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The Burn Wound Healing Process A Review

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***Abstract*— Burn wounds are a serious injury that can lead to significant morbidity and mortality. The burn wound healing process is a complex and dynamic process that involves a number of different cellular and molecular events. The three main stages of burn wound healing are inflammation, proliferation, and remodeling. Inflammation is the first stage of burn wound healing. During this phase, white blood cells (WBCs) and other immune cells are recruited to the wound site to remove dead tissue and bacteria. The inflammatory response also produces a number of growth factors that stimulate the growth of new tissue. The proliferative phase of burn wound healing begins about 3-4 days after the injury. During this phase, new blood vessels, connective tissue, and epithelial cells are formed. The epithelial cells eventually form a new layer of skin over the wound. The remodeling phase of burn wound healing begins about 2 weeks after the injury and can last for months or even years. During this phase, the new tissue is reorganized and remodeled. The scar tissue that forms during this phase is usually thicker and less elastic than the original skin. The healing of burn wounds can be affected by a number of factors, including the size and depth of the burn, the patient's age and overall health, and the presence of infection. Complications of burn wound healing can include infection, sepsis, and death. The latest advances in burn wound treatment include the use of skin grafts, growth factors, and artificial skin substitutes. These advances have improved the healing of burn wounds and reduced the risk of complications.**

Keywords— burn wound healing; inflammation; proliferation; remodelling; complications; treatment.

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I. INTRODUCTION

Burns are a serious injury that can cause significant harm, even death. They can have a major impact on a person's health and well-being. Burns are defined as partial or complete destruction of body tissue due to direct contact with hot objects, flames, flashes, scalds, electricity, chemicals, and the sun.

Most burns only affect the skin tissue. However, some burns can damage deeper tissues, reaching the muscles, blood vessels, and even the bones. Burns that occur on the skin will cause a loss of protective function as the main barrier against bacteria, increasing the risk of infection. Extensive burns are correlated with increased morbidity and mortality, infection, electrolyte imbalance, hypovolemic shock and respiratory problems [1,2,3]. The severity of a burn is determined by the depth of the burn and the amount of body surface area that is affected.

Burns are classified into three degrees: first degree, second degree, and third degree. First degree burns only affect the outer layer of the skin, while second degree burns damage the epidermis and dermis. Third degree burns damage all layers of the skin, and may even extend to the muscles, bones, and nerves. The treatment for burns depends on the severity of the burn. First degree burns can usually be treated at home with cool compresses and antibiotic ointment. Second degree burns may require hospitalization for pain management, wound care, and antibiotics. Third degree burns often require skin grafts to cover the wound [4,5,6].

Burn wound healing is a complex and dynamic process that is affected by a number of factors, including the size and depth of the burn, the patient's age and overall health, and the presence of infection. The three main stages of burn wound healing are inflammation, proliferation, and remodeling [7,8,9].

Inflammation is the first stage of burn wound healing. During this phase, white blood cells (WBCs) and other immune cells are recruited to the wound site to remove dead tissue and bacteria. The inflammatory response also produces a number of growth factors that stimulate the growth of new tissue. The proliferative phase of burn wound healing begins about 3-4 days after the injury. During this phase, new blood vessels, connective tissue, and epithelial cells are formed. The epithelial cells eventually form a new layer of skin over the wound. The remodeling phase of burn wound healing begins about 2 weeks after the injury and can last for months or even years. During this phase, the new tissue is reorganized and remodeled. The scar tissue that forms during this phase is usually thicker and less elastic than the original skin.

Complications of burn wound healing can include infection, sepsis, and death. The latest advances in burn wound treatment include the use of skin grafts, growth factors, and artificial skin substitutes. These advances have improved the healing of burn wounds and reduced the risk of complications [10,11,12].

The purpose of this review is to provide an overview of the burn wound healing process. The review will discuss the three main stages of burn wound healing, the role of the immune system in burn wound healing, the factors that can affect the healing of burn wounds, the complications of burn wound healing, and the latest advances in burn wound treatment.

II. BURNS

2.1. Epidemiologi

Burn wounds are a prevalent health problem worldwide. Burn injuries can have serious consequences beyond increased mortality and treatment requirements. They can also lead to a higher risk of long-term health problems, which can adversely affect the affected individual's quality of life [13]. Burn injuries rank among the top four causes of trauma globally, following traffic accidents, falls from heights, and violence [14]. The incidence of burn wounds varies significantly across the world, often influenced by local factors in each country[15].

According to the World Health Organization (WHO), burns result in approximately 300,000 deaths annually worldwide, primarily in low- and middle-income countries (LMICs)[13]. WHO data estimates that more than 11 million people worldwide seek medical attention for burn injuries each year. In LMICs, burn wounds remain a complex issue compared to developed countries like the USA and Europe[16]. The incidence rate of burn wounds in LMICs is challenging to determine precisely. For instance, data from India indicate 700,000 to 800,000 burn cases per one billion population annually[17].

The causes of burn injuries vary across age groups in different populations. Research conducted by [18] revealed that burn

injuries in children aged 0 to 10 years could account for 64% of all cases within that age group. Burns in children are often caused by scalding from hot water, hot pots, hot beverages, and hot water in bathrooms. In contrast, burns in adolescents are predominantly caused by the use of matches and flammable liquids. In adults, the most common causes of burn injuries are electrical burns and chemical exposures[19]. However, overall, the incidence rates, severity, mortality rates, and hospitalization durations due to burn wounds vary significantly among different countries[20].

In Indonesia, despite the prevalence of burn cases, accurate data is not yet available, which is why the Ministry of Health of Indonesia did not include burn injury incidents in the 2017 Health Profile Report[21]. One of the reasons for this lack of data is the absence of burn treatment units in all hospitals. For instance, from 2007 to 2011, there were 605 burn cases reported in RS. Soetomo[3].

Most burn incidents, nearly 90% in the UK and USA, are classified as minor burns, often not receiving appropriate standard treatment. According to The Royal Perth Hospital Australia (2004), only 39% of minor burns receive appropriate care[22]. This data aligns with Ontario, Canada's emergency departments, where 70% of minor burn cases are neglected, and 45% are not managed with analgesics[23].

Another concern regarding burn wounds is their occurrence in children under six years of age, with a significant portion being younger than two years old. More than 80% of burn injuries in toddlers are classified as grade II burns, mostly caused by direct contact with hot water[18]. The incidence of burn injuries in children increases in low-income countries. WHO data from 2012 in the African region shows infant mortality rates three times higher than in other countries worldwide. Boys under five years old in low-income countries have twice the mortality rate compared to European countries[16].

The epidemiology of burn injuries is complex and there is still much that we do not know. However, it is clear that burn injuries are a significant public health problem that needs to be addressed

2.2. Patofisiology

Burn wounds are a significant threat to human health, as they can disrupt homeostasis and cause both local and systemic reactions that disrupt homeostasis[24,25]. The pathophysiology of burn injuries is influenced by the initial heat distribution upon contact with the skin, duration of exposure to the heat source, and the length of exposure. Burns caused by high temperatures and short exposure can result in similar degrees of injury compared to burns caused by lower temperatures but longer exposure [26,27]. Burn wounds can be categorized into several zones, with the first division described by Jackson based on local pathophysiological changes (Fig. 1) [26,28,29].

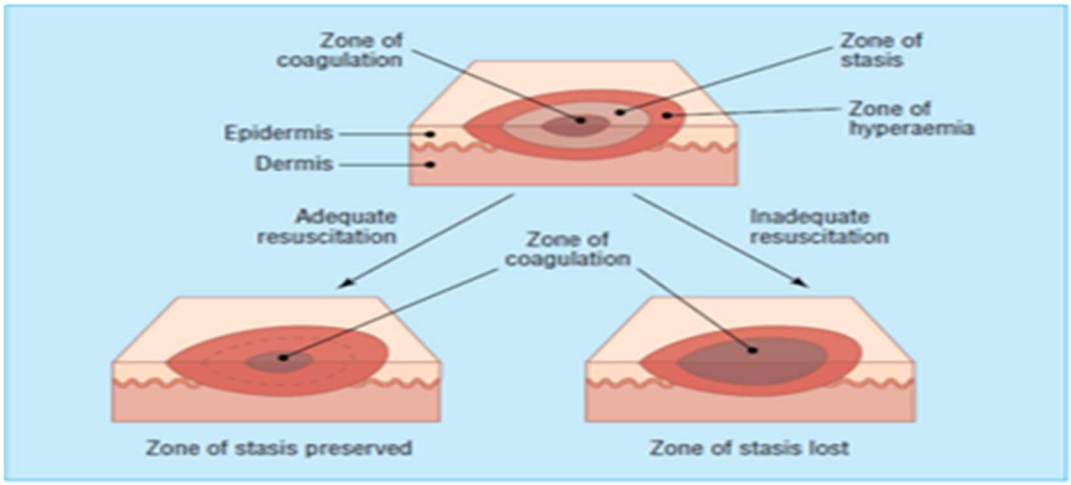

Fig. 1. Burn wound zones according to Jacson [29]

As depicted in Fig. 1 the zone of coagulation is the central part of the burn wound. This zone is characterized by irreversible cell death and no potential for regeneration. Adjacent to the zone of coagulation is the zone of stasis, where cells experience reduced blood flow. However, these cells can still be salvaged with fluid resuscitation and proper wound management. The outermost zone of the burn wound is the zone of hyperemia, where an inflammatory process occurs without tissue necrosis. This

zone is clinically manifested as a pinkish-red appearance[3,28].

Inadequate management of burn wounds can lead to continued ischemia, which can be aggravated by infection. This can result in irreversible tissue damage in the stasis zone. The body's response to burn injuries can also lead to further ischemia at the wound base. This is due to disturbances in blood vessels within the two outer zones, lead to increased capillary permeability. This causes fluid, protein, and electrolyte leakage, leading which lead to increased capillary permeability. This causes fluid, protein, and electrolyte leakage, leading to tissue edema. Fluid loss continues until the re-epithelization process occurs [24,30,31]. Burns surrounding the chest and limbs can cause compression and tourniquet effects, further contributing to tissue ischemia[28,32,33].

The skin is the outermost organ of the body and is inevitably damaged in burn injuries[24,30]. However, improper management can also lead to injuries to the respiratory tract and lungs, which can be life-threatening[28,32]. Endothelial damage from burns can trigger further cell damage due to blood vessel leakage[31].This is because the endothelium is the lining of the blood vessels, and when it is damaged, it allows fluid and cells to leak out of the vessels[30].

The immune response to burns can also contribute to this process. When the immune system is activated, it produces nitric oxide synthase (NOS), an enzyme that causes vasodilation, or widening of the blood vessels. This can lead to further vascular leakage and shock[30]. Shock is a life-threatening condition that occurs when the body does not receive enough blood flow. It can be caused by a number of factors, including burns.

Respiratory tract injuries can occur when burns affect the head and neck area, potentially leading to death if not promptly managed[1,2]. Moreover, systemic damage can occur when the total body surface area affected by burns exceeds 10%. Systemic reactions can cause severe disturbances in homeostasis, triggering the release of insulin-regulating hormones and pro-inflammatory cytokines, leading to hyperglycemia, hyperinsulinemia, hypercatabolic state, humoral and cellular immunodeficiency, fluid imbalance, temperature dysregulation, hemodynamic instability, and impaired nutrient absorption[26].

The systemic response to burns results in changes in the cardiovascular, respiratory, metabolic, and immune systems. Increased blood vessel permeability initiates cardiovascular changes, leading to protein and fluid loss to the interstitial space. Peripheral and splanchnic vasoconstriction follow, along with decreased myocardial contractility and tumor necrosis factor (TNF) release. This state occurs simultaneously with hypovolemia due to burn wounds, resulting in systemic hypotension and organ hypoperfusion[26,34]

At the molecular level, thermal injury triggers complement activation and neutrophil activation, leading to the production of cytotoxic reactive oxygen species (ROS). Increased histamine activity, assisted by xanthine oxidase catalytic agents, causes progressive local responses in blood vessel permeability due to burn wounds. Toxic compounds generated by xanthine oxidase, including hydrogen peroxide and hydroxyl radicals, directly contribute to skin structure damage[31,35,36]. Scarring is a common complication of burn wounds. The scar tissue is not as strong as the normal skin, and it may be different in colour. Contractures are a type of scarring that can cause the skin to tighten and pull the body parts together. This can limit the range of motion of the joints.

2.3. Burns Classification

Burn injuries are classified according to the depth of tissue damage: superficial-thickness burn (degree 1), superficial partial-thickness burn (degree 2), deep partial-thickness burn (degree 3), and full-thickness burn (degree 4)[26,33,37,38]. Superficial thickness burns occur due to brief exposure to heat/flames or prolonged exposure to sunlight, resulting in damage limited to the stratum corneum of the epidermis[37]. Clinically, first-degree burn wounds exhibit mild edema, dry skin, and healing within one week[25,31,38].

Second-degree burns, or superficial partial-thickness burns, involve damage that does not extend beyond the papillary dermis, presenting clinically with blisters with or without epidermal loss. The dermis base appears pinkish-red and moist, with minimal or absent capillary damage (Fig. 2. A). This condition can heal within +2 weeks with minimal scarring and does not require surgical intervention[33,38].

Third-degree burns, or deep partial-thickness burns, affect deeper layers of the reticular dermis. Clinically, third-degree burns exhibit epidermal loss, dry exposed areas that do not blanch upon pressure, reduced sensation in the damaged area, and often show damage to capillaries, especially when examined after 48 hours post-burn (Fig. 2.B). Healing for this type can take 3-4

weeks or more without surgical intervention, often leaving hypertrophic scars[3,31,38].

Full-thickness burns involve damage to the entire dermis, even reaching the bone. Clinically, full-thickness burns present with contractures and thick scar tissue. The appearance may vary, from second-degree burns resembling normal skin to completely charred tissue, depending on the intensity of heat exposure. There is no capillary refill, and occluded capillaries may be visible under the skin (Fig. 2. C). This condition also results in complete anesthesia, where the damaged area does not experience pain or bleeding even when punctured with a needle[3,39,40]

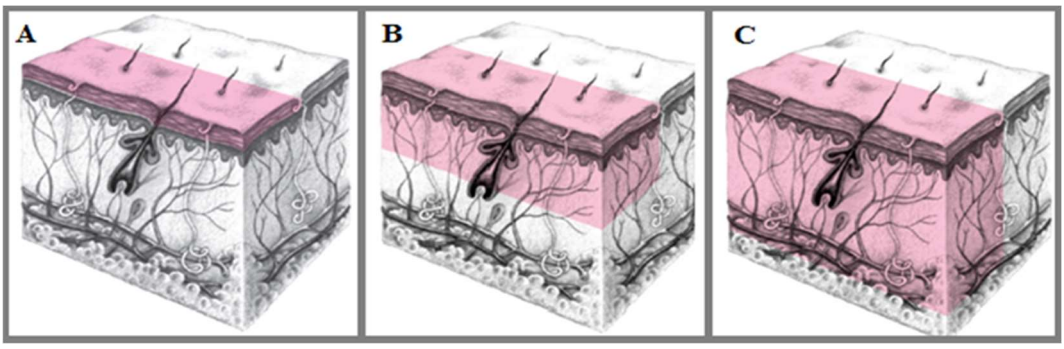

Fig. 2. Classification of burns based on depth of tissue damage[38]. A. Second-degree burn, or superficial partial-thickness burn. B. Third-degree burn, or deep partial-thickness burn. C. Fourth-degree burn, or full-thickness burn.

The depth of skin layer damage in burn wounds can be estimated based on their causes, as shown in Table 1, which presents burn injury factors and their resulting burn depths[41]. Burn wounds are more often superficial and caused by scalding water or hot objects. Burn management is based on the percentage of the body surface area (TBSA) affected by the heat exposure[42] (Fig. 3).

TABLE I. BURN CAUSES AND POSSIBLE DEPTHS [41]

Cause of Burn	**Possible Burn Depth**
Boiling water/ hot objects	Superficial, but may involve the dermis if not properly treated, especially in infants.
Hot oil	*Deep dermal*
Flame	Mixed deep dermal and full thickness
Bases, including cement	Often deep dermal or full thicknes*s*
Weak acid	Superficial burn
Strong acid	Deep dermal burn
Electrical contact	Full thickness

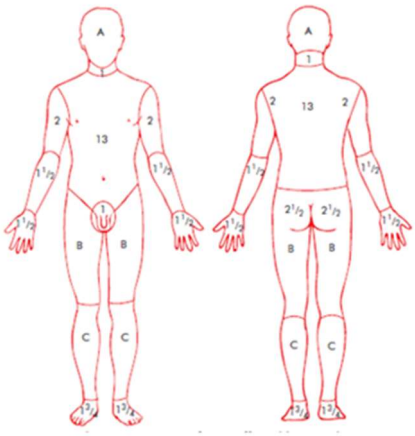

Fig. 3. The Lund and Browder Chart[41]

The estimation of burn injury size is visually presented in Fig. 3[41], commonly referred to as The Lund and Browder chart[43]. The chart employs the Total Body Surface Area (TBSA) scale, where the extent of burn damage to the entire hand is calculated as 1% TBSA and interpreted as a minor burn[32,44,45].

The rule of nines is a widely used, simple method for estimating the percentage of Total Body Surface Area (TBSA) that is affected by a burn. The method divides the body into nine specific areas, each with a corresponding TBSA percentage. The rule of nine is not very accurate, but it is a useful tool for initial assessment of burn victims.

Fig. 4 depicts the rule of nines. The head and neck are allocated 9% of the TBSA, the anterior and posterior torso are each allocated 18%, the anterior and posterior upper limbs are each allocated 9%, and the anterior and posterior lower limbs are each allocated 18%. The genitals are allocated 1%. It is important to note that the rule of nines is not very accurate. The actual TBSA of a burn may be higher or lower than the estimate provided by the rule of nines. However, the rule of nines is a useful tool for initial assessment of burn victims, as it can provide a quick and approximate estimate of the TBSA.

This method divides the TBSA percentage based on specific body regions, including the head and neck, anterior and posterior torso, anterior and posterior upper limbs, and anterior and posterior lower limbs (Table 2)[25]. It is essential to note that the rule of nines designed for adults (Fig. 4.A) is not suitable for estimating burn injury in children (Fig. 4.B)[46]. This discrepancy arises due to the distinct anatomical presentations and proportions of the head and lower extremities in children (Table 3) compared to adults (Table 2). As a result, TBSA estimation for burn injuries in children is performed using varying percentage allocations[47]. The percentages for lower extremities and head in children are differentiated according to age, as illustrated in Table 3[47].

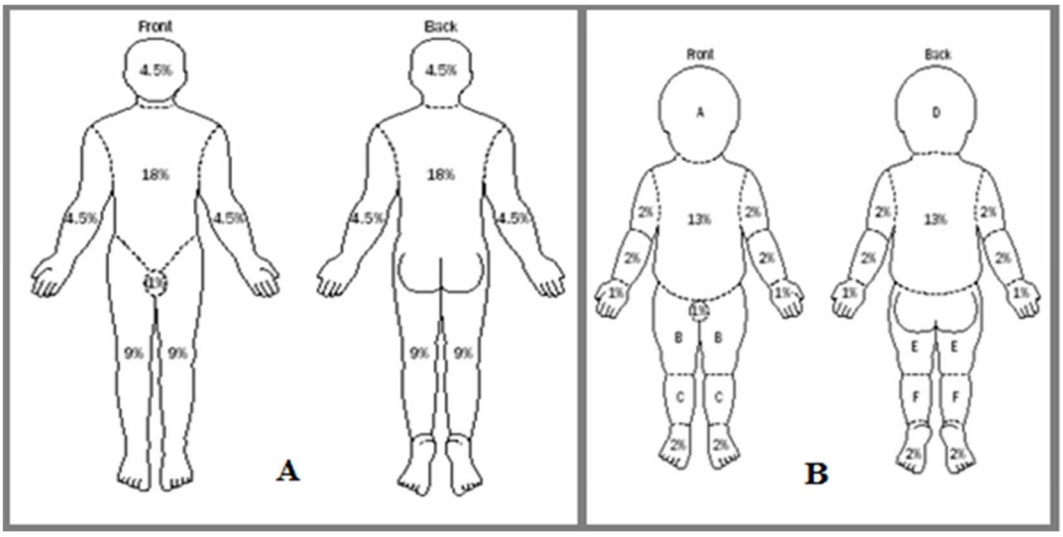

Fig. 4. Rule of Nines for estimating TBSA of burn injuries. A. For adults, B. For children[47]

TABLE II. RULE OF NINES FOR ESTIMATING TBSA OF BURN INJURIES[25]

Body Area	TBSA Percentage
Head and neck	9%
Anterior torso	18%
Posterior torso	18%
Anterior upper limb	9%
Posterior upper limb	9%
Anterior lower limb	18%
Posterior lower limb	18%
Genitalia	1%

TABLE III. PERCENTAGE OF BURN INJURIES IN CHILDREN[47]

Age (years)	Head	Anterior upper limb	Posterior upper limb	Anterior lower limb	Posterior lower limb
0	10%	3%	3%	2%	3%
1	9%	3%	3%	4%	5%
5	7%	3%	4%	5%	5%
10	6%	3%	4%	3%	3%

The table 3 shows that the percentage of burn injuries in children varies by age. For example, the head accounts for 10% of burn injuries in children aged 0 years, but only 6% of burn injuries in children aged 10 years. This is because the head is proportionally larger in children than in adults. The table 3 also shows that the percentage of burn injuries in children is higher on the anterior (front) of the body than on the posterior (back) of the body. This is because children are more likely to experience burns from hot liquids or objects that are held in front of them.

The American Burn Association (ABA) classifies burns that require further management and hospitalization as partial-thickness burns with an area of more than 10% of the total body surface area (TBSA). Partial-thickness burns include burns that affect the face, upper and lower extremities, genitalia, perineum, and large joints; third-degree burns, electrical burns, chemical trauma, inhalation trauma, patients with medical complications, burns with other accompanying trauma, burns in children in hospitals without adequate health care and pediatric facilities, and patients with special interventions[41,44,45]

III. BURN WOUND TREATMENT

Burn injuries can cause damage to the skin, which can lead to the increased expression of certain genes and protein-encoding factors involved in the wound healing process. These factors, known as growth factors, play an important role in the repair of damaged tissue. The understanding of growth factors is essential for the development of effective burn wound treatment and management strategies.

3.1. Burn Wound Management

Burn wound management is tailored to the severity of the burn injury. Twenty years ago, hydrotherapy tanks were the

standard of care for burn wound care. However, this practice is now rarely used due to the risk of hypothermia, cross-contamination, and fluid leakage. Instead, burn wounds are typically cleaned and dressed with topical medications.

Burn wound management aims to provide tailored treatment based on the degree of the burn injury. Twenty years ago, wound care was performed using hydrotherapy tanks. The terms "hydro," "tanking," and "bathing" are still used today, although immersing patients in water is rarely practiced anymore. Despite many burn patients enjoying soaking in warm water, it is considered less beneficial. Placing patients in water can lead to hypothermia even if the water is relatively warm. Cross-contamination may occur between different burn wounds. Fluid leakage due to burns can worsen underlying conditions like hyponatremia. Consequently, the tanking method is no longer utilized[28].

Initial burn wound management must be promptly conducted after the initial assessment to avoid worsening the patient's condition. Wound care should prioritize cleanliness and sterility to prevent infection. The initial steps include cooling and cleansing the wound to prevent further injury and reduce pain, which can be achieved through irrigation using normal saline or sterile water at room temperature. The use of ice-cold water may exacerbate the injury. All clothing, jewelry, and debris must be kept away from the burned area. Wound cleaning with mild antiseptics, such as chlorhexidine, is done to prevent infection[44,45].

Debridement may be necessary when necrotic tissue is present, and antibiotics or other topical preparations are provided along with elevation of the injured area to reduce edema[[3,28,48]. Debridement aims to remove dead tissue by creating a new wound to expedite the wound healing process. Debridement can be performed surgically, with or without anesthesia[45,48].

Topical preparations and dressings are applied after wound cleansing to maintain a moist environment. Silver sulfadiazine has been a mainstay in burn wound care for over 40 years, despite the availability of numerous other wound care products[28]. The use of silver sulfadiazine in burn wound healing may cause a delay of one or two days due to the formation of a layer on the wound surface. Moreover, its application may cause a stinging sensation in patients, which is a relative contraindication for patients with a history of sulfur allergy. Another issue with silver sulfadiazine cream is its tendency to adhere to the wound surface, which requires precautions with dressing changes and necessitates painful wound cleaning for subsequent applications[28,45]

The second most commonly chosen topical treatment is antibiotics applied with dressings. Antibiotic ointments are easily accessible, cost-effective, and user-friendly to avoid the risk of wound deterioration due to infections. Single-agent antibiotic ointments are often preferred to minimize allergy risks, such as bacitracin or mupirocin for patients with methicillin-resistant Staphylococcus aureus (MRSA)[28,30,50,51]

Mafenide acetate is also frequently used in burn wounds. It has excellent depth penetration and a broad-spectrum antimicrobial effect, but it can cause a stinging sensation upon application. The drawback is that mafenide acetate is not readily available outside burn care units[37,52].

The use of acetic acid (0.25% solution) has advantages in reducing Pseudomonas colonization. Other antimicrobial agents used in burn wound care are listed in Table 4[28]. Similar to silver sulfadiazine, antibiotic application may also slow wound healing as it can adhere to the wound surface and damage newly formed epithelial cells[51].

TABLE IV. MECHANISMS OF ACTION AND ADVERSE EFFECTS OF VARIOUS ANTIMICROBIAL AGENTS EMPLOYED IN THE MANAGEMENT OF BURN-RELATED WOUNDS [28]

Agent	Mechanism of Action	Side Effects
Silver sulfadiazine	Inhibits the growth of bacteria and fungi	May cause skin irritation, allergy, and crust formation on the burn
Mafenide acetate	Inhibits the growth of bacteria and fungi	May cause skin irritation, allergy, and burning sensation on the burn
Povidone-iodine	Inhibits the growth of bacteria and fungi	May cause skin irritation, allergy, and skin staining
Chlorhexidine	Inhibits the growth of bacteria and fungi	May cause skin irritation, allergy, and skin staining

gluconate		
Metronidazole	Inhibits the growth of anaerobic bacteria	May cause nausea, vomiting, diarrhea, and hair loss
Clindamycin	Inhibits the growth of Gram-positive bacteria	May cause diarrhea, nausea, vomiting, and skin rash
Gentamicin	Inhibits the growth of Gram-negative bacteria	May cause kidney, muscle, and nerve disorders
Vancomycin	Inhibits the growth of methicillin-resistant Gram-positive bacteria	May cause kidney, muscle, and nerve disorders
Linezolid	Inhibits the growth of methicillin-resistant Gram-positive bacteria	May cause kidney, muscle, and nerve disorders

Wound dressings serve not only to maintain moisture but also to minimize hematoma, edema, reduce dead space, protect against contaminants and other traumas, absorb drainage, create strong oxygen pressure, and restrict movement in the wound area. A moist environment in the wound encourages angiogenesis, which is essential for transferring cellular components involved in wound healing. Burn wound management may also involve surgical procedures, such as escharotomy, Negative Pressure Wound Therapy (NPWT), stem cell therapy, skin grafting, and others[3,49].

The initial wound management phase is also known as the life and limb-saving management sequence, which aims to improve tissue perfusion damaged by heat exposure. During this phase, escharotomy and fasciotomy may be performed. Escharotomy involves incising the eschar to release its constricting effect on the underlying tissues. The eschar can affect tissue perfusion by reducing skin elasticity and inhibiting compensation for increased pressure in a compartment that surrounds an extremity. Therefore, escharotomy serves as a decompression measure in the resuscitation management sequence. The escharotomy method can be performed through operative and non-operative procedures, with the operative method utilizing hydropressure and Ultrasonic Assisted Wound Treatment (UAW). The non-operative method is achieved through enzymatic debridemen[53].

In cases of extensive burns where subcutaneous tissues are exposed, operative closure of the wound is necessary. Wound closure can be achieved through skin grafting or alternative materials such as biological and synthetic dressings[54]. Operative wound closure is carried out for second-degree deep and third-degree burns with extensive tissue damage, including the skin and integument[55]. Skin grafting, either autograft, allograft, or xenograft from cadavers or different species, is the preferred wound closure method for large burns[53,56].

One of the developments in burn wound management is the application of stem cells, which has shown promising results[15,37,57]. Stem cells used in burn wound healing are generally adult stem cells that possess plasticity, enabling them to differentiate into specific cells in the organ they are placed[15]. Several studies on the use of stem cells in burn wounds involve mesenchymal stem cells, bone marrow, umbilical cord, and hair follicles[53,58].

The process of wound healing can be divided into three types: primary, secondary, and tertiary healing[59]. Primary healing is the expected type of healing, with minimal edema, no local infection, a short healing time, and no gap between the edges of the healing wound.

Secondary healing occurs when primary healing fails, with a longer healing time. This is usually caused by infection, extensive trauma, and tissue loss. As a result, the wound may be open and the healing process occurs from the inner layer to the outer layer. Granulation tissue and scar tissue will be produced in large amounts. Tertiary healing is a wound that is left open for several days after debridement. After the wound is clean, the edges of the wound will be brought together on day 4-7[60]. All of these healing processes are grouped into three phases of wound healing: hemostasis and inflammation, proliferation phase, and maturation or remodeling phase[61].

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