INTRODUCTION

Despite numerous advances in wound management, delayed wound healing is a significant health problem particularly in the elderly. In addition to pain and suffering from frequent dressings, failure of the wound to heal also imposes social and financial burdens.[1]

Chronic wounds are defined as lesions that take a long time to heal, fail to heal or recur. They are very common in industrialized countries and cause significant pain and discomfort. The true incidence and economic impact of chronic wounds are difficult to assess because of the wide range of causative diseases and available treatment options. [2-4]

Chronic wounds are more common in elderly patients and in those with multiple health problems. With an aging population one may expect increase in both the incidence and cost of chronic wounds. [4]

Non-healing wounds affect about 3 to 6 million people in the United States, with persons 65 years and older accounting for 85% of these events. Non-healing wounds result in enormous health care expenditures, with the total cost estimated at more than $3 billion per year. [5, 6]

The wound-healing process consists of four highly integrated and overlapping phases: homeostasis, inflammation, proliferation, and tissue remodeling or resolution. [7]

These phases and their biophysiological functions must occur in the proper sequence, at a specific time, and continue for a specific duration at an optimal intensity. [5]

Hemostasis: vascular constriction, platelet aggregation, degranulation and fibrin formation (thrombus) occur.

Inflammation: neutrophil infiltration, monocyte infiltration and differentiation to macrophage and lymphocyte infiltration.

Proliferation: re-epithelialization, angiogenesis, collagen synthesis and external cellular matrix formation.

Remodeling: collagen remodeling, vascular maturation and regression.

There are many factors that can affect wound healing which interfere with one or more phases in this process, thus causing improper or impaired tissue repair. Wounds that exhibit impaired healing, including delayed acute wounds and chronic wounds, generally have failed to progress through the normal stages of healing. Such wounds frequently enter a state of pathologic inflammation due to a postponed, incomplete, or uncoordinated healing process. [5]

Factors Affecting Wound Healing

Multiple factors can lead to impaired wound healing. In general terms, the factors that influence repair can be categorized into local and systemic.

I) Systemic factors

Systemic factors are the overall health or disease state of the individual that affect his or her ability to heal. These factors act through the local effects affecting wound healing.

A) Oxygenation

Oxygen is important for cell metabolism, especially energy production by means of ATP, and is critical for nearly all wound healing processes. It prevents wounds infection, induces angiogenesis, increases keratinocyte differentiation, migration, and re-epithelialization, enhances fibroblast proliferation and collagen synthesis, and promotes wound contraction. [8, 9]

Due to vascular disruption and high oxygen consumption by metabolically active cells, the microenvironment of the early wound is depleted of oxygen and is quite hypoxic. Several systemic conditions, including advancing age, anemia and diabetes, can create impaired vascular flow, thus setting the stage for poor tissue oxygenation. [10]

B) Age

Increased age is a major risk factor for impaired wound healing. Delayed wound healing in the aged is associated with an altered inflammatory response, such as delayed T-cell infiltration into the wound area, delayed re-epithelialization, collagen synthesis, and angiogenesis have also been observed. [11]

C) Sex hormones

Sex hormones play a role in age-related wound-healing deficits. Compared with aged females, aged males have been shown to have delayed healing of acute wounds. A partial explanation for this is that the female estrogens (estrone and 17β-estradiol), male androgens (testosterone and 5α-dihydrotestosterone, DHT), and their steroid precursor dehydroepiandrosterone (DHEA) appear to have significant effects on the wound-healing process. [12]

D) Stress

Stress has a great impact on human health and social behavior. Many diseases such as cardiovascular disease, cancer, compromised wound healing, and diabetes are associated with stress. Numerous studies have confirmed that stress-induced disruption of neuroendocrine immune equilibrium is consequential to health. [13, 14]

The pathophysiology of stress results in the deregulation of the immune system, mediated primarily through the hypothalamic-pituitary adrenal (HPA) and sympathetic-adrenal medullary axes or sympathetic nervous system. (Figure 1) [15, 16]

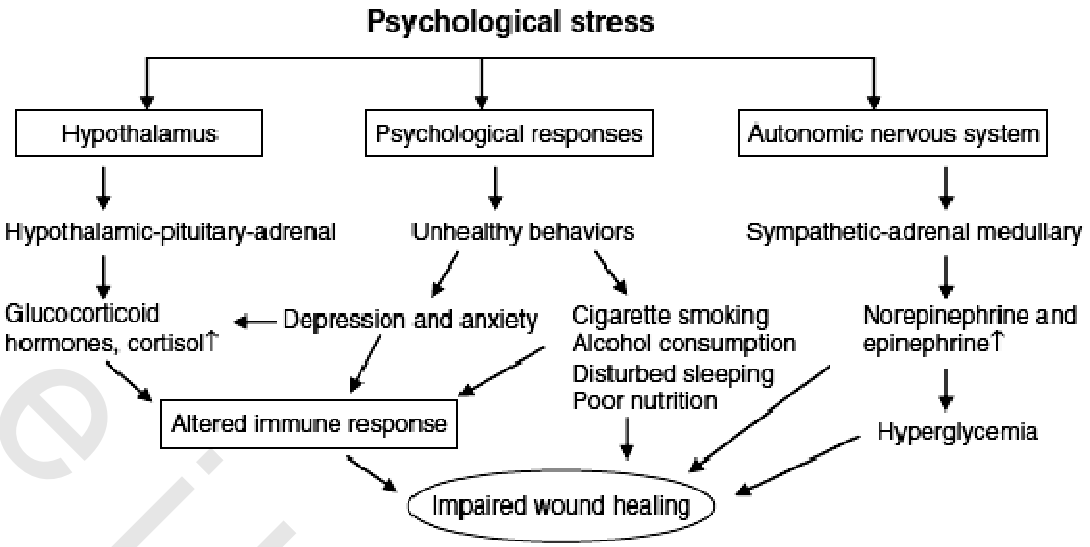

Figure (1): The effects of stress on wound healing. [15]

E) Diabetes

Diabetes affects hundreds of millions of people worldwide. Diabetic individuals exhibit a documented impairment in the healing of acute wounds. Moreover, this population is prone to develop chronic non-healing diabetic foot ulcers (DFUs), which are estimated to occur in 15% of all persons with diabetes. DFUs are a serious complication of diabetes, and precede 84% of all diabetes related lower leg amputations. [17]

The impaired healing of both DFUs and acute cutaneous wounds in persons with diabetes involves multiple complex pathophysiological mechanisms. DFUs, like venous stasis disease and pressure-related chronic non-healing wounds, are always accompanied by hypoxia. [18]

A situation of prolonged hypoxia, which may be derived from both insufficient perfusion and insufficient angiogenesis, is detrimental for wound healing. Hypoxia can amplify the early inflammatory response, thereby prolonging injury by increasing the levels of oxygen radicals. [19]

Hyperglycemia can also add to the oxidative stress when the production of oxygen radical substances exceeds the anti-oxidant capacity. [20]

The neuropathy that occurs in diabetic individuals probably also contributes to impaired wound healing. [21, 22]

F) Medications

Many medications, such as those which interfere with clot formation or platelet function, or inflammatory responses and cell proliferation have the capacity to affect wound healing. The commonly used medications that have a significant impact on healing include glucocorticoid, steroids, non-steroidal anti-inflammatory drugs, and chemotherapeutic drugs.

G) Alcohol consumption

Alcohol exposure diminishes host resistance, and ethanol intoxication at the time of injury is a risk factor for increased susceptibility to infection in the wound. Beyond the increased incidence of infection, exposure to ethanol also seems to influence the proliferative phase of healing. In summary, acute ethanol exposure can lead to impaired wound healing by impairing the early inflammatory response, inhibiting wound closure, angiogenesis, and collagen production, and altering the protease balance at the wound site.[23]

H) Smoking

Most studies have focused on the effects of nicotine, carbon monoxide, and hydrogen cyanide from smoke. Nicotine probably interferes with oxygen supply by inducing tissue ischemia, since nicotine can cause decreased tissue blood flow *via* vasoconstrictive effects. Nicotine stimulates sympathetic nervous activity, resulting in the release of epinephrine, which causes peripheral vasoconstriction and decreased tissue blood perfusion. Nicotine also increases blood viscosity caused by decreasing fibrinolytic activity and augmentation of platelet adhesiveness. In addition to the effects of nicotine, carbon monoxide in cigarette smoke also causes tissue hypoxia. [24, 25]

I) Nutrition

For more than 100 years, nutrition has been recognized as a very important factor that affects wound healing. Most obvious is that malnutrition or specific nutrient deficiencies can have a profound impact on wound healing after trauma and surgery. Patients with chronic or non-healing wounds and experiencing nutrition deficiency often require special nutrients. Energy, carbohydrate, protein, fat, vitamin, and mineral metabolism all can affect the healing process. [26]

II) Local factors

Local factors are those that directly influence the characteristics of the wound itself, such as; presence of necrotic tissues, dry environment, edema, decreased blood flow and infection.

Adjuncts to Wound Treatment:

Complicated wounds need debridement of all non-viable tissue which can produce significant soft tissue defects precluding healing through primary closures, delayed primary closures, or secondary intention. [27]

I-Debridement

Debridement prepares the wound for healing by reducing the bioburden. Without an adequate debridement, a wound is persistently exposed to cytotoxic stressors and competes with bacteria for scarce resources such as oxygen and nutrients; this step is crucial, as most problematic wounds afflict aged patients and occur in the setting of ischemia. Many surgeons under appreciate the importance of adequate debridement. Those surgeons still allow wounds to heal under a "biologic dressing" or eschar suggests an under appreciation of the deleterious side effects that occur during the process of eschar formation. [28]

An eschar begins as a *pseudoeschar* or *slough*, which is essentially a provisional matrix, formed from exudates, serum components at the wound–air interface. If allowed to dry, the gelatinous composition of the pseudoeschar will harden to form the true eschar. While most surgeons recognize the importance of debridement of grossly non-viable or foreign material, the role that a pseudoeschar may play in prolonging the inflammatory stage of wound healing, and hence setting the wound up for persistent bacterial colonization. [28]

The proteinaceous components of the pseudoeschar are a meal for bacteria; hence pseudoeschar should be debrided when it accumulates. This layer can be quite tenacious because proteins are "sticky" and the biofilm generated by bacteria (comprised of complex carbohydrates) is also sticky and not degraded by most proteases. An effective way to do this as the wound heals is through the proper use of the debriding agents. [28]

A) Surgical debridement

Debridement is typically considered to be surgical, but it may also be enzymatic, mechanical, or autolytic (occurring through the action of leukocytes). Enzymatic and proautolytic agents prevent the crosslinking of exudated components and impede the bacteria-sequestering pseudoeschar and biofilms from forming. Some dressings (notably hydrocolloid dressings) have the advantageous ability to rehydrate partially dehydrated and hardened scab tissue, which are then phagocytosed by wound leukocytes. A particularly useful mechanical debrider is the pressurized water jet, which has the ability to penetrate into the wound bed to flush out entrapped particulate matter as well as bacteria. A Waterpik, or even a handheld shower spray, is a low-tech device that patients can use at home. Similarly, a syringe with a 20- gauge needle will generate the 15 psi necessary to lower bacteria counts in tissue. [29]

B) Enzymatic debridment

The rationale for using enzymatic debriding agents is that they will selectively digest necrotic, devitalized tissue and prevent slough and eschar from accumulating. These agents include such products as papain with urea, and are general proteases useful for breaking up

developing proto-eschars and accumulated biofilms characteristic of many open wounds. Their use is sometimes associated with pain, which may limit their use.

Another enzyme widely used is collagenase. These products are not substitutes for mechanical debridement; however, when properly used, they are less traumatic to healthy tissue than surgical debridement. (31)

C) Biologic debridment

Another means of achieving wound debridement is through the use of maggot therapy, which can be remarkably efficacious in removing devitalized material while sparing viable, well-perfused tissue. Some centers use this form of biologic debridement extensively. (29)

II-Hyperbaric oxygen

The use of hyperbaric oxygen (HBO) (typically, 100% O2 saturation at 2 to 3 ATA) raises the dissolved oxygen saturation in plasma from 0.3% to nearly 7%. This rise in oxygen increases the interstitial diffusion distance of oxygen four- to five fold. The initial enthusiasm for HBO led to indiscriminate and unscientific use of HBO for unjustified indications. This led to a significant controversy with a predictable backlash on the part of referring physicians, surgeons, and third-party payers. (30)

However, it is now clear that an appreciation of the wound microenvironment, with a focus on the microcirculation, can direct the proper use of this valuable modality. The broadening use of trans-cutaneous oximetry has permitted evaluation of patients that will likely benefit from HBO. Broadly speaking, if the peri-wound area demonstrates a rise in tcPO2 when the patient inspires supplemental oxygen, the patient is likely to benefit from HBO. (30)

This diagnostic maneuver eliminates the two groups of patients that will not benefit from HBO: those with a normal environmental perfusion, and those with ischemic limbs who need a bypass to restore blood flow to a limb. Occasionally, HBO may be used as a means of limb salvage in a patient with an ischemic wound who is not a candidate for a surgical or endovascular procedure. It must be recognized that there are still a paucity of prospective randomized studies that support its use and the duration and frequency of treatment remains empiric. More recently, there has been some interest in regional oxygen therapy to the wound itself, with even less supporting evidence. (30)

III-Growth factors

The first growth factor approved by the FDA in the United States is platelet-derived growth factor (PDGF), marketed under the name becaplermin (Regranex). It is approved for the treatment of diabetic foot ulcers. It has been widely used “offlabel” for the treatment of a variety of other wound types, such as irradiated wounds and in aged patients. It appears to be effective only in the context of a well-prepared wound bed, which is logical, as an infected bed filled with proteases will rapidly degrade this peptide growth factor. Other growth factors, including vascular endothelial growth factor (VEGF), are currently in clinical trials. (30)

IV-Dressings

The types of dressings can be broadly divided into films, composites, hydrogels, hydrocolloids, alginates, foam, and other absorptive dressings, including VAC. Within these categories of dressings, there are few, if any, prospective, randomized clinical trials that definitively prove the superiority of one type of wound dressing over the other, emphasizing the need for further research in this area.(31)

There is a dizzying array of choices currently available, and to add to the confusion many indications for the use of dressings are promoted by industry. The choice of one over another is best made by considering wound characteristics and treatment goals. The goal in clean wounds that are to be closed primarily or are granulating well is to provide a moist healing environment to facilitate cell migration and prevent desiccation of the wound. Consequently, films can be used for incisions, and hydrogels or hydrocolloids can be used for open wounds. (31)

The amount and type of exudates that are present in the wound will direct the dressing used in wounds that have some degree of bacterial colonization. In general, hydrogels, films, and composite dressings are best for wounds with light amounts of exudates; hydrocolloids are used for wounds with moderate quantities; and alginates, foams, and VAC are best used for wounds with heavier volumes of exudates. VAC is also useful for wounds with heavy amounts of lymph as a consequence of a leak, as well as for fistulae. (31)

Wounds with large volumes of necrotic material should not be treated with a dressing until a surgical debridement had been performed. (31)

A) Gauze

Gauze dressings suffer the burden of being the traditional first choice for the generic care of wounds. The realization that the practice of moist to dry dressings for wound care is actually traumatic and pro-inflammatory has led to a decline in the use of these dressings in the arena of wound care. In addition, the costs associated with these dressings, particularly in personnel expenses, are high compared with modern dressings that need to be changed less frequently. These are often painful to remove, and are non-selective debriders that cause significant damage to healthy tissue. Furthermore, many of them leave behind them fine microfibers that can act as irritants and as foci of a source of infection. However, the material expense of these dressings is very low, and they may be purchased in any drugstore. (32)

They are excellent as surgical bandages and can be used in small, non-complicated wounds or as secondary dressings. They may also be purchased impregnated with petrolatum, iodinated compounds, or other materials useful for keeping the wound bed moist. It should be noted that most dressings have been approved by the FDA as "substantially equivalent" to gauze in their efficacy. There is no definitive evidence that other dressings will heal a wound faster than moist gauze, although they have other advantages. (32)

B) Semi-occlusive dressings

These are sheets that are impermeable to fluids but permit the passage of small gas molecules. They are typically used in combination with gauze or other dressings, and act to maintain the moisture content of clean wounds. Semi-occlusive dressings are commonly used to cover and protect freshly closed incisions and skin graft donor sites, and likely enhance epithelialization when used this way. They should not be used in wounds known to be significantly contaminated, and should be cautiously used in patients with fragile skin prone to tearing. [32]

C) Hydrogel dressings

Hydrogel dressings are particularly useful in maintaining a moist wound bed and rehydrating wounds to facilitate healing as well as autolytic debridement. Thus, they are useful in wounds with small amounts of eschar or that are predisposed to desiccation. Their usefulness is achieved by their intrinsic moisture content and hydrophilic nature. They are usually composed of complex polysaccharides (e.g., starch). Unlike alginates and hydrocolloids, they are not dependent on wound secretions to maintain a moist wound micro-environment. Yet, like these other dressings, they can absorb moderate amounts of fluid from the wound. An additional benefit is that they can be used in infected wounds. They are non-adhesive, and therefore cause minimal pain with dressing changes. Because they do not adhere well to the wound or skin, they usually require a secondary dressing. [32]

D) Hydrocolloids

Typically, these are pastes, powders, or sheets that are placed within the wound and covered with a dressing (in the case of pastes or powders) to form an occlusive barrier that gels as it absorbs mild amounts of exudates. Hydrocolloids consist of gel-forming agents (typically gelatin, carboxymethyl cellulose, or pectin) that are impermeable to gases and liquids. They may be left on the wound for 3 to 5 days; during this time, they provide a moist environment that promotes cell migration and wound debridement by autolysis. However, because of their occlusive nature, hydrocolloids are not to be used in the presence of wounds that are heavily colonized with bacteria, particularly anaerobic strains. These are not highly absorbent, and hence should not be used for highly exudative wounds.[32]

E) Foam Dressings

Foam dressings are made of non-adhering polyurethane, which is hydrophobic, and an occlusive cover. The polyurethane is highly absorptive and acts as a wick for wound fluids, making foam dressings useful in highly exudative wounds. However, because of their high wicking ability, they are not to be used on non-exudating or minimally exudating wounds. [32]

F) Alginates

Alginates (derived from brown seaweed) are particularly useful in wounds characterized by significant amounts of exudate. Their use permits the desired removal of exudated fluids from the wound environment and yet frees the practitioner from the burden of daily or multiple dressing changes per day. These products are not to be used in non-exudative wounds, as they can dry out the wound bed. They come in several forms,

including a rope/ribbon form that is useful for packing wounds with deep pockets. These dressings can absorb approximately 20 times their dry weight in fluid. They should be covered with a semi-occlusive dressing. If the practitioner desires to use these alginate dressings on dry wounds, they should be hydrated with sterile saline prior to being placed on the wound to maintain wound moisture and permit epithelialization and autolysis. A particularly useful alginate dressing is manufactured impregnated with silver. [32]

G) Antimicrobials

Antimicrobial dressings are a generic term for a dressing that contains an antimicrobial agent. The most beneficial agent appears to be silver. Silver is ionized in the moist environment of the wound, and it is the silver ion that has biologic activity. This agent has a broad spectrum of microbicidal activity with low toxicity to human cells. It is further advantageous in that It has tri-pronged mechanism of activity (cell membrane permeabilizer, inhibitor of cellular respiration, and nucleic acid denaturer) this means that it is active against a broad range of micro-organisms in addition to bacteria, and also maintains activity against vancomycin-resistant *Enterococcus* (VRE) and methicillin-resistant *Staphylococcus aureus* (MRSA).[32]

These dressings fill a true need; although it is axiomatic that surgical debridement is the best way to decrease the bioburden of a wound, wounds are rapidly colonized following a seemingly sterile debridement. Furthermore, for certain types of ulcers characterized by an impaired blood supply (ischemic, irradiated wounds) these dressings can be useful as a wound treatment and as a temporizing measure while the patient is optimized for definitive surgical therapy. Cadexomer iodine is another antimicrobial agent and is a slow-release form of iodine formulated to achieve consistently bactericidal levels within the wound bed without the wound cell-damaging effects seen with the use of Povidine-iodine products. Other antimicrobials include silver sulfadiazine, mupirocin, and topical antibiotics, including neomycin, gentamicin, metronidazole, and bacitracin ointments and creams. [32]

H) Skin Substitutes or Human Tissue Equivalents

These are among the first tissue-engineered products applied to clinical use. Besides providing wound coverage, some of these products contain living cells that are cellular factories, secreting broad panoply of growth factors and other bioactive molecules that assist in healing. A downside is their expense. [32]

They need to be applied to meticulously clean wounds with adequate vascularity and the site needs to be immobilized to prevent shearing and graft loss. Representative products include cultured autologous keratinocyte sheets (Epicel, Genzyme Corporation, Cambridge, MA); dermal constructs such as Biobrane (Mylan Laboratories, Canonsburg, PA), Oasis (Cook Biotech, West Lafayette, IN), AlloDerm (LifeCell Corp, Branchburg, NJ), Integra (Integra Life Sciences Corp, Plainsboro, NJ), TransCyte (Smith & Nephew, Largo FL), and Dermagraft (Smith & Nephew, Largo FL); and bilayered tissue engineered constructs consisting of keratinocytes and fibroblasts such as OrCel (Ortec International, New York, NY) and Apligraf (Organogenesis, Canton, MA). The indications for their use are highly patient and center specific. It is especially useful for sites prone to contracture (neck, axillae) and to replenish contour in burn wounds and donor sites. In addition, it can enable coverage of tendons, bone, and surgical hardware, and in selected situations can obviate the need for more complex wound closures, such as flaps. [32]

Vacuum Assisted Closure Therapy

Vacuum-assisted closure (V.A.C.) therapy involves the controlled uniform application of continuous or intermittent negative pressure to the wound bed. [43]

EVOLUTION

Drainage of wounds after surgery is a long established surgical practice since the introduction of suction drainage in the early 1950s and later the evacuated glass bottle by Redon. [33] In the 1980s, the first articles on negative pressure wound therapy were published in the Russian literature. Negative pressure was used –80 mm Hg, in combination with aggressive debridement to significantly reduce bacterial counts in purulent wounds. [34,35]

In 1989, Chariker et al. [36] published their experience on topical negative pressure (TNP) therapy in 7 patients with entero-cutaneous fistulas. They used moist gauze that was placed over the wound surface and a flat drain (**Figure 2**) placed over the gauze covered by a bio-occlusive dressing. The drain was connected to an already existing vacuum line such as a standard hospital wall suction source with continuous suction at approximately -60 to -80 mm Hg pressure. This method became known as the Chariker-Jeter technique. [36]

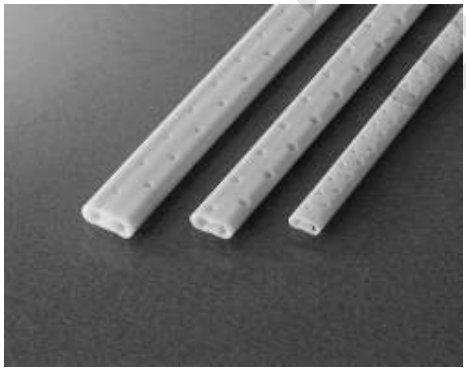

Figure (2): flat drain

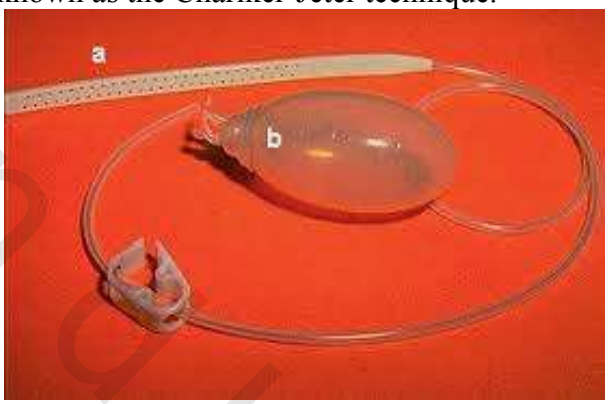

Figure (3): Jackson-Pratt suction catheter

In the early 1990s, Fleishman et al. [37-39] introduced suction drainage combined with Redon drainage tubes (**Figure 4**) and foam dressings as the interface instead of gauze dressings.

Figure (4): Redon tube

Figure (5): Integrated tubing

In the same period, a commercially available vacuum-assisted closure device (VAC) was introduced by Argenta and Morykwas in 1993 using polyvinyl-alcohol (PVA) and polyurethane (PU) foam dressing (PVA/PU), integrated tubing (**Figure 5**) and advised pressure settings of -125 mm Hg pressure. [40, 41]

The second commercial supplier of VAC systems in the medical industry received Food and Drug Administration approval in 2004. This device was called Versatile-1 wound vacuum system using the Chariker-Jeter approach. This technique recommends using a negative pressure range of- 40 to- 80 mm Hg, a Jackson-Pratt suction catheter (**Figure 3**) and a dressing kit consisting of non adherent antimicrobial gauzes. Versatile-1 was acquired in 2007 by other commercial supplier and re-named V1STA. After this, several other manufacturers joined the competing VAC arena. [42]

The most important differences between these systems are the filler material used (foam vs non adherent antimicrobial gauze), the connecting suction catheter (integrated tubing vs. flat or round drain), and the intensity of the negative pressure (ranging from 50 mm to 125 mm Hg). [42]

Mechanisms of action

The following mechanisms have been attributed to VAC therapy: creates a moist environment, reduces edema, increases local blood flow, stimulates angiogenesis and formation of granulation tissue, stimulates cell proliferation, reduces size and complexity of the wound, removes soluble healing inhibitors from the wound, and reduces bacterial load.

1-Moist environment

A moist wound bed enhances re-epithelization, matrix material availability, growth factor activity, and wound healing potential. Thus, as an occlusive type wound dressing like most others, it is suggested that VAC therapy provides a moist wound-healing environment that is favorable for the repair process. However, this is purely based on expert opinion because no study has ever been undertaken to measure the moistness of the wound environment either in VAC-treated wounds or in any other occlusive dressing. [44]

2-Edema reduction

Localized edema occurs secondary to tissue injury and can result in increased interstitial pressure. This increased interstitial pressure may then occlude microvasculature and lymphatic drainage, which can lead to decreased nutrients and oxygen delivery. Only two articles describing the effect of VAC therapy on wound edema reduction were found. The first was a clinical case study that described 7 patients with bilateral burns on the hand. The researchers observed the elimination of a larger amount of fluid and a clinically obvious edema reduction in the VAC-treated side in comparison with the contralateral side treated with silver sulfadiazine cream. [45]

The second study was an animal study using a pig with bilateral defects on the back. Histologic analysis was performed on wounds covered with a split-skin graft treated with tie-over bolster dressing versus VAC therapy. The VAC-treated side showed significantly less wound edema, significantly faster narrowing of the separation plane between the graft

and the recipient wound bed, and earlier termination of the acute inflammatory reaction. Both articles were of low-level evidence because of the small number of inclusions; further research is warranted before this mechanism can be attributed to VAC therapy. [46]

3-Blood flow

Morykwas et al. [41] reported the effect of VAC therapy on the blood flow in pigs. A laser Doppler probe was placed inside the wound, and negative pressure therapy was applied in increasing increments of 25 mm Hg up to 400 mm Hg at 15-minute intervals. Blood flow increased 4 times using 125 mm Hg and was set as the optimal pressure. A second observation was that with intermittent therapy (2 min rest periods after 5 to 7 minutes of suction) the most optimal blood flow was maintained. Worldwide, a negative pressure of 125 mm Hg became the baseline setting for the treatment of all kind of wounds. There is a discrepancy when comparing this with the early Russian "Kremlin" publications that advised maximum pressures of around -75 to -80 mm Hg. Researchers noted extensive tissue edema, separation and splitting of muscle fiber, inflammatory infiltration, and fresh hemorrhages in wounds treated with a negative pressure above 100 to 125 mm Hg.[47] In an animal study by Wakenfors et al, [48] a laser Doppler was used to measure microvascular blood flow to an inguinal wound and sternal wound model using negative pressure from 50 to 200 mm Hg. VAC treatment induced an increase in microvascular blood flow a few centimeters from the wound edge. In the immediate proximity of the wound edge, a zone of relative hypoperfusion was observed. This zone was larger at high negative pressures and was especially prominent in the subcutaneous tissue. They concluded that the negative pressure is transduced differently in the soft and the dense tissue and that a low negative pressure of 75 mm Hg for soft tissue and 100 mm Hg for muscle during treatment may be beneficial to minimize possible ischemic effects. Lindstedt et al [49] measured microvascular blood flow in the myocardium before and after VAC therapy of -25 mm Hg and -50 mm Hg. They observed that both pressure levels induced a significant increase in microvascular blood flow in normal and in ischemic myocardium. Higher levels between -75 mm Hg and -150 mm Hg did not induce microvascular blood flow changes. [50]

Much higher levels were published by Timmers et al [51] who conducted a randomized clinical trial (RCT) evaluating the response of cutaneous blood flow in healthy intact forearm skin using 2 different foam types (PVA and PU). Continuous negative pressure was used in the range of 25 to 500 mm Hg, with stepwise increase. Skin blood flow was measured with non-invasive laser Doppler probes incorporated into the foam. Significant increase in cutaneous blood flow was found with both foams up to a negative pressure of 300 mm Hg, with over a 5-fold increase in the cutaneous blood flow with the PU foam and nearly a 3-fold increase with the PVA foam.

Radioisotope perfusion imaging performed by Kairinos et al[52, 53] showed that perfusion of intact skin beneath VAC therapy decreases for increasing suction pressure and with circumferential dressings. They advised that VAC therapy should be used with caution on tissues with compromised perfusion, particularly when they were circumferential.

4-Angiogenesis and granulation tissue formation

Fabian et al. [54] published an article on the efficacy of VAC and hyperbaric oxygen as adjuncts in the treatment of ischemic full-thickness wounds in a rabbit model. They observed a statistical significance in favor of VAC dressing with suction versus VAC dressing without suction for peak granulation tissue and granulation tissue gap reduction. Hyperbaric oxygen alone did not significantly affect the rate of healing in this model.

Chen et al [55] examined the effects of VAC therapy versus control (e.g., petrolatum gauze) on the microcirculation of full-thickness wounds in rabbit ears in a randomized prospective study. It was noted that VAC therapy promoted the capillary blood flow velocity, increased the capillary caliber and blood volume, stimulated the endothelial proliferation and angiogenesis, narrowed the endothelial spaces, and restored the integrity of the capillary basement membrane significantly more than the control treatment.

A third animal study disclaimed similar results, full-thickness wounds on the back of diabetic mice were excised and treated with VAC therapy or its isolated components (eg, an occlusive dressing alone, occlusive dressing with negative pressure at-125 mm Hg, PU foam with occlusive dressing without suction, and a PU foam with downward compression of 170 g/cm2). A two fold increase in vascularity was seen in wounds exposed to the PU foam and to VAC therapy compared with the occlusive dressing group without the foam with or without negative pressure. [56] Several other animal and clinical studies [41, 57, 58] also proclaimed increased granulation tissue formation, however, using subjective measurements such as the volume or the depth reduction of the wound instead of histological examination.

Labler et al [59] described a prospective, clinical, non-randomized study in traumatic wounds treated with VAC therapy. They found significantly higher interleukin 8 and vascular endothelial growth factor levels in wound fluid of wounds treated with VAC therapy. Furthermore, histological examination revealed increased neovascularization illustrated by CD31 and Von Willebrand factor immunohistochemistry in wound biopsies of VAC-treated wounds. Therefore, they conclude that increased granulation tissue formation and increased vascularization are proven mechanisms of VAC therapy.

5-Mechanical stress and cell proliferation

It is postulated that because of the porosity of the reticulated foam dressing, VAC therapy applies a pulling/ compressing force causing the foam in the wound bed to collapse after which a sub-atmospheric force is transmitted to surrounding tissues. This force deforms the extracellular matrix on the cells where it affects various cell structures and signaling pathways that are highly integrated leading to cellular proliferation. [60] Several in vitro stretching systems have been used to understand the molecular events that occur better. [61]

Saxena et al. [62] studied the effects of negative pressure–induced material deformations in a simulated VAC therapy in a computer wound model. They compared the deformation morphology of the computerized wound model with histological sections of wounds treated with VAC therapy and showed that most elements stretched by sub-atmospheric pressure experienced deformations of 5% to 20% strain, which are similar to in vitro strain levels shown to promote cellular proliferation.

In another study with a diabetic mouse model, full-thickness wounds were excised and treated with the VAC therapy device or its isolated components. Results were quantified with a 2-dimensional immune-histochemical staging system based on blood vessel density (marker CD31) and cell proliferation (marker Ki-67) 7 days after wounding. VAC therapy was observed to induce the highest cell proliferation rates, with up to 82% Ki-67–positive nuclei compared with the other groups (19%–38% Ki- 67–positive cells).[56]

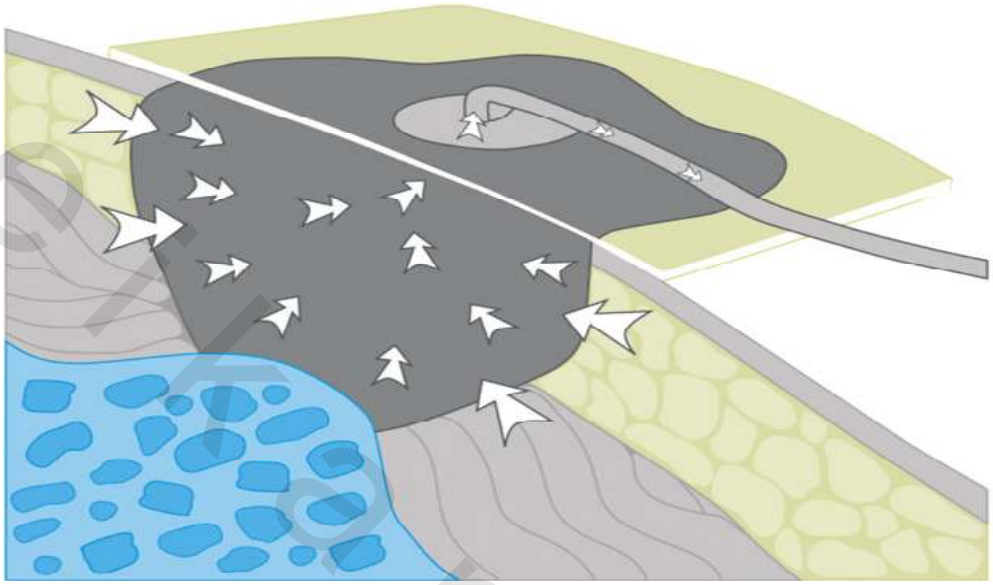

Figure (6): Schematic drawing of the vacuum assisted closure therapy (VAC). [43]

6-Reduction of wound size and complexity

Several Randomized Clinical Trials (RCTs) described a form of wound area closure (e.g., time to closure, mean time to reach 50% reduction, wound area reduction, and wound volume reduction). In studies reporting wound area reduction in diabetic and venous leg ulcers, a positive response was found with VAC therapy in all. In 4 studies on pressure ulcers, a larger decrease in wound size was observed compared with the controls. Three studies including acute wounds of different etiology and burns reported conflicting results, with 2 showing significant reduction, whereas no reduction was observed in the remaining study. To conclude, several RCTs that describe wound surface area measurements; a significant reduction of wound area/volume was noted in favor of the VAC therapy which acts by using the concept of reverse tissue expansion. [63-65]

7-Exudate removal

Wound exudate may contain an excess of matrix metalloproteinases (MMP) and their inhibitors and may also be associated with poor wound healing and inhibited cell growth.[66,67]

Stechmiller et al. [68] published the alterations in the pro-inflammatory cytokines, proteases (MMP-2 and 3), and inhibitor of metalloproteinase (TIMP-1) during VAC therapy. However, their sample size was too small to note any significant differences.

Greene et al [69] described a reduction in MMP-9/ neutrophil gelatinase-associated lipocalin, MMP-9, latent MMP-2, and active MMP-2 by 15% to 76% in 3 patients treated with VAC therapy.

Moues et al. [70] observed a relevant modulation of the relationship of MMPs to TIMPs in VAC treated wounds compared with conventionally treated wounds with a significant lower ratio of total MMP-9/ TIMP-1 and levels of pro–MMP-9. These publications indicated that the modulation of MMP concentration is a mechanism of action induced by VAC therapy.

8-Bacterial load reduction

The first study investigating bacterial load used was done by Morykwas et al. [41] an acute pig wound model, which was inoculated with human isolates of bacteria. It was observed that between days 4 and 5, the VAC-treated wounds had a decreased bacterial load, whereas the control wounds showed elevated bacterial levels. Since then, this study has been the internationally leading opinion.

In contrast, a retrospective clinical study by Weed et al. [71] in 26 wounds of varying etiology reported a significant increase in bacterial colonization upon VAC therapy and remained in a range of 10^4 to 10^6 bacteria/gram of tissue. Importantly, they changed the foams only once per 3 to 5 days.

In a randomized trial, Moues et al. [63] compared VAC therapy with conventional moist gauze therapy in 54 patients who required open wound management before surgical closure. They observed quantitative reduction in the number of bacteria but did find a significant shift in bacterial species using tissue biopsies. *Staphylococcus aureus* showed a significant increase in these wounds; non-fermentative gram negative bacilli showed a significant decrease in wounds after VAC therapy.

In a randomized trial by Braakenburg et al, [65] superficial swabs showed a tendency toward increased bacteriologic colonization in VAC treated wounds.

Pinocy et al [72] managed 24 deep groin infections (following prosthetic vascular reconstruction) with Redon drain-based VAC and PVA foam. One dressing change was performed at day 7. A semi-quantitative study of the results from wound swabs reported that on day 7, 18 of 24 cultures were negative and by day 14, all cultures were negative for bacterial colonisation.
Wu et al [73] also reported a semi-quantitative improvement in wound contamination using NPWT.

Nonetheless, VAC therapy can be successfully used in wounds that are severely infected in combination with debridement and adjuvant antibiotics. VAC increases local tissue oxygen levels which reduces or eliminates the growth of anaerobic organisms, that have been correlated to decreased healing rates. Additionally, the increased flow should make greater amounts of oxygen available to neutrophils for the oxidative bursts that kill bacteria. as described in median sternotomy wounds and infected spinal surgical wounds with implanted material. [74]