integrity of the skin or underlying tissues/organs resulting from physical or thermal damage including surgery, cuts, scratches, pressure, burns, puncture and immunodeficiency or disease [1,5]. The severity of a wound depends on diameter and depth of the wound and the damage caused in the epidermis and dermis layers of the skin [6,7]. It takes several days or weeks for a wound healing process which ends with wound closure [8,9].

Many ways have been used to classify wounds and there is no standard classification for wounds. According to the healing duration of a wound and the nature of the repair process, it can be classified as acute or chronic. Acute wounds usually happen in a short time, heal rapidly and can be predicted by the repair process [10]. Most of them heal completely and uneventfully resulting in durable closure with minimal scarring and no complications, in 8 to12 weeks [2,4]. Acute wound fluid helps to stimulate fibroblasts and to produce endothelial cells which contain rich leukocytes and essential nutrients [11,12]. This presents as serous fluid in the wound bed and support the normal wound healing process in acute wounds [13]. Acute wounds are usually traumatic or surgical tissue injuries [10].

The healing process and pattern of chronic wound are different from acute wounds. Chronic wounds are difficult to heal or take a long time to heal and might have some complications [14]. It is caused by the defective remodeling of the ECM, which is a result of the failure to reepithelialize and reduction of growth factors [15-18]. In addition, chronic wound fluid has high levels of proteolytic enzymes having an adverse effect on wound healing by interfering cell proliferation, particularly of keratinocytes, fibroblasts and endothelial cells [18,19]. With this understanding of these differences between acute and chronic wound, principles of selecting different dressing methods are established. To convert chronic wounds to acute wounds is a possible way for healing chronic wounds in a short period.

Wound healing process

The healthy skin and underlying tissues can be divided into five major parts as shown in Figure 1: epidermis, corium, sub cutis, fascia and muscle [11]. When skin suffering from a mechanical injury or irritation or some disease, a breach with certain width and depth will

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occur on the skin. To make this breach contracted and then occlusive is the process of a wound healing.

Wound healing is a dynamic and complex process. Simply, the wound healing process is a general phenomenon of growth and tissue regeneration. For the normal wound involve a series of coordinated events, including bleeding, phagocytosis, chemotaxis, coagulation, initiation of an acute inflammatory response to the initial injury, regeneration, migration and proliferation of connective tissue and parenchyma cells, as well as synthesis of collagen and extracellular matrix components, remodeling of new parenchyma and connective tissue and collagen deposition [20].

The current wound healing model consists of four general phases [21-26]: (i) the coagulation and haemostasis phase, which begins immediately after injury; (ii) the inflammatory phase, which occurs shortly after injury to tissue and during which swelling takes place; (iii) the proliferation period, in which new tissues and blood vessels are formed; (iv) the maturation phase, in which tissues laid down during the proliferation stage are remodeled. These activities occur in an ordered manner overlapping with each other, and they are in a well-connected cascade [27,28]. The overlap of these stages of healing is illustrated in Figure 2 [1]. The entire process can last for many months.

The appearance of wound in the four phases may change from black to yellow, then red and finally pink. The four colors to some extent overlap with the above four healing phases, but they are not identical. Table 1 summarizes the clinical manifestation and wound care methods of different phases in wound healing process.

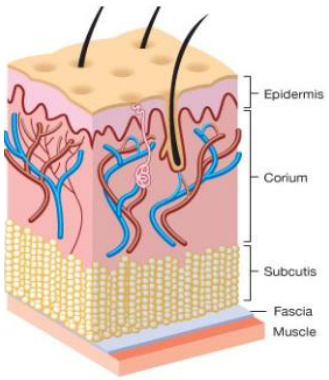

Figure 1: The structure of the skin [11]..

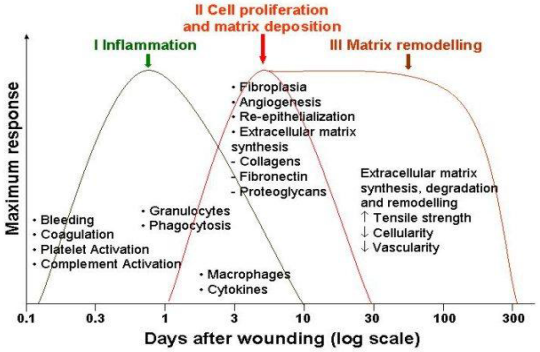

Figure 2: Phases of repair in normal wound healing [1].

Periods of wound healing process	Black period	Yellow period	Red period	Pink period
Clinical evaluating	Eschar-black/ brown necrotic tissue, can be hard or soft, with or without light exudate	Slough-yellow, tan dead tissue (devitalized), moderate exudate	Red, cobblestone appearance (healing, filling in), heavy exudate (decreasing)	Epithelization, dimension reduction, less exudate
Aims of wound care	To remove eschar	To clear decayed tissue	To absorb exudate, keep moist wound environment, and accelerate granulation	To protect new epithelial tissue
Recommended wound dressings	Hydrogel	Hydrogel and films/foam dressing	Foam dressing, alginate dressing	Films dressing

Table 1: Four phases of wound healing process.

Table 1 shows that the red period has the most heavily exuding. The absorbent wound dressings are recommended according to the moist wound healing principle which was initially discovered by Since George Winter in 1962 [29]. He found that occlusive dressing facilitated epithelialization in porcine wounds, and therefore he concluded that maintaining a moist wound environment was beneficial to the wound healing. Contrary to the traditional concept that a wound should be dry to form a scab and promote healing, wet environment instead can lead to maceration and tissue breakdown to allow a wound heals faster. According to this, sophisticated dressings providing moist, absorbent, interactive and non-toxic environments for healing was developed, but they were not suitable for all wounds and sometimes need to be monitored closely to avoid clinical infection.

Absorbent wound dressings

General wound dressing concept: According to the moist healing process, a moist wound environment is the key factor to debridement and is obtained by using occlusive or semi-occlusive absorbent dressings [30-32]. There are a variety of methods that can be used to dress an exuding wound and keep a moist environment [33]. So the healing of a wound depends not only upon medication but also upon the use of proper dressing techniques and suitable dressing materials. The ideal characteristics of a wound dressing include: [34-36]

- Impermeability to water and bacteria;
- Freedom from particulate matter;
- Thermal insulation;
- Absorption and retention of exudate;
- Prevention of trauma on removal;
- Removal of toxic substances;
- Prevention of dehydration;
- Allowing for gaseous exchange;
- Pain relief and comfort.

Modern dressings are required to create the optimal environment for wound healing. They should be easy to apply and can reduce the nursing time with fewer dressing changes and pains of removal with less adherence between wound surface and dressing layer [7,37,38]. A modern absorbent wound dressing normally consists of three layers,

i.e., an absorbent layer, a wound contact layer and an out layer. The absorbent layer is used to absorb exudates, blood and body fluids, providing a humid environment on the wound surface. The wound contact layer with low adherence should easily be removed with less pain and less disturbing for new tissue growth. The outside layer is an adhesive diffusion layer. While fixing a wound dressing on the skin, the outer layer can provide a barrier against microorganisms, dirt and other foreign substance. A modern wound dressing model from literature [7] is presented in Figure 3.

Exudates and absorbent dressings: Based on the types of wounds and periods of healing, different wound dressings are available for the effective management of wounds [23,39,40]. Since this review focuses on the absorbent dressings for exuding wounds, reducing exudate levels is the main task for absorbent dressing. A balance of the degree of wet is vital to an exuding wound. A dry wound bed may cause the underlying collagen matrix and the surrounding tissue becoming desiccated, which inhibits the contraction and healing of the wound [41]. A moist wound environment is mainly sustained by exudate. The exudate mostly consists of water, but it also contains electrolytes, nutrients, proteins, inflammatory mediators, proteases such as matrix metalloproteinases (MMPs), growth factors and waste products, as well as white blood cells such as neutrophils, macrophages and platelets [40, 42,43]. The wound exudate is produced by vasodilation during the early inflammatory stage of healing under the influence of elevated levels of inflammatory mediators and activators such as histamine and bradykinin [13,44-46]. However, an excessive exuding wound may prevent cell proliferation and lead to maceration and excoriation of skin [43]. Both dry wounds and wet wounds can be painful and discomfort to the patient [19]. The appropriate dressing may create an optimal wound healing environment. It helps to reduce the times of dressing changes, reduce pain and skin maceration, accelerate wound healing, be cost-effective and improve patient's life quality. The exudate management of dressing is carried out through absorbing it and/or allowing it to evaporate or some of them form a gel with the exudate. Today, advanced absorbent dressing materials include cotton, viscose or polyester textiles, polyurethane or silicone foams, alginates, hydrocolloids and Hydrogels [43,47]. Besides traditional gauze dressings, the most popular absorbent dressings in the market, foam dressings and alginate dressings as well as the relevant silver-containing dressings will be discussed below.

Silver absorbent dressings

Infection and pathogens: Wounds may be contaminated by bacteria when being impregnated to soil or road dirt. The hypoxia and destruction of wound during dressing may increase the amount of necrotic tissue and debris in the wound to support bacterial growth. The continued presence and multiplication of bacteria may potentiate the inflammatory and raise the risk of infection [3,48].

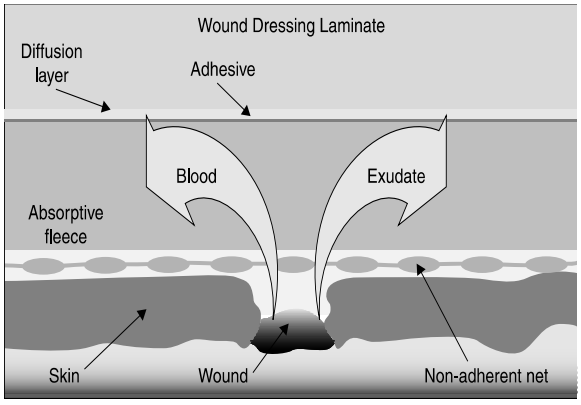

Figure 3: The modern wound dressing model [7].

Infection occurs when pathogens such as bacteria, fungus, viruses, parasites and other living microbes enter wound tissues from wound surface. The common microorganisms causing infection include *Corynebacterium*, *Propionibacterium*, coagulase-negative *Staphylococcus* and viridans streptococcus from surrounding skin; *Staphylococcus aureus, Escherichia coli*, *Klebsiella*, *Proteus* from external environment, and Streptococcus, coliforms and anaerobes (*Prevotella*, *Bacteroides* and *Peptostreptococcus*) from deep wound [49,50]. The existence of a wound means the skin, the first line of defense to foreign invaders, has been damaged. The colonization and invasion of bacterium compete for nutrients that are limited and helpful to wound healing. Bacteria release harmful proteins to blocking proliferation of skin cell or kill normal cells, preventing the formation of collagen and cross-linking, and therefore reducing cellular activities and tissue repair. These damages may result in increased exudate, odor, pain, and even the alteration of acute wound to non-healing chronic wound [50,51]. Consequently, an antimicrobial dressing is necessary for preventing infection.

The Antimicrobial Action of Silver Dressings

Antimicrobial wound dressings are helpful for patients to reduce risk of infection and get rid of suffering pain. Silver is a widely used antimicrobial agent in health care products. It has been applied for centuries in sanitization, health care, and to inhibit bacteria in food, but it has only been introduced into wound care as an antibacterial in recent years. The metallic silver (Ag) has no antibacterial action or ionic charge, whereas its cation (Ag^+) is highly reactive. Organisms do vary in their susceptibility to silver, but it has been proved that silver has activity against the commonly encountered pathogens, *Staphylococcus aureus*, *Escherichia coli* and *Pseudomonas* spp. Although the mechanism of the antibacterial action of silver to gram-positive and gram- negative bacteria is still not fully understood, more and more researchers found the changes of cell morphology when bacteria contacts with silver ions or particles. The interaction between silver and bacterium cell results in the shrinkage of cytoplasm membrane and the separation of cell wall. The breach of cell wall allows cellular contents diffuse in exterior and finally causes the death of cell [52].

Silver ions or silver particles are usually added to the dressing through coating on dressing surface or mixing in the composite before molding. Coating is a commonly used method to give a material specific performance on its surface. Solutions with silver ions or particles can form a continuous film on the surface of dressing matrix. Spraying also can spread liquid on surface but the liquid is poor dispersed. Another way to treat a material with solution is to pad the wetted material with pressure. The liquid permeation could be controlled with padding pressure, but the whole material would be wetted and squeezed instead of the surface. For alginate fibers or hydrocellulose, silver particles could be embedded in the dressing by blending silver particles with spinning solution [53].

Silver ion or nanoparticles in absorbent wound dressing can react with and destroy the bacteria contained in exudate. Figure 4 is developed by Smith & Nephew Cooperation to illustrate how silver foam dressing (Allevyn Ag) works [54]. The dressing attracts bacteria while absorbing exudate (Figure 4a); the antimicrobial silver has been

released and activated (Figure 4b); silver weakens and breaks down the bacterial cell wall, and interferes with cell metabolism in a variety of ways, thereby killing the bacterium (Figure 4c).

Traditional silver gauze dressings

Generally, cotton gauzes are applied as dressings because they are soft, flexible and cost-effective. Gauzes are the most commonly used wound dressings today. The traditional wet-to-dry technique utilizes saline-moistened gauze, which is applied over the wound and allowed to dry. When the gauze dressing becomes dry, adhering debris and necrotic tissue can be removed from the patient and wound debridement occurs [7,31].

A considerable amount of investigations have focused on cotton gauzes treated with silver antimicrobial agents. Mohamed Gouda [55] in situ synthesized and deposited nano-silver-oxide (nano-Ag-oxide) into cotton gauze fabrics by reduction of silver nitrate solutions. The reduction rate of colony count percent (RBC) of cotton gauze fabrics containing nano–Ag-oxide against gram-positive bacteria (*S. aureus*) was 99% and gram-negative bacteria (*S. typhimurium*) was 97%, higher than those obtained with gauze fabrics containing nano-Zr-oxide. It had obvious inhibitory effect against gram-positive and gram-negative bacteria and showed no clinical signs of skin irritation.

Parikh DV [56] developed an antimicrobial Ag/Na carboxymethyl cotton burn dressing by partial cation exchange of sodium from sodium carboxymethyl cotton gauze by silver nitrate. According to the positive antimicrobial evaluation results, the dressings containing the silver antimicrobial agent could protect wound surfaces from microbial invasion and effectively suppress bacterial proliferation. The increased retention of silver nitrate solution on the dressing lessened replenishment of solution, which would reduce nursing time.

A simple one step synthetic route was used to prepare silver nanoparticles by reduction of silver nitrate on cotton gauze [57]. The test result showed that the cotton gauze with silver nanoparticles inhibited different Candida strains and its antimicrobial activity was high. However, cotton gauze allows moisture to evaporate from the wound surface. Thus, gauzes tend to be dry rather than maintaining the moist environment to facilitate wound healing. In addition, cotton gauze is easily to adhere to the wound and requires frequent changes, causing trauma and pain to the patients [58].

Silver foam dressings

Foam dressings are generally made from polyurethane foam [59]. While all the foam dressings are hydrophilic, their absorbent rates and absorbency vary with composite and thickness. Fast absorbent rates can accelerate vertical wicking and keep exudate off the wound to decrease maceration. Good absorbency may allow the patients to change dressings less frequently. Some foam dressings provide absorption capacity up to 7 days [60]. A range of shapes and sizes are available for relieving pressure of challenging areas (Figure 5). Foam dressings are mainly applied to heavily exuding wounds, especially during the inflammatory phase following debridement and sloughing, when drainage is at its peak [61]. They are also recommended for deep cavity wounds to prevent premature closure as they can maintain a moist environment by absorbing exudate. Foams can be applied in weeping ulcers, such as venous stasis, but not recommended for dry superficial wounds.

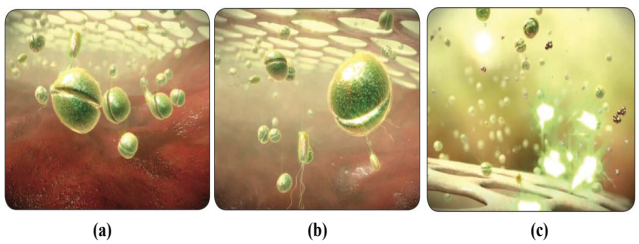

Figure 4: The antimicrobial action of silver in an absorbent wound dressing [54].

Foams may be impregnated or layered in combination with silver to improve their antibacterial performance and to promote wound healing process. A specialized antimicrobial silver foam dressing S-ROCF was evaluated in vitro for efficacy against Staphylococcus aureus and Pseudomonas aeruginosa pathogens. The antimicrobial testing result showed a 99.99% reduction in colony forming units, and continuously effective after 72 h of simulated V.A.C. Therapy. The antimicrobial and mechanical characteristics of the aged foam were found to be as good as unaged foams through an accelerated aging process [62].

Bo Jørgensen [63] discovered that the silver-releasing dressing, Contreet Foam, provided superior performance than traditional moist foam wound healing dressing, Allevyn Hydrocellular, in the treatment of chronic venous leg ulcers. There was a significant greater reduction in ulcer area, less odor and fewer leakages in the Contreet Foam group than in the Allevyn Hydrocellular group.

It was suggested that the silver-releasing foam dressing brought a great amount of benefits in the treatment of wounds. Their good absorbency reduced leakage and maceration to surrounding tissue, suggesting good exudate management capabilities. The antimicrobial performance of silver foams contributed to the healing process and the decrease of infection. They could also cut down the wound malodor by reducing maceration and infection. Currently, there are many silver foam dressings on the market, such as Allevyn Ag from Smith & Nephew, Mepilex® Ag with Safetac® technology from Mölnlycke Health Care, Biatain Ag Non-Adhesive or adhesive with a patented silver complex from Coloplast. Although silver foam dressings can solve tough problems during the exuding stage of healing process, the price of commercial foam dressing is very expensive, usually dozens of times higher than normal cotton gauze, which limits the utilization of foam dressings [64], especially in developing areas.

Silver alginate dressings

Alginate wound dressings are made of soft non-woven fibers derived from brown seaweed. When placed within the wound bed, alginate dressings react with serum and exudate by exchanging sodium ions with calcium ions that are exuded from the wound. The exchange in ions creates a fibrous gel, providing a moist and warm wound environment [65]. Three forms are available for alginate wound dressings (Figure 6). Alginate sheets may be placed on wound beds to absorb drained exudate. A collagen–alginate wound dressing is also an effective dressing for the management of foot ulcer [66]. A calcic-sodium alginate dressing was utilized as an effective dressing in the treatment of pressure ulcers, bleeding and/or infected vascular ulcers [67]. Alginate ropes are effective and easy to use for the treatment of cavity wounds by tightly filling wound tunnels or areas of undermining [68]. Alginate-tipped applicators can be used to probe wounds. Different from foams, alginate dressings have also been applied to donor site healing due to consistently better healing under the calcium alginate [46,69,70].

Figure 5: Foam wound dressings with different size and shape on the market.

Figure 6: Alginate wound dressings on the market.

However, a majority of alginate dressings may trap bacteria, which often gives rise to wound malodor and brings unpleasant experience to patients. Silver-containing alginate dressings can reduce bacteria in a certain degree. Yimin Qin [53] developed a silver-containing alginate dressing through first mixing a silver sodium hydrogen zirconium phosphate Alphasan RC5000 with sodium alginate solution, then suspending fine particles uniformly under a high rate of shearing, finally spinning fibers and forming non-woven alginate dressing. The result showed that these silver-containing alginates are highly effective against bacteria. Trial C [71] compared the efficacy and tolerability of the silver alginate matrix, Askina Calgitrol Ag with those of a standard silver-free alginate dressing, Algosteril. They were similar in the regression of local signs of infection, tolerance, acceptability and usefulness. However, Askina Calgitrol Ag improved the bacteriological status of the wounds. Steven L Percival [72] demonstrated the broad antimicrobial activity of a silver alginate dressing on wound isolates grown in the non-biofilm and biofilm state. It was found that the silver alginate dressing was able to inhibit the growth of all microorganisms tested, including strains of Candida albicans, meticillin-resistant Staphylococcus aureus, S. aureus, vancomycin-resistant Enterococci, Enterococcus faecium, staphylococci and viridans streptococcus.

Alginates are highly permeable and non-occlusive, and therefore they require a secondary dressing, most commonly gauze [66,67,73]. Except the combination with gauzes, alginate dressings have been used with carboxymethyl cellulose, showing a statistically significant improvement to healing [74]. The key point to solve the non-occlusive problem of alginates is to maintain the moist wound environment after absorbing several times mass of fluid.

Conclusion

Many ways have been used to classify wounds, acute and chronic wounds are classified based on the healing duration of a wound and the nature of the repair process. These two kinds of wounds follow different patterns of healing. Acute wounds heal rapidly and completely, whereas chronic wounds take a long time to heal. The wound healing process consists of four stages, hemostasis, inflammation, proliferation and remodeling. Exuding often occurs in the inflammatory stage when absorbent wound dressings are specially used. Bacteria from wound environment and exudate may cause infection, and therefore antimicrobial agents are necessary. As silver is the most widely used substance to obtain antimicrobial effects, a considerable amount of silver-containing absorbent dressings have been developed in recent years. The methods of dispersing silver in dressings include coating or spraying silver-containing solution on the wound dressing surface, padding the wetted dressing with pressure, embedding silver nanoparticles in non-woven fibers. When silver dressings absorb exudate from wounds, the antimicrobial silver will be activated and then breaks down the bacterial cell wall to kill the bacterium. Silver foam dressings and silver alginate dressings are the most popular advanced antimicrobial dressings, which are applied to exuding wounds and performed much better than traditional gauze dressings.

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