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**RESEARCH ARTICLE**
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# UNIQUE NURSING METHODS FOR THE CARE OF PERMANENT WOUNDS IN AUTOINFLAMMATORY OR AUTOIMMUNE PATHOLOGIES

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**Abstract:**

**Background**: Chronic wounds are a major worldwide health concern that are negatively affecting people's quality of life and placing a financial and personal burden on healthcare systems. The intricacy of persistent wounds demands an efficient management strategy that incorporates patients and/or their surroundings and guarantees that medical personnel get the most recent training in care methods. Chronic wounds exhibit diverse forms depending on contributing factors, with auto-inflammatory and autoimmune disorders playing a prominent role. Immune-mediated disorders, characterized by modifications in innate and adaptive immune responses due to genetic flaws, fall into this category. Conditions fostering chronic wounds include chronic inflammation, prothrombotic phases, immune complex-associated vasculitis, and treatment resistance consequences.

**Patient-Centric Approach:** To prioritize patients during chronic wound healing, this work focuses on nursing management, specifically addressing individuals with auto-inflammatory/autoimmune disorders. It aims to highlight cutting-edge strategies and therapies for effective patient care.

**Advanced Wound Healing Strategies:** The study explores the potential of nano hydrogels, particularly those with a three-dimensional porous structure, for enhanced wound healing applications. Specifically, a gellan-cholesterol nano hydrogel containing the antioxidant polyphenol baicalin is investigated for its ability to accelerate the wound healing process. This hydrogel, with its non-sticky nature, respects the wound bed, facilitates oxygen permeation, and simplifies topical treatment.

**Encapsulation of Medications:** The hydrogel's capacity to encapsulate medications, such as baicalin, demonstrates noteworthy outcomes in terms of skin healing and the suppression of inflammatory

indicators. The study emphasizes the flexibility of delivery techniques, aligning with the increasing interest in injectable applications.

**Innovative Nano Hydrogel Compositions:** In addition to baicalin-containing hydrogels, an alternative nano hydrogel incorporating VEGF, natural polysaccharides, nano silicates, and k-carrageenan shows promise by enhancing cell adhesion and proliferation. This diversification in nano hydrogel compositions opens avenues for advanced wound healing strategies.

**Conclusion:** The comprehensive approach to chronic wound management, involving nursing care and innovative nano hydrogel therapies, represents a significant step toward addressing the global burden of chronic wounds. These advancements offer potential breakthroughs in patient-centered care and contribute to the ongoing evolution of wound healing practices.

A significant global health issue, chronic wounds are becoming more common. They have a crippling impact on many people's quality of life, and managing them has a significant financial and personal impact on the healthcare system. For this reason, it's essential to implement an effective management system involving the patient and/or his environment and training staff in the most recent care techniques. Depending on the factors that make a wound chronic, several forms of chronic wounds exist. Being classified as autoinflammatory/autoimmune, most immune-mediated disorders typically entail modifications of innate and adaptive immune responses brought on by flaws in several genes.

Conditions that encourage the development of chronic wounds, such as chronic inflammation, prothrombotic phases, immune complex-associated vasculitis, or consequences of treatment resistance, are examples of autoinflammatory and autoimmune disorders. To put the patient at the center of attention during the healing of chronic wounds, this work focuses on the management of nurses in caring for patients with autoinflammatory/autoimmune disorders and chronic injuries. It also presents some of the most cutting-edge management strategies and therapies.

Nano hydrogels' distinctive three-dimensional porous structure, which allows for ideal liquid absorption while preserving a pleasant, humid environment, has made them attractive candidates for enhanced wound healing applications. This work investigates the possibility of using a gellan-cholesterol nano hydrogel containing the antioxidant polyphenol baicalin (found in Scutellaria baicalensis) to speed up the healing process after wounds. Because the hydrogel is not sticky, it respects the wound bed, permits oxygen to pass through, and makes topical treatment easier for patients.

The hydrogel's ability to encapsulate medications—in this case, baicalin—has shown noteworthy results in terms of skin healing and the suppression of inflammatory indicators. The study emphasizes how flexible the delivery techniques are, which is in line with the growing interest in injectable usage. An additional nano hydrogel including VEGF, natural polysaccharides, nano silicates, and k-carrageenan has demonstrated improved cell adhesion, and proliferation

**Keywords**: rheumatological ulcer, chronic Wound, inflammation, tissue regeneration.

## INTRODUCTION:

Over the past 45 years, there has been a considerable rise in life expectancy worldwide due to economic and medical advancements. As a result, a sizeable portion of the population is simultaneously afflicted by a number of pathologies, some of which can affect how other pathologies develop. It is known as comorbidity. The normal wound healing process can become pathological due to a number of conditions including comorbidity and age, which may prevent wound closure and make the condition chronic. Therefore, due to their rising prevalence and improved awareness of the

associated morbidity and socioeconomic cost, chronic wounds have grown in importance as a therapeutic problem in recent years (Przekora, 2020).

Additionally, the patient experiences physical pain and emotional distress, and the medical team is overworked because the Wound must be constantly monitored for closure, infection prevention, and worsening. The patient's overall health condition and the specifics of the wound (local and systemic variables) impact chronic wounds. The key to effective wound care is recognizing and eradicating variables that impede wound healing. Inflammatory and autoimmune illnesses are the primary initiating cause of chronic wounds, a cause that is frequently overlooked or underappreciated (Paul & Sharma, 2004).
A better approach to this condition is now possible thanks to significant advancements in the understanding of basic science's cellular and molecular components, as well as creative and technological advancements in biomedical engineering treatment modalities. As a result, these advancements have led to the adoption of evidence-based practices as the new norm in healthcare. Therefore, wound care must always begin with an integrated strategy, necessitating the training of nursing staff, the provision of personal and material resources, and the development of programs tailored to the needs and psychological situations of the patient. Thus, a new standard of care will be attained, considerably enhancing the patient's quality of life and enabling more effective utilization of healthcare resources (Mohebali & Abdouss, 2020).

This study is a review of the literature on chronic wounds, an issue that is becoming more and more common and is very expensive for healthcare systems all over the world. The problem is anticipated to worsen as a result of the rise in chronic diseases and the lengthening of life expectancy, which will necessitate the training of more professionals to handle it. Define the idea of a chronic wound and explain the many forms according to their etiology are the main goals of this work. Describe the phases of healing and how pathological healing affects the healing of wounds. List the many inflammatory and/or autoimmune disorders, together with the kinds of injuries they induce. Describe the role of the nurse in treating these kinds of wounds as well as the newest treatments being researched (Borojeny, Albatineh, Dehkordi, & Gheshlagh, 2020; Mohebali & Abdouss, 2020).

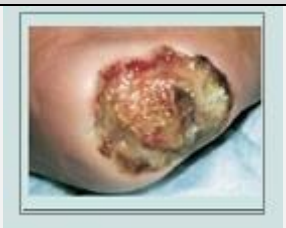
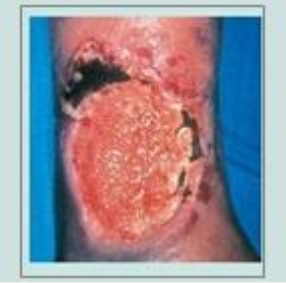
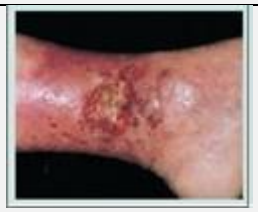
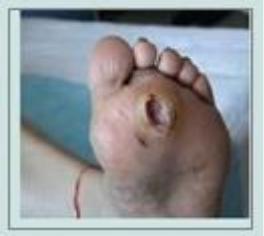
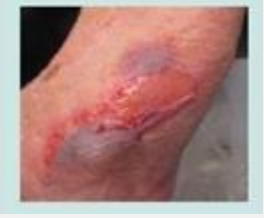
## METHODOLOGY:

The National Library of Medicine's Medical Object Headings (MeSH) and the Virtual Health Library's Descriptors in Health Sciences (DeCS) were combined for the search that produced this updated bibliographic review work by employing the logical operators AND, OR, and NOT. Chronic Wound, autoinflammatory disorders, healing, and skin regeneration are terms used in the MeSH and DeCS vocabularies. The following informational sources were consulted: Online databases include Dialnet, Google Academic and PubMed-Medline (Kharaziha, Baidya, & Annabi, 2021).

## CHRONIC INJURIES, EPIDEMIOLOGY, PRIMARY CAUSES, IMPLICATIONS FOR PHYSIOLOGY AND PSYCHOSOCIAL HEALTH

Chronic wounds are ones whose anatomical and functional integrity cannot be restored within a maximum of 3 months following the application of standard care based on the features of the Wound or that do not follow an orderly, regular, and chronologically timely healing sequence. Chronic wounds have several similar traits with different aetiologies at the molecular level, including an abundance of proinflammatory cytokines, proteases, reactive oxygen species (ROS), and senescent cells, as well as persistent infection and a lack of mesenchymal stem cells. They frequently exhibit malfunction. More information will be provided on chronic Wound pathophysiological mechanisms and etiology (Las Heras, Igartua, Santos-Vizcaino, & Hernandez, 2020).

Several types of chronic wounds are discussed below according to their etiology, even though there are numerous classification criteria for them: Atypical wounds, diabetic or neuropathic ulcers, venous ulcers, arterial ulcers, pressure ulcers (P.U.), and venous ulcers (table 1).

| Table 1 shows the various kinds of chronic wounds. | |
|---|---|
| **TYPES OF INJURIES / Common location** | **ETIOLOGY** |
|  <br>pressure ulcer /<br>sacrum, heel, ischium | Tissue ischemia secondary to pressure occludes blood capillaries. |
|  <br>Venous ulcer /<br>lower extremities | Venous anomalies that compromise the blood return, causing an increase in venous pressure leading to inflammation in the endothelium and will finally lead to alterations of the dermis precipitating ulcer formation. |
|  <br>Arterial ulcer /<br>feet, ankles, heels, fingertips | Ischemia and tissue rupture secondary to arterial insufficiency (inability nutrients reach the tissues) by atherosclerosis and stenosis of the arterial lumen |
|  <br>Diabetic ulcer/<br>sole, fingertips | Hyperglycemia causes excess metabolites toxicants that cause damage to cells Schwann and in neurons causing a motor and sensory neuropathy. Also leads to hyperlipidemia that leads to atherosclerosis and damage to the endothelium. |
|  <br>atypical wound/<br>Extremities, Back of the hands | Inflammatory, vasculitic, infectious etiology, metabolic, genetics. |

**P.U.s are pressure sores.**

Any skin lesion that results from constant pressure on a bony plane or prominence, friction, shearing, or a combination of these that produces ischemia results in the deterioration of the dermis, epidermis, and subcutaneous tissue and can extend to muscles and bones is referred to as a pressure ulcer (P.U.). For the tissue to suffer irreparable ischemia damage, a pressure of almost double the capillary closure pressure (around 20 mmHg) must be sustained for two hours. Tissue hypoxia, which encourages anaerobic cellular respiration, is the cause of this injury. This action alters the cell membrane, and

vasoactive chemicals are released. Long-term, protracted exposure causes necrosis and cell death (Olsson et al., 2019).
The force that prevents relative motion between two surfaces is known as friction. It happens when a patient's skin comes into contact with objects like wheelchairs or bed sheets. The damage brought on by the pressure force can be increased by the superficial wounds created by this mechanism of action. Transepidermal water loss rises when skin integrity deteriorates, leading to moisture accumulation that encourages skin adhesion to contact surfaces and worsens tissue injury. Shear pressures inhibit lymphatic circulation and the expulsion of cellular waste materials in addition to creating ischemia in the tissues, which results in indirect damage (Bazaliński, Kózka, Karnas, & Więch, 2019).

**Leg Vascular ulcer**
Open lesions between the knee and ankle joint known as venous leg ulcers (VLU) develop when there is chronic venous insufficiency (CVI). Reduced extremity The more severe effects of chronic venous disease (CVD) are referred to as CVI. The term "CVD" refers to a wide range of venous irregularities in which blood return is substantially compromised, primarily as a result of the calf muscle pump's inability to return blood from the legs to the heart, which raises blood pressure. Constant venous pressure in the lower limbs. Its symptoms range from superficial yet asymptomatic to serious ones. Telangiectasias, varicose veins, reticular veins, edoema, pigmentation and/or eczema, lipodermatosclerosis, white atrophy, and venous ulcers are a few of these (Kolluri et al., 2022).

Clinical symptoms of CVI are brought on by ambulatory venous hypertension, which is brought on by venous flow restriction, valvular-venous reflux, or both. Beginning with a change in the stress that the blood puts on endothelial cells, this has an impact on microcirculation. They consequently express selectins, release prothrombotic precursors, chemokines, inflammatory chemicals, and vasoactive agents. Leukocytes will transmigrate from the bloodstream to the venous wall as a result of all of this, starting the inflammatory cascade, producing cytokines, and increasing the expression of extracellular matrix metalloproteinases (MMPs). This involves a chain of actions that includes dermal alterations that result in skin changes and the development of ulcers (Abd El-Aleem, Abd-Elghany, Ali Saber, Jude, & Djouhri, 2020).
It seems that the interplay of genetic and environmental factors is crucial to the emergence and development of CVI. A high BMI, little physical activity, a high rate of pregnancies, long periods of time spent in the same position, whether sitting or standing, usage of the contraceptive pill, and smoking are all factors that make the condition worse with age and female (Schneider, Stratman, & Kirsner, 2021).

**vascular ulcer**
It happens as a result of arterial insufficiency, which reduces the amount of nutrients and oxygen that reach the tissues, leading to ischemia and tissue destruction. Peripheral arterial disease, which is brought on by both atherosclerosis and narrowing of the arterial lumen, is the most frequent aetiology associated with this particular type of ulcer. Small and medium-sized vessels can occasionally be affected by this condition, which is typically thought to be a disease of the big artery vessels. Examples include Buerger's disease, arteriovenous malformations, microthrombotic disorders, or coagulopathies (Carstens et al., 2021).
Thromboangiitis obliterans (TAO), often known as Buerger's disease, is a segmental, progressive, nonatherosclerotic illness that typically affects the small- and medium-sized arteries in the upper and lower extremities. Unidentified intimal antigen is thought to be the catalyst for the Buerger inflammatory process. Distal ischemia is caused by venous problems, such as thrombophlebitis. It is caused by segmental occlusions of the distal arteries of the lower extremities, with frequent involvement of the upper extremities. Although its etiology is uncertain, cigarette use is a significant factor in its beginning and recurrence (Donnelly, Emslie-Smith, Gardner, & Morris, 2000).
Associated with diastolic hypertension are painful ulcerations on the lower leg, known as Martorell ulcers. Arteriolar vessel blockage is the underlying reason.

**Alzheimer's ulcer**

One of the most dangerous side effects of diabetes mellitus, an endocrine disorder that impairs insulin secretion and produces variable degrees of peripheral resistance to it, which ultimately results in hyperglycemia, is diabetic ulcers. This type of ulcer, primarily affecting the hands and lower limbs, induces cramping, dryness, a lack of sweat, and pain even when the patient rests. They are the outcome of vascular disease, metabolic dysfunction, and diabetic neuropathy (Palumbo & Melton, 1985).
Furthermore, endothelial damage, hyperlipidemia, and the long-term onset of atherosclerosis are all brought on by hyperglycemia and changes in glucose metabolism. Glycated proteins harm the endothelium and the neurons by promoting the release of ROS, which then encourages the generation of cytokines that promote inflammation and atherosclerosis. Glycated proteins, on the other hand, have been found to cause apoptosis and stop the migration of endothelial stem cells, which contain the development of new blood vessels (Adler, Boyko, Ahroni, & Smith, 1999).

**unusual Wound**

Any wound that does not heal properly is considered to be unusual. These wounds have an odd look, are disproportionately painful, are found in areas where there should not ordinarily be an injury, and do not heal after 3 to 6 months of proper conventional care. The etiology of these wounds may be inflammatory, vasculitic, infectious, metabolic, or hereditary, among other things (Mathew-Steiner, Roy, & Sen, 2021).

**Epidemiology at the now and upcoming tendencies**

Chronic wounds are a diverse group of wounds that together represent a severe public health issue because they place a heavy burden on people's personal and societal resources, have a poor health-related quality of life (they can result in disability, anxiety, social isolation, depression, etc.), and have high management costs. The incidence of chronic wounds is anticipated to rise further due to the ageing population, diabetes, obesity, and infections. They can also cause major medical issues, such as infections, sepsis, loss of mobility, an increased risk of hospitalization, the requirement for limb amputation, and even death if they are not adequately controlled and treated (Wilkinson & Hardman, 2020).

This makes chronic wounds a severe social, economic, and health issue, together with the loss of healthcare due to the COVID-19 pandemic in the last three years. Additionally, in the past 15 years, there has been an increase in interest in our nation's ability to treat chronic wounds, leading to the development of wound care centre units that, for the most part, are housed in hospitals or integrated into other healthcare facilities, giving all patients access to one healthcare area. Others are found in hospitals, primary care facilities, university centres, or private consulting centres (Comino-Sanz, López-Franco, Castro, & Pancorbo-Hidalgo, 2021).

**Chronic wounds and their related comorbidities**

Although the primary focus of this study is on the care of immune system-related chronic wounds, the circumstances or factors that may favour their development or complicate the Wound's course are briefly discussed here.

***Genetics***

These hereditary diseases impact collagen, elastin, and mucopolysaccharides in connective tissue. One of the most prevalent connective tissue disorders is Ehlers-Danlos syndrome. Its primary traits include skin fragility, joint suppleness, and hypermobility, all of which make Wound healing challenging and frequently hypertrophic. This diverse set of illnesses can affect the amount of collagen or how it is structured. Due to enzyme abnormalities, the development and organization of the extracellular matrix may be impacted in other situations (Raziyeva et al., 2021).

***Systemic***

There is a subset of systemic disorders with metabolic origins, including diabetes above mellitus and obesity, that slow wound healing. The latter is characterized by an excessive buildup of adipose tissue and body weight disproportionate to the individual's height. Obese patients' skin is brittle because collagen deposition does not keep pace with skin area expansion. Additionally, these patients have lower levels of leptin, a hormone that promotes Wound healing, among other things. It alters transepidermal water loss and causes xerosis by affecting the integrity of the skin barrier. On the other hand, obesity is the key factor contributing to the microvascular system's dysfunction (Burgess, Wyant, Abdo Abujamra, Kirsner, & Jozic, 2021).

It has to do with venous insufficiency brought on by venous valve failure, high intra-abdominal pressure, and vascular stress. The lack of vascularization in adipose tissue results in local hypoxia, which delays the delivery of the immunological components necessary for wound healing and medications, raising the risk of infection and slowing recovery. The most prevalent causes of chronic kidney disease, which can also result from some autoimmune illnesses (such as systemic lupus erythematosus), are diabetes and hypertension. Chronic renal failure slows granulation, delays edema formation, disrupts keratinization, and creates vast voids between epithelial tissue, impeding Wound healing (Comino-Sanz et al., 2021).

A decrease in angiogenesis, cell proliferation, and chronic inflammation are also caused by it. Uremia also stops collagen and hydroxyproline from forming and fibroblast growth. Even during dialysis, some too-big molecules build up to hazardous quantities, increasing tissue fragility, producing ROS, or causing a persistent inflammatory state. However, the decreased phagocyte activity, ischemia, and microcirculatory abnormalities in dialysis patients enhance their risk of infection.

***autoimmune and inflammatory pathologies***

This group of illnesses comprises a variety of conditions that manifest differently and affect the immune system's regular operation. They may result in immune system-mediated tissue damage, persistent inflammatory conditions, or aberrant immune cell function. Additionally, the medications used to treat these diseases can occasionally stop or postpone the healing of wounds. As discussed in chapter 3, inflammatory and autoimmune illnesses such as pyoderma gangrenosum, hidradenitis suppurativa, or certain vasculopathy frequently manifest as chronic wounds (Farahani & Shafiee, 2021).

***negative behaviours***

Smoking and other harmful behaviours are significant factors in the slow healing of wounds. The three substances that make up a cigarette, nicotine, carbon monoxide, and hydrocyanic acid, have the most impact on the healing of wounds. Vasoconstriction brought on by nicotine encourages local ischemia and can result in a 40% reduction in blood flow. The duration of this impact is roughly 45 minutes. Additionally, it prevents the growth of fibroblasts, macrophages, and precursors to red blood cells. Tissue hypoxia results from carbon monoxide's significantly stronger affinity for hemoglobin than oxygen (Abazari, Ghaffari, Rashidzadeh, Badeleh, & Maleki, 2022).

***Infections***

One of the most common hazards connected with a wound is infection, which can result in an inflammatory state and delay the proliferative and remodelling stages of healing. Germs' impact on the complement system and platelets can also affect Hemostasis. The germs in the Wound will also result in thrombocytopenia and platelet agglutination.

***Post-radiotherapy***

Ionizing radiation is used in radiotherapy to harm healthy cells as well as tumour cells to kill tumour cells by destroying their DNA. Enzymes react to this damage and either repair it or make it worse, which causes mutations with undesirable side effects. Radiation has a more significant impact on tissues that renew quickly, including the skin. Radiation-induced skin damage triggers an

inflammatory response in the underlying supporting tissue. Granulation takes longer to form and does so with less efficiency when it does. Ischemia, fibrosis, necrosis, and tissue atrophy are all consequences of damage to the microvasculature in radiation-damaged tissue. Radiation exposure can also cause fibroblasts to stop functioning, which leads to fibrosis and poor wound healing (Zhou et al., 2019).

***economic and psychosocial effects***

Chronic wounds are common and are connected with significant and rising healthcare expenses. This emphasizes the need to initiate early diagnosis and therapy. In 1996, the first investigation on the link between chronic wounds and depression was conducted. Numerous studies have shown that people with chronic conditions have notable depression prevalence. Most of the time, people with chronic ulcers need on going medical care. They will typically need home care or frequent trips to health facilities. They feel unwell and like a burden to their environment (Ahmadi et al., 2019).

The patient experiences anxiety, resignation, and a lack of optimism regarding the efficacy of the treatment due to the chronic nature and lengthy recovery times. Additionally, we must consider additional elements like discomfort, an inability to walk, a loss of independence, and a decline in social contact. Patients will also have more general burdens, including melancholy, anxiety, sleep difficulties, and wound-specific obligations (odour, exudate, pain, etc.). There are also a sizable number of patients with limited activities and a large cost burden from their care and treatment requirements, which may impede their social inclusion.

Families are the primary source of social support for these patients, who also receive emotional support and wound care. These patients have a small number of highly intimate non-family relationships. It's important to emphasize how well the patient and nurse chemistry has grown. This sort of patient generally has less access to social support and contacts. They also feel guilty over the strain they put on their friends and family (Zhou et al., 2019).

## IMMUNOLOGY FOR HEALTH

Normal Physiology of Healing Hemostasis, inflammation, proliferation, and remodelling-maturation are the four stages of the physiological healing process (Figure 2).

***Phase of Hemostasis***

Under normal circumstances, it happens immediately after the injury and over the next 3–4 days. To stop blood loss, begin with vasoconstriction in the afflicted area. The procedure includes fibrin deposition and maturation, thrombin production, adhesion and aggregation of platelets, and platelet activation. To seal the injured vessel and stop bleeding, the endothelium first releases the von Willebrand factor, which stimulates platelets to activate and adhere to collagen. Primary Hemostasis is the term for this procedure. The active endothelium also releases the tissue factor (T.F.), which is crucial in starting the coagulation cascade (Nazempour et al., 2020).

T.F. starts the so-called extrinsic pathway of coagulation. It is in charge of factor VII's activation. This triggers further mechanisms that result in the production of thrombin microdoses. This potent platelet agonist stimulates some clotting factors, leading to an increase in the number of active platelets, a larger surface area for clotting factor activation, and the production of macro doses of thrombin. By encouraging the synthesis of mesh fibrin, which gives the clot stability, this molecule causes secondary Hemostasis.

Mechanisms that restrict this process are put in place concurrently with the clot's creation to restore blood flow. On the one hand, coagulation is stopped through a variety of mechanisms, including direct inhibition of thrombin by antithrombin (T.A.), indirect inhibition of thrombin by tissue factor inhibitor (TFI), and actions carried out by thrombin itself through interactions with other endothelial and hepatic proteins (Cheng, Farrokhi, Ghahary, & Jalili, 2018).

On the other hand, after it has served its purpose, a process known as fibrinolysis causes the clot to be destroyed. An enzyme called plasmin is created from plasminogen by tissue plasminogen activator.

Urokinase can also activate plasmin when it's present. Fibrin and fibrinogen will degrade by the action of plasmin.

***period of inflammation***

Cell death from tissue injury results from both necrosis and apoptosis. DAMPs (danger-associated molecular patterns) are inflammatory stimuli released as a result. Additionally, after the incision stops bleeding, vasodilation increases blood flow locally and across the surroundings, attracting immune cells that fight infection and aid survival. Neutrophils are chemoattracted to the activated complement system proteins released by the injured endothelium. So, for the first 24 to 48 hours, neutrophils predominate, and their primary job is to clean the Wound by getting rid of the clot, the germs, and the damaged tissue (Nieman et al., 2014).

The phagocytosis of pathogens, the production of antimicrobial proteins, proinflammatory cytokines that heighten the inflammatory response, growth factors, and metalloproteinases that break down the extracellular matrix (ECM) are all a result. Once they have finished acting defensively, the infiltrating neutrophils die, significantly increasing the necrotic burden and causing a proinflammatory cycle. Upon entering the area of the lesion, monocytes that have been activated by DAMP recognition by Pattern Recognition Receptors (PRRs) also secrete proinflammatory cytokines like Interleukin 1 (IL-1), tumour necrosis factor-alpha (TNF-) and transforming growth factor beta (TGF-) (Awad-Igbaria et al., 2022).

Macrophages control the lymphocytes' adaptive immune response as well as the removal of pathogens, foreign objects, apoptotic neutrophils, and damaged tissue components. Mast cells in the damaged area's connective tissue become activated, releasing cytokines that encourage neutrophil recruitment and proteases that break down the ECM. At the end of the inflammatory phase, macrophages release cytokines and growth factors that promote the proliferation of fibroblasts and endothelial cells and the production of the matrix (granulation tissue). In the later stage of tissue remodelling, T lymphocytes have a more vital modifying role (Nazempour et al., 2020).

***Phase of proliferation***

This phase starts with the activation of fibroblasts, which then increase by secreting structural proteins that form collagen, fibronectin, and ECM proteins. This increases the resistance of the tissue and the vessels that irrigate it. This results in the formation of granulation tissue, a vascularized fibrous tissue. Following this procedure, fibroblasts develop into myofibroblasts and take part in the contraction of the Wound, which finally causes granulation tissue and surface epithelium to fill the wound area. The remodelling phase can start at this moment, so angiogenesis and the development of new blood vessels from existing ones occur (Cheng et al., 2018).

TFG-, platelet-derived growth factor (PDGF), and fibroblast growth factor (Fibroblast Growth Factor, or FGF), secreted by platelets during the hemostasis phase, work together with factors released by tissue under hypoxic conditions, such as hypoxia-inducible factor 1 (HIF) and vascular endothelial growth factor (also known as vascular endothelial growth factor, or VEGF), to cause this initial phase of tissue repair.

***Renovation phase***

Re-epithelization of the injured tissue is what it entails. To accomplish this, neutrophils and monocytes activate and promote the proliferation of the keratinocytes located at the borders of the Wound, around the hair follicles and sebaceous glands nearby. Additionally, keratinocytes move across the various wound layers, from the dermis to the surface, changing in morphology. To help the cell move, they elongate, flatten, and create actin filaments and pseudopodia. Growth factors generated by keratinocytes and activated dermal fibroblasts in the dermis control all this. The Wound is covered by these proliferation-migration mechanisms (Zhou et al., 2019).

***Physiopathology of persistent inflammation***

Chronic wounds have healing stasis because of chronic inflammation, a significant factor. Typically, the etiology is multifaceted, resulting in a hostile environment where proinflammatory cytokines, chemokines, proteases, and their inhibitors are out of balance. Cell proliferation is inhibited by the protracted inflammatory state, which stops the Wound from healing. This cycle is maintained by altered cellular or systemic responses, tissue hypoxia, repetitive trauma, and elevated bacterial loads (Ahmadi et al., 2019).

The increased infiltration of neutrophils into the afflicted tissue is one of the fundamental causes. This produces excessive ROS generation, directly harming cell membranes and the ECM before causing premature cell death. Proinflammatory cytokines generated by active neutrophils and macrophages also trigger the production of proteases and MMPs. The production of growth factors rises in chronic wounds. Still, their bioavailability is low, leading to an imbalance that increases ECM degradation and inhibits cell migration, fibroblast proliferation, and collagen synthesis. These proteins also degrade growth factors by decreasing MMP inhibitors. This cycle then repeats as ECM breakdown products encourage inflammation (Mathew-Steiner et al., 2021).

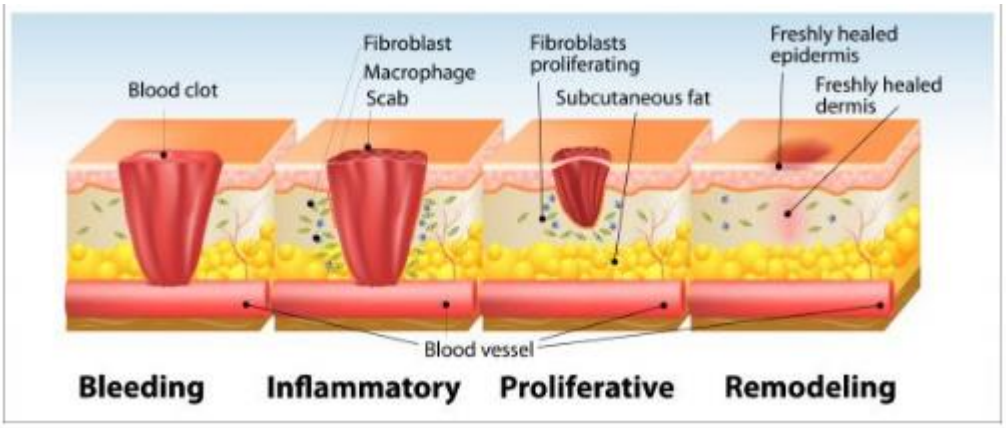



***Figure 1*** *shows the stages of wound healing.*

To establish tissue hemostasis, platelet activity first induces coagulation. Additionally, when there is damage, immune cells are alerted and recruited, which results in an inflammatory reaction. This will encourage fibroblast growth, which will aid in producing fresh extracellular matrix and the development of new blood vessels. In the end, the stimulation of keratinocyte proliferation and migration from the dermis to the epidermis remodels and heals the tissue.

**AUTOINFLAMMATORY AND AUTOIMMUNE DISEASES WITH CHRONIC WOUNDS**

As previously said, chronic wounds develop due to the healing process being stopped in the inflammatory phase and being unable to move on to the proliferation phase, which causes angiogenesis to worsen and the deposition of extracellular matrix. Epidemiological studies show that nearly 80% of leg ulcers have a vascular etiology. In comparison, in just over 20% of cases, the causes are more complex and have an immunological component that must be taken into consideration (as in pyoderma gangrenosum); there are multiple pathways and their interactions that contribute to the inflammatory state.

Conditions that encourage the development of chronic wounds, such as prothrombotic phases (as in antiphospholipid syndrome), vasculitis linked to immune complexes, or side effects brought on by treatment resistance, are examples of autoinflammatory and autoimmune disorders. Being classified as autoinflammatory/autoimmune, most immune-mediated diseases typically have deficiencies in innate and adaptive immune responses due to mutations in numerous genes. Not all predispositions are hereditary because triggering events (such as stress, diseases, trauma, etc.) can act in addition to the genetic component.

An essential gene that controls the innate or adaptive immune response, respectively, can develop mutations or abnormalities, leading to some rare disorders that are exclusively autoinflammatory or exclusively autoimmune. Regarding involvement, autoimmune illnesses, including particular immunity, can have systemic manifestations (syndromes with several organs and tissues damaged), while others are organ-specific. Autoinflammatory disorders are systemic, meaning they can harm any tissue or organ. Others are organ-specific (autoantibodies directed against elements of the endocrine, blood, neuromuscular, skin, or other systems), affecting various organs and tissues (Deldar, Monsefi, Salmanpour, Ostovar, & Heydari, 2021).

A diverse collection of illnesses known as autoinflammatory disorders frequently cause a wide range of ulcerations on the skin and mucous membranes. They are caused by inappropriate innate immune activation brought on by mutations and changes in the signalling pathways that control the natural immune response to physical injury or tissue damage. This leads to unchecked inflammasome activation and significant generation of active IL-1. As a result, myeloid effector cells are attracted to the wound site and become uncontrollably activated, producing proteases that damage the skin's structural elements.

These illnesses are now categorized according to their pathophysiological mechanisms, such as inflammasomepathies, disorders of the activation of the NF-B pathway, infections caused by the abnormal folding of innate immune system proteins, complement disorders, etc., thanks to a better understanding of the molecular causes. Immunosuppressive and immunomodulatory therapy regimens work well for the majority of these disorders. On the other hand, therapeutic resistance transforms the acute inflammatory response into a persistent, unresolved process that causes tissue deterioration (Huang et al., 2021).

The earliest systemic autoinflammatory disorders to be reported had Mendelian inheritance. However, it is now known that there are other diseases with unknown and non-hereditary causes. Chronic hereditary autoinflammatory illnesses and hereditary periodic fever syndromes comprise the two main categories of inherited systemic autoinflammatory diseases.

Acute, self-limiting, repeated, and variable-length inflammatory events manifest in the first group of diseases. This group's predominant illness is familial Mediterranean fever. However, it does not result in persistent wounds; instead, it primarily appears as fever, aseptic inflammatory serositis that primarily affects the peritoneum and pleura, muscle soreness, or severe atopy. Chronic rather than episodic illnesses caused by inherited autoinflammatory processes may occasionally experience exacerbations. The condition in question is sterile pyogenic arthritis, pyoderma gangrenosum, and acne syndrome (sometimes known as PAPA in English).

Starting at a young age, it primarily develops at the joint and skin level. Large joints are typically affected, starting as recurrent monoarthritis with purulent synovial fluid. As the patient ages, skin symptoms like cystic acne, particularly after puberty, and pyoderma gangrenosum (or P.G., which we shall discuss later), typically manifest after trauma and injections, also develop. Some patients have also been found to have hidradenitis suppurativa (H.S.), a chronic inflammatory illness in which an excessive innate immune response results in suppurative inflammation of the hair follicles, which clog.

***recurring injuries in autoimmune illnesses***
***gangrenous pyoderma***

P.G. is still among the most challenging dermatological conditions to recognize and manage. It often manifests beyond 50, with a somewhat higher frequency in women. According to epidemiological research, P.G. often displays before other systemic autoimmune disorders, such as ulcerative colitis or inflammatory bowel disease, in patients with P.G. It is a rare form of neutrophilic dermatosis characterized by painful ulcers that develop quickly. The lesions typically present as a small wound on a lower extremity that extends into a soft, nodular, or pustular inflammatory papule before quickly rupturing and turning into a necrotic ulcer.

The purple undercut border indicates active disease and anticipated ulcer growth despite a validated quantitative score for activity or severity. According to their development course, ulcers may differ

morphologically in size, colour, or depth (figure 3). It has roots in an autoinflammatory process in which innate immune cells attack the tissue without an infectious stimulus and produce excessive amounts of inflammatory cytokines (Ma et al., 2022).

Trauma, which causes the release of IL-36 and IL-8, is the primary mechanism underlying lesion formation. Psoriasis and PG-related conditions such as ulcerative colitis, Crohn's disease, and hidradenitis suppurativa are also facilitated by IL-36. Furthermore, autoantigens are released as a result of tissue injury. The protein tyrosine phosphatase type 6 (PTPN6) modifies the signals sent by the T-cell antigen receptor and cytokine receptors and appears crucial in pathogenesis. As a result of the overactivation of the inflammasome caused by the threonine phosphatase-interacting protein 1 (PSTPIP1), which is involved in the regulation of intracellular signals of the inflammatory response, neutrophil-mediated autoinflammation is seen.

P.G. ulcers have an undercut edge with a distinctive red-violet colour that results from the dermis' destruction by neutrophil infiltration, which leaves the epidermis alive but compromises its blood flow. In addition, this infiltrate makes the ulcer bed highly exudative. TNF has a wide range of inflammatory actions. Still, it also plays a crucial role in developing P.G. because it promotes neutrophil migration by increasing vascular adhesion, IL-8 production, and inflammasome activation. However, current data from gene expression analyses in papule biopsies and immunohistochemistry staining in lesions suggests that CD4 T cells play a role in developing this illness.

As an immune-mediated disease rapidly progressing, P.G. is treated with quick-acting medications like systemic corticosteroids and cyclosporins to interrupt the inflammatory process. To get the therapeutic dose, however, generally, high and prolonged levels of these medications are needed, which increases the likelihood of adverse responses such as renal failure or hypertension, among others. To lessen the negative effects of this treatment, immunosuppressants that save steroid hormones are being used in combination.

There haven't been any conclusive studies on ulcer treatment. Therefore, we can only rely on professional judgment. Everyone agrees on the significance of proper daily hygiene, applying compression therapy to reduce edema, provided that our patient does not have arterial insufficiency, and pain management given that ulcers brought on by P.G. are among the most painful. The patient's stress, anxiety, and sadness may result from inadequate pain management. Topical or intralesional corticosteroids applied to the ulcer's edge may be effective for lesions smaller than 2 square centimetres. In a trial including 5 patients, total remission was achieved in every single one after 6 weeks of topical tacrolimus therapy.

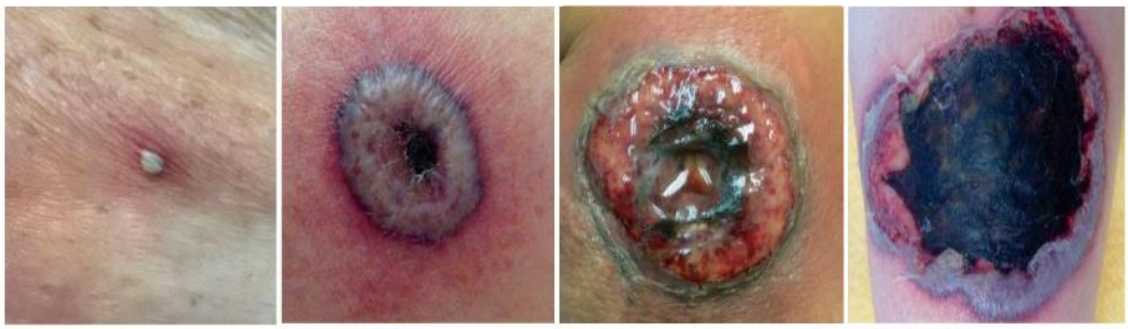


***Figure 2*** *shows the development of typical chronic wounds from pyoderma gangrenosum with and without immunosuppressive therapy.*

An initial pustule that develops into a violaceous ulcer with peripheral erythema and a frequently undermined edge after a few days is the typical beginning of the condition. The ulcer may deepen after one or two weeks, and after a few weeks, the vascular damage produces tissue necrosis, resulting in a crust. Immunosuppressive medication inhibits the exudate and inflammatory erythema, allowing the scar to heal and eventually take on its distinctive cribriform and stony appearance with the author's permission.

***suppurative hidradenitis***

Acne inversa, commonly known as hidradenitis suppurativa (H.S.), is a persistent pilosebaceous follicle inflammatory condition with systemic symptoms. The inguinal, buttock, perianal, and axillary regions are the most common locations where patients with this illness develop painful. Patients have a lower quality of life due to the pain brought on by purulent discharges and their unpleasant smell. Its complex etiology involves genetic, environmental, behavioural, hormonal, and microbial variables.

Immune activation is further encouraged by bacterial dissemination on these skin surfaces, particularly in blocked hair follicles. Inflammation affects more than only the skin; H.S. patients frequently also have inflammatory bowel disease, metabolic syndrome, type 2 diabetes, atherosclerosis, and spondyloarthritis. A mutation in the genes producing -secretase, an intramembrane enzyme that interacts with numerous transmembrane proteins, such as the Notch receptor, has been found in H.S. patients, decreasing its activity. This mutation has been linked to genetic causes of H.S.

The Notch signals encourage regulatory T cells' immunosuppressive activities, inhibit the differentiation of hair follicle stem cells into keratinocytes, and support T cell-controlled hair regrowth. According to studies conducted on mice, either a rise in the activity of the protein above or its lack results in an increase in the number of keratinocytes and, when blocked, the transformation of hair follicles into cysts. 90% of patients smoke or have smoked tobacco in terms of lifestyle. Nicotine promotes the onset and progression of the condition by causing epidermal hyperplasia, which can result in hyperkeratosis and blockage of the hair follicles. Additionally, it promotes the synthesis of IL-10 and the accumulation of bacteria within cells (Cheng et al., 2018).

Obesity affects 50% of patients, and metabolic syndrome affects 40%. Given the inflammatory state it produces, the metabolic changes it brings about, and the increased skin contact area, obesity can aid in developing this condition. Because fewer sebaceous glands exist in these locations, friction between the skin exacerbates mechanical damage. Due to this harm, more DAMPs are produced, and skin bacterial invasion is encouraged. This will cause innate immune cells to become activated and release TNF and IL-1, which in turn will trigger the expression of numerous chemokines.

This will encourage the infiltration of immune cells into the perivascular and perifollicular tissue, improving the inflammatory response in these regions. In addition, less IL-22 is produced, stimulating bacterial growth and inhibiting the healing of cell damage in the affected area. As a result, a persistent inflammatory response is made. The dermal fibroblasts are triggered and create MMPs, which breakdown the tissue, favouring the enormous infiltration of granulocytes and the development of pus. The follicle then ruptures as a result of its subsequent dilatation. These occurrences may also result in the development of sinus tracts and fistulas, tunnels that drain pus.

Conversely, these inflammatory mediators may enter the bloodstream and encourage systemic inflammation, which may be a factor in the comorbidities seen in H.S. patients (insulin resistance, metabolic changes, and elevated cardiovascular risk). Due to the lengthy diagnosis process, the small selection of evidence-based therapy, and the lack of curative medications, patients with H.S. frequently have unmet medical requirements. It is advised to modify the course of treatment based on the patient's condition and the severity of the disease. Antibiotics or anti-inflammatories are used as part of pharmacological treatment. When the disease is localized and of mild to moderate intensity, it has been seen that lesions improve when topical clindamycin is used (Ma et al., 2022).

The most efficient treatment is a systemic antibiotic because if it is more severe, it is frequently accompanied by systemic inflammation and the comorbidities already described. Tetracycline antibiotics have been demonstrated to be effective in numerous investigations. Additionally, it has been shown that taking rifampin and clindamycin together for 10 to 12 weeks would lessen pain, lesions, and suppuration. Regarding anti-inflammatory medication, it has been demonstrated that

applying glucocorticoids intralesionally, such as triamcinolone, significantly reduces pain. Additionally, there is evidence in favour of using biologic therapy.

Adalimumab, an anti-TNF antibody given subcutaneously once a week, has been shown to reduce discomfort, lesions, and dermatologic quality of life for at least three years. Other biological treatments based on monoclonal antibodies that target inflammatory cytokines like IL-1, IL-17, or IL-23, as well as inhibitors of different molecules that mediate inflammation (phosphodiesterase-4, granulocyte growth or G-CSF, C5a, etc.) are currently being investigated.

Surgery is considered for people with severe chronic lesions that don't respond to medicines, anti-inflammatories, or permanent lesions, like tunnelling. The surgical procedure used will depend on how severe the injury is. On the other hand, the use of a laser to destroy damaged hair follicles through photo thermolysis (using a CO2 laser for widespread chronic lesions or yttrium and aluminum garnet with neodymium impurities for lesions in confined areas) has shown promise in lowering erythema, edema, suppuration, and discomfort.

*Inflamed nodule* *Ulcers, scars and fibrotic bands*

***Figure 3*** *shows the development of the typical chronic Hidradenitis suppurativa wounds. An inflammatory nodule typically appears in the area of the skin folds and causes friction with the apocrine glands after 1-2 weeks of the usual onset; chronic inflammation for a further 1-2 months results in the development of sinus tracts and fistulas. The chronic inflammatory response blocks the follicle, leading to the formation of characteristic cysts or comedones.*

The follicle and skin rupture causes ulcers and pus abscesses, and repeated attempts to treat the diseased area result in scarring and fibrotic bands or plaques.

***chronic injuries brought on by autoimmune disorders***

Autoimmune diseases (A.D.) are a diverse collection of illnesses whose causes are typically unclear but frequently connected to immune cells recognizing protein constituents of cells and tissues. This recognition leads to a persistent inflammatory response that, over time, damages anatomical structures. As a result, some unfavourable situations cause persistent skin ulcers on the lower limbs. According to their epidemiology, these illnesses are difficult to detect. Although their actual prevalence is unknown, they are believed to primarily affect women (who account for up to 75% of cases) and 3–10% of the world's population. Rheumatoid arthritis, Sjögren's syndrome, systemic lupus erythematosus (SLE), antiphospholipid syndrome (APS), scleroderma, and vasculitis are the most frequent adverse reactions (Nieman et al., 2014).

Several susceptibility genes, including those in the HLA complex and PTPN22, as well as external environmental variables (infections) and internal factors (hormones, stress, etc.), all play a role in the complicated and, in some cases, poorly understood etiology of A.D. Corticosteroids and immunosuppressants, such as monoclonal antibodies like belimumab, are the most effective treatments for AD-related inflammation. Since there is no antibiotic response, doctors may prescribe B lymphocyte stimulator, also known as BLyS, in SLE or rituximab, an anti-CD20, in rheumatoid arthritis.

***Vasculitis***

Complex and quite diverse processes are all a part of cutaneous vasculitis, yet they all share an inflammation and necrosis of the skin's blood vessels. Different clinical symptoms that typically affect the lower limbs include Liveo reticularis, inflammatory subcutaneous nodules, palpable purpura, necrosis, and secondary ulcerations, depending on the size of the afflicted vessels (small, medium, or enormous).

Vasculitis is the most prevalent nonspecific skin lesion in between 20 and 40% of patients of systemic lupus erythematosus. Since it results from the deposition of cryoglobulins, antibodies that precipitate with the cold, it typically affects tiny arteries (capillaries and venules) and is included in cryoglobulinemia.

***R.F., or Raynaud's phenomenon***

It is a typical ischemia problem that can manifest as a side effect of autoimmune conditions like scleroderma. It is distinguished by recurring episodes of vasospasm in the fingers and toes, resulting in pale, cyanotic, and red skin. The vascular changes develop in three stages: a painful spasm, asymmetrical finger whitening, the emergence of cyanosis, and, lastly, reperfusion, which results in the development of erythema. The vascular disease is made worse in 50% of instances by the action of excruciating digital ulcerations, functional impotence, and necrosis. Complex vascular ischemia and likely mechanical mechanisms are involved in the pathogenesis of ulcers (Zhou et al., 2019).

Calcinosis, Raynaud's phenomenon, esophageal motility issues, sclerodactyly, and telangiectasias are all symptoms of the CREST syndrome. Although the autoimmune pathophysiology of this uncommon disease, which affects women four times more frequently than males, is understood, the disease's etiology is still unknown. R.F. often manifests as a first sign of CREST syndrome. An immunological vasculopathy brings on vascular ulcers linked to systemic sclerosis.

An abnormal immune response is triggered by initial vascular injury brought on by ischemia-reperfusion, such as Raynaud's syndrome. Both antibodies against intercellular adhesion molecules-1, which encourage the generation of reactive oxygen species (ROS), and antibodies against anti-endothelial cell antibodies (AECA), which trigger apoptosis, are produced. Infiltration of inflammatory cells and pericyte proliferation brought on by these attacks on the vascular wall will aid in the growth of proliferative-obliterative and destructive vasculopathy. Tiny vessels will be more likely to rebuild under the first scenario but disappear under the second, leading to vascular blockage. In addition, intravascular fibrin deposits and platelet activation will happen.

An ischemic ulcer will develop in tissues with inadequate fibrinolysis and hypercoagulability and a dysregulation of the vasodilation-vasoconstriction processes. In conclusion, to provide the best care and treatments and achieve efficacy, it is vital to consider the likelihood of an immune-mediated disease as the underlying cause when chronic and recurrent wounds without apparent reason are suspected. The management of persistent injuries is then addressed using research-supported nursing techniques (Mathew-Steiner et al., 2021).

## FROM THE NURSING FIELD: MANAGEMENT OF CHRONIC WOUNDS IN AUTOINFLAMMATORY AND AUTOIMMUNE DISEASES

Current nursing practise in the treatment of underlying autoimmune and inflammatory disorders. Most autoinflammatory and autoimmune diseases are chronic and frequently have no known cure. They impact almost every part of a person's life, much like any chronic illness. Consequently, a global strategy incorporating various professionals is crucial for its best management. The importance of nursing care cannot be overstated. On the one hand, it serves as the patient's primary point of contact with other medical specialists (such as rheumatologists, dermatologists, psychologists, and social workers). On the other side, nurses are responsible for monitoring and educating patients to encourage patients' autonomy in managing their illness and foreseeing difficulties.

The actions that nurses take are all directed toward achieving these goals. It has been demonstrated that patient involvement in treating chronic wounds increases the clinical and psychological advantages, improving the quality of life. Education is a crucial component of fighting these diseases. "Patient-centered care" has been adopted over the past ten years in several healthcare settings, and it is especially essential for treating patients with chronic conditions. Although this strategy must be customized, some general principles exist (Mathew-Steiner et al., 2021).

Education should improve the patient's quality of life by ensuring that the patient is knowledgeable about the disease and understands how to treat it, creating a therapeutic regimen based on the recommended treatment, encouraging treatment adherence, and preventing and managing epidemics as needed. Patients have a variety of complicated information needs. Therefore, it's essential to conduct follow-ups where knowledge is updated and new material is provided in response to those needs. Follow-up is also crucial to offer psychological support and identify comorbidities and treatment-related adverse effects.

Given that many of these disorders lead to other pathologies, nurses must take action when they see risk factors, signs, or symptoms that can be changed and strive to avoid sequelae. It entails encouraging healthy lifestyles and removing factors that favour these illnesses' emergence and the comorbidities accompanying them. Good sleep (favours the anabolic renewal processes), low psychological stress, abstinence from alcohol (increases the risk of infections and lowers collagen production), abstinence from tobacco (affects all phases of healing), abstinence from narcotics (cocaine has a vasoconstrictor effect), and abstinence from medications that interfere with coagulation or re-epithelialization (certain medications, such as ci To alleviate pain and reduce inflammation in the event of a disease aggravation and to enhance patients' quality of life, the nurse will also suggest physiotherapy exercises and good lifestyle choices.

The proper care and healing of wounds brought on by this kind of pathology are some of the nursing interventions that significantly impact patients' quality of life (see Table 1 for the many types of bandages and dressings). The nurse must take the patient's temperature, consider any pertinent medical history, and analyze the patient's current nutritional state and eating habits, with an emphasis on fluids, proteins, calories, vitamin B, vitamin C, and iron, which are essential for wound healing (Ahmadi et al., 2019).

Establishing a path of injury treatment requires determining the cause or etiology. Additionally, you should assess the Wound's state in terms of infection, discomfort, size, edge, bed look, or odour indicators. Establishing a treatment plan at regular intervals, not too often, and infrequently is crucial to treating injuries. The healing procedure must be carried out as sterilely as feasible. The level of pain that the patient experiences is important while managing a wound; if it is excessively unpleasant, premedication may be used before healing.

The patient, their family, or other healthcare professionals must all get education, evaluation, and healing skills to recognize infection and other complication symptoms, use the proper healing techniques, and know when to alert the nurse. In this regard, the recent experience during the COVID-19 pandemic has taught us a great deal. During this time, it was essential to modify the management of chronic patients, including those with chronic wounds. Since providing in-person care in these situations is impossible, telehealth and remote monitoring systems have been more widely adopted, strengthening the role of the patient and her environment in healthcare.

The early detection of complications is one of the key worries that healthcare providers have when giving patients with chronic wounds home care. The outcome was much better than anticipated: many patients could appropriately tend to their wounds with appropriate instruction for both themselves and their environment. It is therefore required to develop a coordinated telecare system, in which nurse

training is fundamental, to extend this experience and practise of telecare in chronic wound care and, in turn, to provide suitable training for each patient (Ahmadi et al., 2019).

As previously noted, a thorough evaluation of the Wound is necessary to identify and possibly avoid complications. Even though the nursing team is equipped with instruments like the Wound Assessment Triangle, providing the patient with sufficient instructions for managing himself and his surroundings is still essential. A straightforward and user-friendly monitoring method that enables the patient to quickly spot the ulcer's deterioration with each dressing change and determine whether to contact the monitoring specialist immediately is needed.

***Traditional wound care: a wet atmosphere promotes healing***

Debridement may be necessary in addition to cleansing, dressing, and wound care. It has been shown that healing in a moist environment has advantages over conventional healing in a dry climate, including reduced discomfort and a shorter recovery time. In the proliferative phase of the inflammatory response, keratinocyte and fibroblast proliferation rises, collagen production increases, angiogenesis is stimulated, and autolytic debridement is made more accessible.

Grafts and unique healing materials are two examples of advanced wound healing techniques. Partial thickness autograft is a gold standard for wound healing. The graft is taken from the patient's donor location (thigh, back, etc.) and implanted in the injured area. The graft's healing process heals more quickly than traditional treatments, and the result is more attractive. However, it still results in side effects, including scarring or contracture at the location of the lesion. This therapy's main drawbacks are the amount of skin that can be donated, together with discomfort and infection at the donor site.
Autologous grafts made from cultivated keratinocytes have been employed as a different form of graft since the 1980s. The procedure entails taking cells from a skin biopsy, allowing them to multiply in a dish, and grafting the tissue onto the incision. These are suitable for chronic and acute wounds and do not run the danger of rejection, in contrast to split-thickness grafts. The graft attachment to the bone is essential to this therapy's success.

The ability of the graft to adhere to the basement membrane, which is required for the transplanted cells to live, multiply, and differentiate, is crucial to the success of this therapy. The efficacy of this treatment relies on the pathology; as a result, leg ulcers have a success rate of 30%, giant cell nevi are more varied (20–90%), and grafting occurs in 40% of instances when there is infection. After the graft has been applied, the lesion will fully heal in around 28 days. Complications can arise when using this method as well. Due to its thinness (4-6 layers of cells), the transplant is more prone to infection or enzyme lysis. An essential characteristic of dressings is maintaining the moisture required in the bed for various functions, such as facilitating regeneration, infection prevention, or debridement (Awad-Igbaria et al., 2022).

Due to the drawbacks of grafts, new strategies have been developed, such as using polymers as a delivery medium to encourage cells to adhere correctly and lessen graft contraction, blister formation, and ulceration at the graft site. Graft injury. The graft forms more quickly, and the cells multiply more quickly, lowering the risk of wound infection. Hyaluronic acid illustrates a polymer utilized for this purpose, as its biodegradation and biocompatibility are excellent for cell development and proliferation. Its clinical application for wound healing has a promising future because it has recently been demonstrated to also increase keratinocyte growth in vitro.

Hyaluronic acid must be lysed to promote cell growth, as evidenced by earlier studies that found its breakdown products boost cell proliferation. Its structure makes the ECM cells' migration, multiplication, and mobility more accessible, which helps the dermis heal more quickly. Biopolymers' molecular weight is a crucial component. Low molecular weight hyaluronic acid lyses substances that cause tissue injury and inflammation. On the other hand, high molecular weight hyaluronic acid can

obstruct angiogenesis and impede the delivery of nutrients. However, hyaluronic acid, with a medium molecular weight, promotes wound healing. However, there are restrictions associated with comorbidities in high-risk patients when using this polymer. As a result, transplant success is decreased by artery blockage or Wound infection (Cheng et al., 2018).

## NEW APPROACHES TO THE CARE OF CHRONIC WOUNDS

In the past ten years, biomedical engineering has advanced so that novel methods for creating the ideal environment for wound healing are now conceivable. Non-toxicity, protection of the Wound from the outside environment, including debridement and mechanical stress, the ability to exchange gases and liquids freely, absorption of Wound exudate, ease of removal without damaging the underlying tissue, immunity to infections and bacterial infiltration, thermal insulation, and a minimum requirement for dressing replacement are among the essentials.

The four categories of wound dressings are passive, interactive, advanced, and bioactive.

- The simplest dressings, like cloth gauze, which provide a thin barrier against mechanical stress, are examples of passive dressings. This kind of material, however, might stick to the wound bed, leading to frequent and challenging wound replacement.
- The polymer films and foams in interactive dressings allow them to permeate gases and liquids while preventing bacterial invasion.
- Advanced dressings preserve wound wetness, enhancing the kinetics of tissue regeneration. Alginates and hydrocolloids are two examples of advanced dressings that can soak up a moderate amount of Wound exudate.
- Bioactive dressings are those that contain biological scaffolds or medication delivery mechanisms and actively aid in the regeneration of wound tissue. They are the focus of current research on wound treatment. The following techniques for bioactive wound dressings are provided because they promise to improve chronic Wound healing significantly. They are defined as stem cell carriers, biosensors, and eventually as components of nanosystems for the regulated release of medications.

### *Gel dressings containing stem cell-filled material.*

Despite partial thickness autograft being the Gold Standard in wound healing, alternatives should be sought because of its drawbacks. There are several active research areas where highly intriguing advancements are being achieved. Because of their remarkable capacity to differentiate into various cell strains, self-renew, and release cytokines necessary for wound healing, stem cells are one of them. Mesenchymal stem cells produced from bone marrow are employed, either autologous (from the person) or allogeneic (from a donor). Adipocytes, myocytes, chondrocytes, keratinocytes, and osteoblasts can all develop from this cell type (Şakul et al., 2023).

Due to its use, angiogenesis and granulation tissue development have increased, speeding up the healing of wounds. The method used to harvest the cells is this therapy's biggest drawback. In addition to being uncomfortable, it causes issues when they are collected. This is why researchers are looking into utilizing a different class of mesenchymal cells produced from adipose tissue, which is present in abundance. Liposuction is a less complicated, more straightforward method that can be used to achieve it. Mesenchymal stem cells produced from adipocytes also secrete angiogenic factors and lessen the production of scars. It can be used topically, subcutaneously, intradermally, or intramuscularly, or it can be given as an injection. Combining mesenchymal stem cells with fibroblast support produced the best results.

### *Biosensor-equipped cosmetics.*

Research into the use of environmental sensors has been spurred by the high expenses and infection risk associated with chronic wound healing. The goal is to be able to monitor wound progression or deterioration, improve care, and lower associated costs. Extended treatment times for chronic wounds or professional practises we engage in, like changing needless dressings, come at an added cost

because they not only cause the Wound to take longer to heal but also put it at risk of spreading infection.
The primary objective of utilizing dressings with sensors built in ("smart dressings") is to modify therapy and care based on signals produced by damaged tissue recorded by the sensor electrodes. The sensors can identify changes in pH, protease, or uric acid levels, enabling early detection of infections mostly to blame for sluggish wound closure and prompt reporting. The ability to detect substantial changes in the wound environment is made possible by advances in biological sensor technology, which can be included in dressings (Altiok, Altiok, & Tihminlioglu, 2010).

Late indicators of infection include common macroscopic symptoms such as purulent discharge, erythema around the borders, discomfort, odour, etc. As a result, early diagnosis would encourage the appropriate use of antibiotics and other treatments designed to treat infections, enabling an earlier course of treatment. There are more sensors for this. Some sensors detect temperature changes, odours that signal the presence of bacterial metabolic products without removing the dressings, and optical sensors that use porous silicone to detect infection by Gram-negative bacteria.
There are several that are more intricate, such as pH indicators. Although they help track the regenerative process, their use is challenged by the pH changes in the Wound depending on its healing stage. On the other hand, hydration control is crucial in designing intelligent dressings to ensure appropriate wound closure. A wound will macerate if it receives too much or too little moisture. Since it must be balanced to reap its benefits, it must be monitored.
The ability of the sensor to send an alarm to the patient's mobile device so that they are alerted and can call medical personnel is another benefit of employing dressings with biosensors.

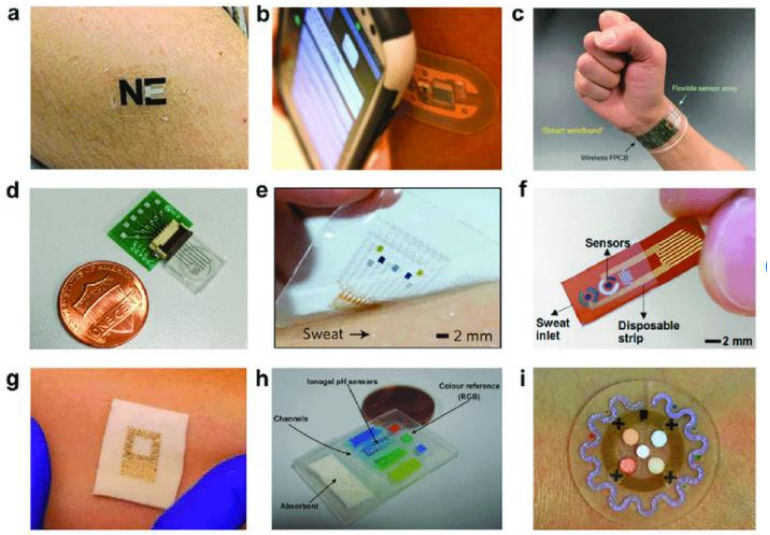



***Figure 4*** *Flexible biosensors to track the development of chronic wounds.*

They can be created using various materials (A-D) and formats (E-H). Modern nanotechnology provides the chance to revolutionize, develop new cures, or boost the efficiency of current treatments. Due to their capacity to delay or prevent drug degradation and maintain drug release over time, nanosystems for controlled drug administration, also known as drug delivery systems or DDS, have a great deal of potential to enhance the therapeutic efficacy of drugs.
Different biocompatible materials (particles, fibres, matrices, gels, etc.) can be assembled in different geometric conformations to create nanosystems for drug delivery. For instance, nanofibrous structures, liposomes, polymeric nanoparticles, inorganic nanoparticles, lipid nanoparticles, and nanohydrogels exist.
Phospholipids form the double-layer structure of liposomes, which are amphipathic vesicles with hydrophilic interiors and hydrophobic exteriors. It is one of the most effective nanocarriers for topical medication delivery. They can house hydrophilic medications like growth factors inside of them. The

drug is encapsulated and is maintained in release by the double layer. Applying it to the Wound creates a moist environment in the wound bed. Deformable liposomes, or transferosomes, are the new generation of liposomes (Pakdeesuwan et al., 2017).
With the advantages of conventional liposomes, their flexibility enables them to penetrate the skin's stratum corneum and reach the deep epidermis. It was demonstrated in a mouse model that using it with growth factors sped up wound healing by as much as 58%. Baicalin transferases applied daily have also been proven to inhibit edema and inflammatory indicators in the skin. The quick and inevitable medication release that occasionally occurs with this treatment is one of its drawbacks. The fundamental obstacle to its current widespread use is low repeatability and stability.

Another study area is solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs), developed to circumvent liposome constraints. Its colloidal form aids in the medication's controlled release and flexible administration. Recombinant human epidermal growth factor (EGF) is abundantly present. Its combination use with both structures has demonstrated significant advancements in wound closure, inflammatory process suppression, and re-epithelialization during the healing process. In a different study, andrographolide, a diterpenoid from the herb Andrographis panicle, was loaded onto lipid nanoparticles and implanted onto chitosan support containing hyaluronic acid (Xiong et al., 2022).
This support had sufficient porosity and had effective medication release control for up to 72 hours. When used on burns of the second degree, it lessens the formation of scars. It enhances the healing process, likely due to the antioxidant effects of chitosan, hyaluronic acid, and nanoparticles. Polymeric nanoparticles are biocompatible colloidal systems that, when coupled with polymers, shield medications from protease breakdown and release them gradually to lessen the need for frequent administration. Currently, gelatin, chitosan, alginate, and polylactic acid are used to make the majority of polymeric nanoparticles. According to studies, polylactic-glycolic acid copolymer nanoparticles coated with the antimicrobial peptide LL37 may be used to hasten the healing of wounds.
Although no impact on keratinocyte proliferation has been recorded, its antibacterial efficacy against Escherichia coli and its cell migration-stimulating qualities have been proven. Increased tissue granulation, collagen deposition, and neovascularization were seen in wounds treated with these compounds and regulating the inflammatory response. Amphotericin B has typically been administered intravenously. However, this sort of DDS has been utilized to replace it with silane-based hydrogel nanoparticles to lessen its cytotoxicity. The new application raised the antibiotic's potency by 72.4% to 91.1%.

Additionally, the fungal biofilm's metabolic activity was lowered by 80–95%. On the other hand, it has been observed that this tactic improves the advantages of gene therapy for skin regeneration. Nanoparticles have been created that are capable of transporting the vascular growth factor (VEGF) gene to mesenchymal stem cells, improving cell survival and, as a result, transplant success, to address the issue of low angiogenic factor expression and low cell survival after transplantation (Gerardi, Pinto, Baruzzi, & Giovinazzo, 2021).

Studies have also been conducted on the operation of nanofibrous structures, which are three-dimensional supports or layers of nanofibres made from chains of natural or synthetic polymers. They are made to replicate the ECM and offer favourable conditions for cells, improving the interaction of those cells with medications. Additionally, it was shown in in vitro tests that treatment with the nanofibers accelerated re-epithelialization and significantly increased the gene production of TGF-, collagen, and EGF in treated cells. They can be used independently or in conjunction with other treatments, such as stem cells, to improve their capacity for differentiation and healing by raising the number of fibroblasts, collagen deposits, and antioxidant enzyme activity while lowering the expression of proinflammatory cytokines (Şakul et al., 2023).

## CONCLUSION:

Lastly, the application of nano hydrogel. It is a polymer whose formulation is "ideal" because of its three-dimensional porous structure, which permits liquid absorption while simultaneously creating a healthy, humid environment and minimizing tissue dehydration. Because it is not sticky, it respects the wound bed and lets oxygen in. Because of its smooth texture, patients can use it topically with ease. Additionally, it is pretty effective in encapsulating pharmaceuticals. A gellan-cholesterol nano hydrogel containing baicalin, an antioxidant polyphenol from the Scutellaria baicalensis plant, was examined to see if it may hasten the healing of wounds.

It has been shown to have the best effect on skin repair and inflammatory marker inhibition. Because of how adaptable its administration is, interest in using it as an injectable is growing. It has also been claimed to use a nano hydrogel made of k-carrageenan, nano silicates, and natural polysaccharides with VEGF added. Cell adhesion and proliferation have increased through its use, and clot formation time has decreased. To fully grasp its therapeutic potential, more in vivo study is necessary.
These are typically deeper wounds that occasionally require bandages to manage excess exudates, such as alginates or foam pads, in the case of inflammatory ulcers brought on by immune system dysregulation (such as those linked to inflammatory and autoimmune illnesses). Hydrogel dressings efficiently increase autolytic debridement and patient comfort when the skin is dry and necrotic.

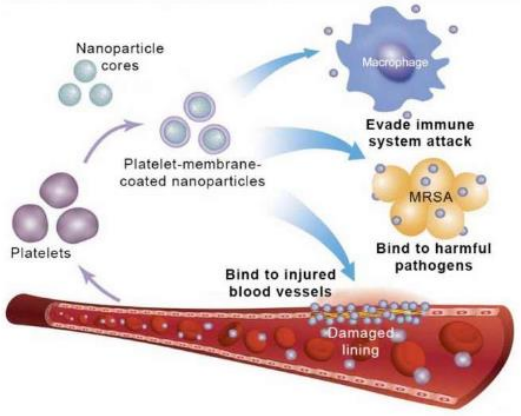



***Figure 5*** *shows nanosystems for the regulated release of medications for wound healing and skin regeneration.*

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