

# Advances in understanding and management of chronic wounds: translational medicine approaches

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## Abstract

Chronic wounds represent a global health challenge, affecting millions of patients and resulting in substantial morbidity, mortality, and economic burden. Great advances are being made in understanding the basic molecular and cellular mechanisms that maintain wounds in a chronic state. Despite these developments, no new pharmacological treatments have been approved for over two decades. This lack of progress reflects limitations in preclinical models, stringent regulatory requirements, and patient heterogeneity. The diverse patient population is characterized by multiple comorbidities and wounds of multifactorial origin, which complicates diagnosis and hinders the development of effective therapies.

Focusing on human studies and translational models, this review provides an overview of the biology of chronic wounds, current treatment options, and recent developments. Emerging translational strategies are shifting the paradigm from passive management with traditional wound dressings to personalized, multimodal interventions, as well as advances in biomarker identification, including omics- and cell-based functional biomarkers. Combined with artificial intelligence, these innovations hold the potential to initiate a new era of precision medicine for chronic wound care.

**Key words:** Chronic wound, advanced wound care, translational medicine, biomarker, personalized medicine



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## 1. Introduction

Wounds are injuries to the skin that can be superficial, such as erosions affecting only the epidermis and healing without scarring. There are also deeper injuries, such as ulcers, encompassing both the epidermis and the underlying dermis, which heal with scars [1]. In both cases, acute wound healing is achieved by a tightly controlled process of sequential, overlapping phases of hemostasis, inflammation, proliferation, and remodeling. In contrast, chronic, non-healing wounds are those that do not heal in an orderly and timely fashion [2]. They have been referred to as a silent epidemic [3] and are a major clinical, social, and economic issue worldwide [4]. In developed countries, including the US and the EU, it has been estimated that 1 to 2% of the total population will experience a chronic wound at some point in life [5, 6]. The patient population comprises more than 10 million individuals in the US alone [3]. This number is expected to increase due to the aging population and growing incidence of metabolic diseases [7].

In addition to high morbidity, chronic wounds cause increased mortality. The 5-year mortality rate due to diabetic foot ulcers (DFU) is 46.2% and 56.6% after minor and major amputations, respectively. This is higher than the pooled mortality rate for all cancers (31%) [8]. While typical diabetes comorbidities such as cardiovascular and renal disease contribute to the mortality, DFU remains a risk factor for death after multivariate analysis [9]. Moreover, in non-diabetic patients with chronic lower extremity wounds, a high mortality rate (28% in 2 years) has been documented [10]. Hospital-acquired pressure ulcers alone are responsible for 60,000 deaths annually in the US [11].

Chronic wounds also cause a big economic burden, not only because the costs for treatment amount to 2–5% of total health care costs [6, 12, 13] but also due to loss of productivity of patients and caregivers.

Current treatment options are unsatisfactory, and no new drugs have been approved in this field for more than 20 years [14]. Chronic wounds have a multifactorial etiology and are dependent on different variables, e.g., the underlying disease (such as diabetes, arterial occlusions and venous insufficiency), age, nutritional status, the microbial environment [2, 15, 16]. This poses a challenge for the development of new therapies, especially since regular cell culture and animal models do not adequately represent chronicity [17–19].

In this review we will present the underlying biology, as well as current and future therapy options, focusing on human studies and translational models.

## 2. Physiology of wound healing

Cutaneous wound healing is a tightly regulated biological process requiring the coordinated actions of numerous cellular players to restore the integrity and function of damaged skin. It proceeds through four overlapping but distinct phases: hemostasis, inflammation, proliferation, and remodeling [20].

**Hemostasis** marks the immediate response to injury, wherein blood vessels constrict to limit blood loss, and activated platelets aggregate with fibrin to form a stable clot. Beyond hemostasis, platelets release key growth factors, such as PDGF (Platelet-Derived Growth Factor), TGF- $\beta$  (Transforming Growth Factor  $\beta$ ), and VEGF (Vascular Endothelial Growth Factor), as well as chemokines, initiating inflammatory and cellular recruitment cascades [21, 22].

**Inflammation** follows rapidly, serving to clear pathogens and debris while priming the wound bed for repair. This phase is driven by recognition of Damage-Associated Molecular Patterns (DAMPs) and Pathogen-Associated Molecular Patterns (PAMPs) via Pattern Recognition Receptors (PRRs) expressed by both immune (macrophages, neutrophils, dendritic cells) and non-immune (keratinocytes, fibroblasts) cells. DAMPs, including ATP, DNA and intracellular heat-shock proteins, elicit sterile inflammation, while PAMPs, as bacterial toxins or viral single-stranded RNA, stimulate immune responses to infection [23, 24].

These molecular cues initiate a coordinated response involving different cell types. Keratinocytes release cytokines and chemokines, recruit immune cells, and secrete antimicrobial peptides [25, 26]. Dermal adipocytes modulate macrophage responses *via* adipokines and lipids [27]. Fibroblasts adopt a pro-inflammatory phenotype, secreting cytokines and MMPs (Matrix Metalloproteinases) that shape the wound environment [28]. Neutrophils infiltrate the wound and eliminate microbes *via* ROS (Reactive Oxygen Species), proteases,

and NETs (Neutrophil Extracellular Traps) [29]. Monocytes differentiate into pro-inflammatory macrophages that clear debris and pathogens, stimulate angiogenesis, and amplify the inflammatory milieu [20].

**Proliferation** begins as inflammation resolves, driven by a phenotypic shift in macrophages toward a pro-resolution state following efferocytosis of apoptotic neutrophils and a metabolic switch to oxidative phosphorylation [30]. Re-epithelialization involves keratinocytes forming a migratory front and a surrounding proliferative zone [31]. Cells at the wound edge undergo partial epithelial–mesenchymal transition, increasing expression of migration-associated integrins and MMPs to traverse the provisional matrix [32]. While pro-inflammatory macrophages support re-epithelialization early, fibroblasts become central in the proliferation phase by producing growth factors that boost keratinocyte migration [31].

Concurrently, fibroblasts proliferate, migrate into the wound bed, and differentiate into myofibroblasts. These cells deposit type III collagen, contract the wound, and release angiogenic factors to promote capillary sprouting [33, 34]. Macrophage-derived TGF- $\beta$  supports myofibroblast differentiation, although excessive activity contributes to fibrosis and scarring. Notably, tissues that exhibit scarless healing, such as fetal tissues, oral mucosa, and reindeer velvet, are characterized by minimal inflammation and low macrophage recruitment [35, 36].

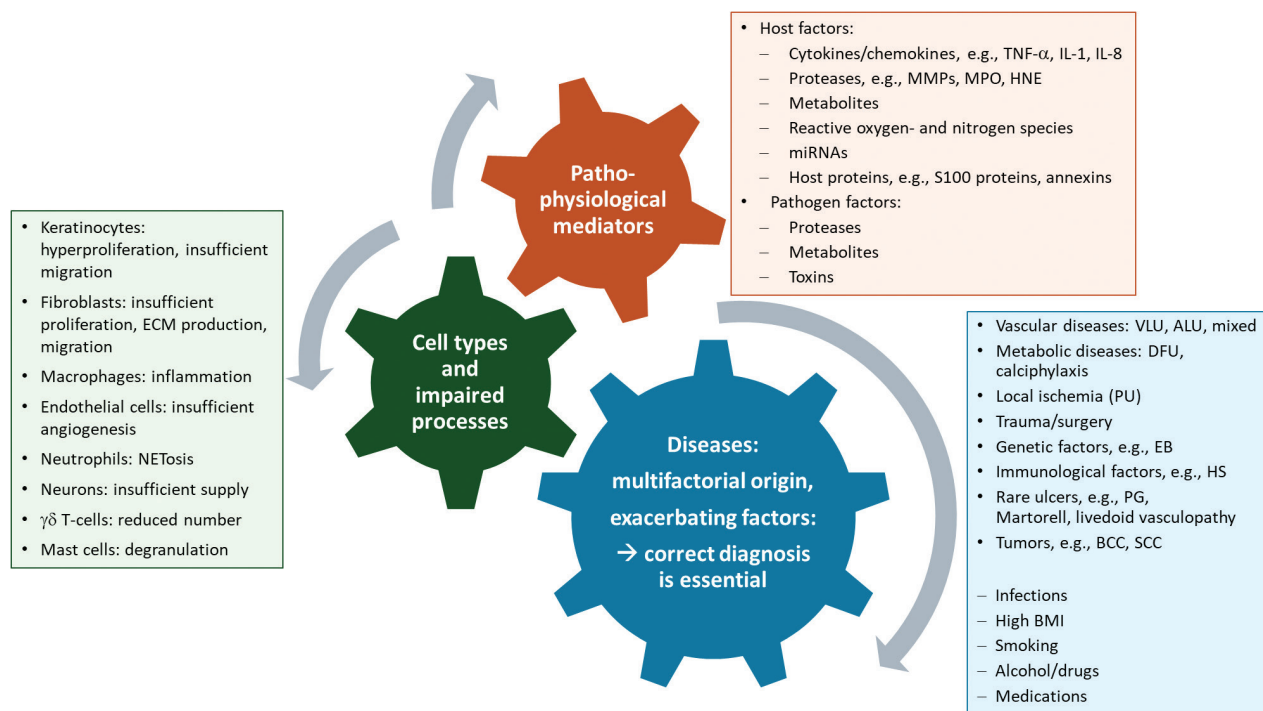
**Remodeling** involves the gradual replacement of type III collagen by cross-linked type I collagen, restoring tensile strength [37, 38]. Mechanical cues stimulate myofibroblasts to deposit ECM (Extracellular Matrix) and close the wound [39]. Apoptosis and senescence of myofibroblasts are essential for terminating the repair process and preventing fibrotic overgrowth [40, 41].

**Chronic Wounds:** Unlike acute wounds, chronic wounds fail to progress through the canonical healing phases. Despite diverse etiologies, they share core features such as persistent inflammation, impaired epithelial and fibroblast function, ischemia, and microbial dysbiosis (Fig. 1).

While elevated pro-inflammatory cytokines (e.g., IL-1 $\beta$ , IL-8) in chronic wound fluid historically supported the notion of excessive inflammation [43–45], recent -omics data suggest a more nuanced picture. Chronic wounds often exhibit deficient rather than exaggerated immune activation, with reduced numbers of pro-inflammatory macrophages in VLU (Venous Leg Ulcers) and non-healing DFUs (Diabetic Foot Ulcers) [31, 46, 47]. In contrast, healing DFUs show fibroblast subtypes enriched in inflammatory mediators like CHI3L1 and IL-6 [48]. Thus, dysregulated—not merely prolonged—immunity appears to be central to chronicity.

Microbial factors further exacerbate dysfunction. While commensals may promote healing through non-inflammatory immune signaling [49, 50], biofilm-dominant pathogens in DFUs and other chronic wounds maintain a state of immune activation via continuous PAMP release [51–54]. These biofilms, however, evade immune clearance, perpetuating a cycle of impaired immunity and persistent infection.

At the edge of chronic wounds, keratinocyte hyperproliferation with impaired migration is common. In DFUs and VLUs, downregulation of FOSL1 and upregulation of miR-193b-3p have been linked to migration impairment [31, 55]. Meanwhile,  $\beta$ -catenin and c-MYC activation contribute to excessive proliferation [56, 57]. Yet, this phenotype is heterogeneous, with some DFU wounds showing reduced keratinocyte proliferation due to deficient EGF/HGF (Epidermal Growth



**Figure 1.** The complexity of chronic wounds. The details are extensively reviewed in [2, 42]. Abbreviations: Extracellular matrix (ECM); tumor necrosis factor (TNF); interleukin (IL); Matrix metalloproteinase (MMP); Myeloperoxidase (MPO); human neutrophil elastase (HNE); venous leg ulcer (VLU), arterial leg ulcer (ALU); diabetic foot ulcer (DFU); pressure ulcer (PU); epidermolysis bullosa (EB); hidradenitis suppurativa (HS); pyoderma gangrenosum (PG); basal cell carcinoma (BCC); squamous cell carcinoma (SCC); body mass index (BMI).

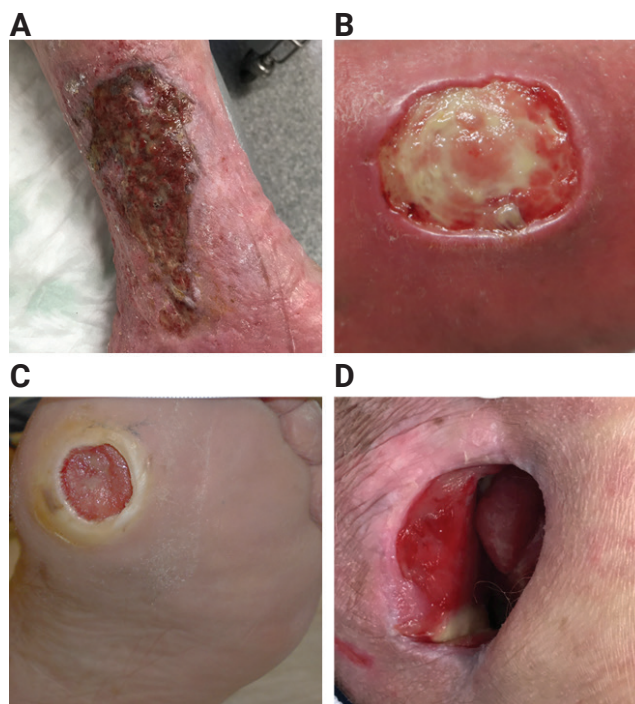
Factor/Hepatocyte Growth Factor) signaling, while increased keratinocyte apoptosis is reported in some PU (Pressure Ulcer) wounds [31, 58].

Fibroblast dysfunction is another hallmark. Cells isolated from chronic wounds show impaired migration, reduced proliferation, and poor growth factor responsiveness [59–61]. Spatial profiling of VLU and DFU samples revealed an absence of proliferative fibroblasts, and single-cell transcriptomics showed lower expression of ECM/inflammation-related genes in non-healing wounds, underscoring the dual role of fibroblasts in ECM deposition and immune modulation to mediate healing [31, 46, 48].

Vascular insufficiency, whether macrovascular (e.g., arterial ulcers) or microvascular (e.g., diabetic wounds or VLUs), limits oxygen and nutrient supply and is another feature common to many chronic wounds. While transient hypoxia promotes healing in acute wounds by induction of myofibroblasts and ECM deposition, persistent hypoxia in chronic wounds is deleterious, promoting cell death and limiting angiogenesis [42]. Chronic wounds also display imbalanced angiogenic signaling and protease-mediated degradation of growth factors such as VEGF [62, 63], exacerbating the impaired angiogenesis in chronic wounds.

### 3. Classification of chronic wounds

Chronic wounds are classified based on their etiology, and there are frequent overlaps. The most common wound types are venous leg ulcers, arterial ulcers or a combination of the two (mixed ulcers), diabetic foot ulcers, and pressure ulcers (Fig. 2). For more detailed information, the reader is referred to comprehensive



**Figure 2.** Common types of chronic wounds: **A)** venous leg ulcer, **B)** arterial ulcer, **C)** diabetic foot ulcer, and **D)** pressure ulcer. Photos are courtesy of Dr. Barbara Binder, Graz (**A**), Prof. Anke Strölin, Tübingen (**B, C**) and Prof. Lars P. Kamolz, Graz (**D**).

review articles on classification and treatment [2, 64–70] and position papers of the European Wound Management Association (EWMA; <https://ewma.org/>).

**Venous leg ulcers** are caused by venous valve insufficiency and venous hypertension, frequently associated with varicose veins or thrombosis. Increased capillary pressure and edema can lead to skin breakdown, typically in the gaiter regions, especially the anterior to medial malleolus and the pretibial lower third of the leg. Ulcers are usually shallow with irregular edges and a granulating base, often with heavy exudate. The surrounding skin shows edema, varicosities, hyperpigmentation (hemosiderin), and lipodermatosclerosis [67].

**Arterial ulcers** arise from advanced peripheral arterial disease (PAD) causing limb ischemia that prevents wound healing. By definition, PAD begins at an ankle-brachial index (ABI) of  $< 0.9$ , but the ABI of patients with an arterial leg ulcer is typically below 0.6 or even lower when chronic critical limb ischemia (CLI) is already present [71]. Arterial leg ulcers are extremely painful and typically located on the pretibial area, the distal lateral lower leg, on the tips of toes, or on bony protrusions on the foot [72, 73]. The prognosis depends largely on the degree of PAD, extent and depth of the wound, and degree of tissue infection [71, 74]. Mixed arterial and venous ulcers combine features of the two [73].

**Diabetic foot ulcers** arise from a combination of diabetic polyneuropathy, repetitive mechanical stress, and peripheral artery disease, which typically affects the lower-leg arteries most severely in cases of long-standing, poorly controlled diabetes mellitus [75, 76]. Motor-, sensory-, and anatomic neuropathy contribute to foot deformity, loss of protective pain sensation, and dry skin – factors that increase the likelihood of developing a DFU [76]. Diabetic polyneuropathy leads to denervation of the short foot muscles, causing the foot skeleton to lose stability and collapse, resulting in deformations that are exposed to intense pressure and

shear forces, particularly in the metatarsophalangeal joint of the big toe, the sole above the middle metatarsal heads, the backs of the toes, and the lateral edge of the foot. Moreover, the diminished sensation associated with diabetic neuropathy prevents patients from adequately perceiving pressure-induced tissue damage. Consequently, repetitive stress may progress unnoticed, leading to large defects in the skin and soft tissues of the diabetic foot [77]. In parallel, impaired perfusion and increased susceptibility to infection common in diabetes mellitus further exacerbate tissue vulnerability and increase the risk of severe complications [76, 78]. Prevention consists of optimal foot support, ideally by wearing orthopedic shoes, and revascularization to improve tissue perfusion. Given the high recurrence rate (40% within 1 year to 65% within 5 years [75]), combined with the fact that neuropathy renders the lesions painless, careful monitoring of the feet is necessary to avoid recurrence or complications like infection and osteomyelitis, which can further delay wound healing and frequently lead to amputation [79].

**Pressure ulcers** typically develop in bedridden or wheelchair-bound patients upon prolonged unrelieved pressure over bony prominences such as the sacrum, trochanters of the thighs, ischial tuberosity, heels, or over the spine or back of the head. In addition to immobility, other risk factors include poor nutritional status (malnutrition), friction, shear stress, or moisture. These wounds may be accompanied by undermining or tunneling. Many pressure ulcers can be prevented by regular repositioning and appropriate support surfaces [80].

**Atypical ulcers** are considered wounds that do not belong to the most typical wound categories, i.e., venous, arterial, mixed, pressure, or diabetic foot ulcers, and they account for approximately 20% of all chronic wounds. Differential diagnosis needs to be broad to include rare as well as more common entities [81]. Some of the more common atypical ulcers are ecthyma (chronic ulcers caused by bacterial infections), vasculitis (inflammatory condition that destroys the wall of blood vessels, leading to ischemic necrosis and chronic wounds), pyoderma gangraenosum (rare ulcer based on autoinflammatory dysregulation of neutrophil granulocytes), Martorell ulcers (caused by hypertensive ischemic atherosclerosis), and the related calciphylaxis, which occurs in patients with terminal renal failure, as well as drug-induced chronic wounds, such as hydroxyurea ulcers (see [81, 82] for comprehensive reviews of atypical ulcers). Also belonging to atypical wounds are those with underlying genetic diseases including epidermolysis bullosa, with gene mutations leading to loss of adhesion and affecting epidermal integrity [83], sickle cell anemia [84] or Klinefelter syndrome [85]. Some atypical wounds are also of neoplastic origin, e.g., Marjolin's ulcer, a squamous cell carcinoma arising in a chronic wound or scar. Other skin tumors, e.g., basal cell carcinoma, malignant melanoma, cutaneous B cell lymphomas, and Kaposi sarcoma, present as non-healing wounds [67]. Diagnosis usually requires biopsy and specialized testing to identify the underlying cause [73].

For all chronic wounds, accurate diagnosis is crucial to guide therapy. A structured, practical approach such as the ABCDE rule is recommended [86]:

- **Anamnesis/case history:** The medical history should include patient age, duration and recurrence status of the wound, BMI, comorbidities such as diabetes mellitus, chronic kidney disease or autoimmune disease, cardiovascular risk factors (e.g., smoking, hypertension, dyslipidemia) and other risk factors like alcohol consumption, poor nutritional status and

medications that might delay healing or affect debridement, such as immunosuppressive drugs or anticoagulants, respectively [65, 87]. The history of venous thromboembolism and/or anticoagulation should also be assessed.

- **Bacteria:** All chronic wounds are colonized, regardless of etiology and signs of infection [88, 89]. They often harbor complex polymicrobial communities, predominantly in the form of biofilm, that evade host immunity and are resistant to antimicrobial treatments [52]. Although the microbial community varies greatly between individual chronic wounds, *Staphylococcus aureus* and *Pseudomonas aeruginosa* are the most common bacteria, both of which tend to develop multidrug-resistant colonies [52, 53]. Therapy is guided by the degree of infection, which is described by the International Wound Infection Institute as a continuum ranging from contamination to systemic infection [90–92]. Diagnostic tools include clinical scoring systems such as WAR (Wound at Risk) [93] or TILI (Therapeutic Index for Local Infections) [94], autofluorescence imaging methods [95] to guide debridement and sampling (e.g., biopsies, curettage, swabs), followed by culture-based or molecular sequencing tests such as 16S rRNA for bacteria or internal transcribed spacer region for fungi to determine the pathogens [52, 91]. DFUs, deep ulcers, or ulcers over bony prominences are particularly susceptible to osteomyelitis, which should be assessed using probe-to-bone tests or Magnetic Resonance Imaging (MRI) [65].
- **Clinical examination** includes location of the wound and assessment of wound bed, wound edge, and skin surrounding the wound following the Triangle of Wound Assessment defined by the World Union of Wound Healing Societies (WUWHS) [96]. The presence of granulation tissue, slough or necrotic tissue, and the amount, color, and odor of exudate should be assessed. Furthermore, the status of wound edges and potential undermining should be checked, and the surrounding skin should be examined for color changes, induration, warmth, and edema. Clinical signs of infection, such as foul odor, purulent discharge, increasing pain, or advancing erythema/cellulitis around the wound, should be noted [65]. These and other parameters are addressed in the TIME [97], TIMERS [87] or MOIST [98] assessments.
- **Defective Vascular System:** Because perfusion is critical for healing, vascular assessment is essential for every limb with a chronic wound [73]. At a minimum, this should include measurement of the ankle arterial pressure and the Ankle-Brachial Index (ABI). ABI < 0.9 suggests arterial disease, and < 0.5 indicates severe ischemia where healing is unlikely without revascularization. Further vascular examinations include sequential pulse oscillography and selective angiography. In patients with diabetes or renal failure, evaluation of a Toe-Brachial Index (TBI) is recommended because calcified arteries can falsely elevate ABI [99]. In addition, for the assessment of venous insufficiency, Doppler or duplex ultrasound is used. Importantly, both the superficial and deep venous systems must be assessed for obstruction and/or reflux at four points [69].
- **Extras** include wound biopsies to clarify atypical ulcers and to rule out neoplasms, tests for polyneuropathy in diabetic patients, or serological tests for vasculitis or calciphylaxis [86]. While a small punch biopsy is sufficient to confirm or rule out skin cancer, to investigate suspected

vasculitis or other types of atypical wounds, a 4–5 mm wide and 3–4 cm long skin spindle biopsy should be removed vertically (in the direction of the limb axis) for routine histology, as well as for additional examinations such as immunofluorescence and microbiology [81]. Internal medicine issues are handled according to best practice and usually require additional examinations that would go beyond the scope of this review.

Often, chronic wound evaluation is multidisciplinary—involving dermatologists, wound care specialists, vascular surgeons, endocrinologists, podiatrists or orthopedic surgeons, and other specialists. Regular documentation of wound dimensions and characteristics is recommended to objectively assess the healing trajectory [65].

## **4. Current wound healing strategies**

### **4.1. Standard of care**

The standard of care for chronic wounds involves a structured, etiology-driven approach incorporating local wound management and systemic interventions. Frameworks such as TIME remain widely used [98, 100], although recent criticism has questioned the evidence base for some routine procedures [101]. The TIME framework focuses on Tissue management, Inflammation and Infection control, Moisture balance, and Epithelial/Edge advancement, playing a key role in standardizing care.

#### **T – Tissue management**

The removal of non-viable and/or infected tissue fragments from the wound edge and bed *via* debridement is essential for reducing microbial load and inflammatory mediators [102]. In this process, toxins and matrix metalloproteinases, which impair wound healing, are also removed. In the case of deep, infected wounds, the application of negative pressure or suction (negative pressure wound treatment (NPWT)) immediately after debridement can further enhance the benefits for wound healing. Wound cleansing and regular debridement have been shown to significantly improve healing outcomes and are considered first-line therapy for most chronic wounds [103]. Repeated surgical and biological debridement are effective in reducing bioburden, ideally alongside antimicrobial therapy [104, 105]. Enzymatic agents like collagenase are alternatives, though their impact on bioburden remains unclear [106]. The extent to which regular removal of biofilm is beneficial for wound healing, even in the absence of signs of infection, is a matter of controversy [101].

#### **I – Inflammation and infection control**

Wound infections exist along a continuum of contamination, colonization, localized and systemic infection, and therapy should be tailored according to the stage of infection [91]. Local antimicrobial agents (e.g., iodine, silver,

polyhexanide, hydrogen peroxide, hypochlorous acid) are preferred for contaminated, colonized, or locally infected wounds, while systemic antibiotics are reserved for overt or spreading systemic infection [69, 74, 90, 107]. Distinguishing inflammation from infection is essential; anti-inflammatory agents may be indicated for wounds with a dominant inflammatory component [108].

#### M – Moisture balance

Maintaining optimal wound hydration is essential in chronic wound management to prevent desiccation and maceration [100]. Dressings should match exudate levels: hydrogels for dry wounds, foams or alginates for highly exuding ones [109]. NPWT manages exudate efficiently by removing excess fluid and consequently protecting the skin surrounding the wound and accelerating healing [110, 111].

#### E – Epithelial/edge advancement

This aspect focuses on evaluating the wound edge and correcting factors that inhibit wound closure, such as rolled or undermined wound margins. Surgical interventions may be necessary to remove undermined or hyperkeratotic edges or to promote closure via skin grafting [97]. NPWT also assists in reapproximating wound edges and facilitates granulation tissue formation at the periphery. It is frequently employed as part of grafting procedures [111]. Approximately 20% of all chronic wounds do not heal or only partially heal despite appropriate treatment [112]. In these cases, tissue transfer may be considered, including autologous procedures such as punch grafts [113], as well as alternatives with skin equivalents and matrix materials.

In addition to general wound management, etiology-specific interventions are critical for promoting sustained healing and preventing recurrence. In venous leg ulcers, compression therapy is foundational, and surgical correction of underlying venous insufficiency is often required to prevent recurrence [69]. Healing of arterial ulcers requires surgical revascularization to restore perfusion; adjunct therapies alone are insufficient [74]. For diabetic foot ulcers, ulcer off-loading is the cornerstone of treatment, as these wounds often arise from neuropathy and mechanical stress. In addition, ischemic DFUs may also require revascularization [114]. Off-loading *via* repositioning schedules and specialized support surfaces is essential for healing and recurrence prevention of pressure ulcers, while surgical closure may also be considered in selected cases [107]. Inflammatory wounds such as pyoderma gangrenosum or vasculitis require immunomodulatory therapy alongside wound care [108].

### 4.2. Advanced wound care

Advanced therapies are employed to stimulate healing when conventional treatments alone are insufficient. Most guidelines recommend a minimum of four weeks of appropriate standard care, with ongoing assessment of the healing response, before initiating advanced interventions [65, 115].

## Biologic and pharmacologic therapies

Various recombinant growth factors have been developed and are used in different countries, including PDGF (Regranex®) in the USA, EGF (Heberprot-P®) in Cuba, and FGF (Fibroblast Growth Factor) (Fiblast® Spray) in Japan. However, outcomes have been inconsistent, and many of these therapies show limited efficacy in clinical practice [116]. More promising results have been achieved with autologous biologic preparations that naturally contain a combination of growth factors and cytokines, such as platelet-rich plasma [117] and platelet- and leukocyte-rich patches (e.g., 3C Patch®) [114, 118], both acquired by centrifugation of the patients' own blood and topically applied onto the wound.

Allogeneic skin substitutes are another important category of biologic therapy, including bioengineered live cell constructs (e.g., Apligraf®, Dermagraft®) as well as dehydrated placental-derived products (e.g., EPIFIX®, EPICORD®). These skin substitutes provide structural ECM and growth factors and have demonstrated clinical efficacy to enhance wound healing [119, 120].

Beyond the use of topical antimicrobials and systemic antibiotics [90], pharmacologic interventions for chronic wounds remain limited. Some evidence supports the use of systemic agents such as pentoxifylline and sulodexide in promoting healing of VLU [121, 122].

Recently, two new treatments have been approved specifically for wounds caused by loss of basal membrane adhesion in patients suffering from epidermolysis bullosa: Oleogel-S10 (birch triterpenes) [123], and the gene therapy beremagene geperpavec that delivers non-mutated type 7 collagen [124].

## Device-based and material-based interventions

Negative Pressure Wound Therapy (NPWT) is widely used for managing exudate, stimulating granulation tissue, and improving perfusion. Chronic wound fluid has been shown to inhibit cellular proliferation *in vitro* [44], and its removal may partly explain the positive clinical effect of NPWT. NPWT is indicated for large or deep wounds, post-debridement beds, and heavily exuding wounds [125, 126]. Hyperbaric Oxygen Therapy (HBOT), which involves breathing 100% oxygen at increased atmospheric pressure in a closed chamber, and topical oxygen therapy are recommended as adjuvant therapy for ischemic DFUs and arterial ulcers, although high cost and limited availability restrict HBOT use [74, 127]. Cold Atmospheric Plasma (CAP) is a novel approach combining antimicrobial activity with stimulation of angiogenesis and cell proliferation. Early trials show accelerated healing in leg ulcers [128, 129].

Several biophysical technologies, such as electrical stimulation [130], extracorporeal shockwave [131], and laser therapy [132, 133] are in early clinical use and have been shown to improve healing when used with standard of care in clinical trials. Ultrasound therapy is also used to aid in debridement, bioburden control, and pain reduction [134].

Advanced wound dressings incorporate bio- and nanomaterials that go beyond passive protection by actively modulating the wound microenvironment. Collagen-based dressings modulate protease activity and preserve endogenous growth factors, supporting healing in DFUs, VLUs, and pressure ulcers [135]. Hyaluronic acid-based dressings provide a scaffold for cellular migration

and neovascularization [136]. Antimicrobial dressings, such as those releasing silver ions, help reduce bioburden and inflammation in infection-prone wounds [136]. Synthetic biodegradable dressings, such as NovoSorb® BTM, support neodermis formation and tissue remodeling in complex wounds, including pressure ulcers [137]. Accelerated healing of DFUs by dressings based on self-assembling peptides like G4Derm®, is attributed to its inherently antimicrobial and scaffolding properties [138]. These technologies represent a significant shift from traditional wound coverage with absorbent dressings to active, regenerative biomaterials.

The clinical benefit of advanced wound therapies available on the market has been reviewed in Sharma et al. [139]. A summary of advanced therapies recommended by official guidelines can be found in Suppl. material 1: table S1. Crucially, no single advanced therapy is universally effective. Patient-specific factors, including wound etiology, bioburden, comorbidities, and local tissue biology, must be considered for treatment selection. The concept of precision medicine in wound care is still in its infancy, with a pressing need for improved diagnostics to tailor therapies to the biological characteristics of individual wounds [2].

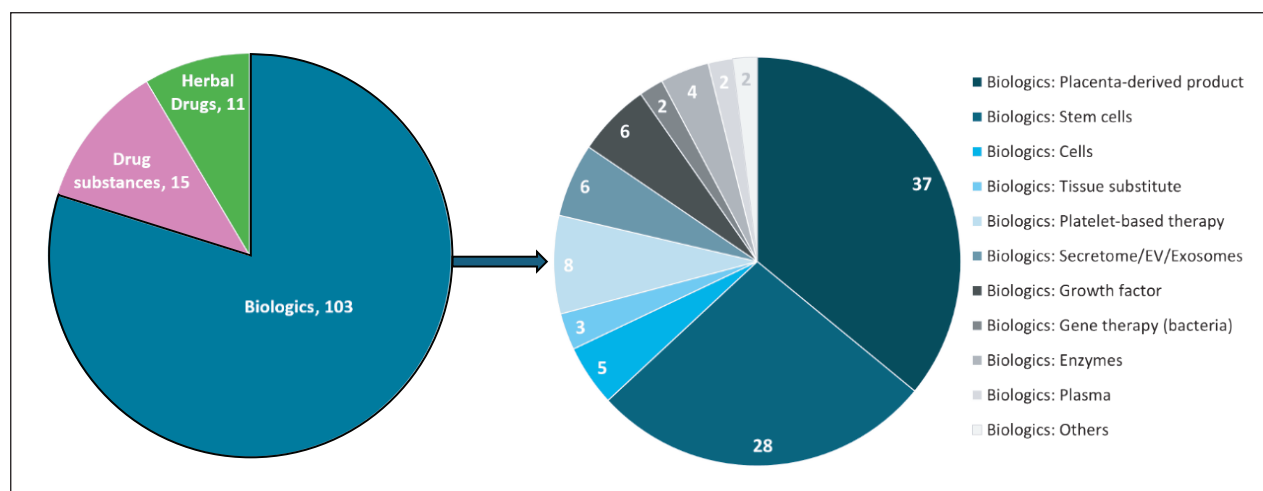
## 5. Emerging translational approaches

Recent advances in translational research in wound healing treatments reveal a fundamental shift from passive wound management to active, multi-modal, and increasingly personalized therapeutic interventions. Most of the trials in the clinicaltrials.gov database comprise medical devices and observational parameters. There is a paucity of clinical studies with novel pharmacological treatments for chronic skin ulcers, with the majority focusing on biologic therapies and diabetic foot ulcers as an indication (Fig. 3 and Suppl. material 1: table S2).

Acknowledging the failure of past single-agent approaches in the complex pathophysiology of chronic wounds, a new class of multimodal therapies addressing the multifactorial nature of chronic wounds is reaching clinical maturity. They encompass trials focusing on placental-based products and stem cell therapies. Placenta-based products deliver a supporting scaffold as well as a natural cocktail of growth factors and healing promoting substances [140]. Stem cell therapy holds promise to enhance tissue regeneration due to their ability to adaptively respond to tissue injury and inflammation by providing paracrine signals which alter the wound environment toward a pro-healing state or even directly participate in tissue regeneration when applied topically [141]. An important development was the identification of the ABCB5 surface marker on skin stem cells, which is used for isolating homogeneous populations of stem cells from discarded skin tissues, thus decreasing the variability of the treatment and fulfilling the stringent standards of good manufacturing practice [142]. A special class of therapy in clinical development is AUP-16, a genetically engineered live bacterium delivering directly onto the wound a cocktail of three human proteins: Colony Stimulating Factor (CSF-1), Fibroblast Growth Factor 2 (FGF-2), and Interleukin 4 (IL-4). Through this mechanism, AUP-16 exerts a multi-target mode of action, simultaneously modulating inflammation, angiogenesis, and proliferation [143]. Furthermore, therapy using genetically corrected stem cells for the treatment of epidermolysis bullosa has progressed from preclinical *ex vivo* correction of patient

keratinocytes to early clinical trials, demonstrating durable restoration of laminin 332 and sustained wound healing in junctional EB [144, 145]. Current efforts and clinical studies focus on the challenging delivery and sustained expression of corrected collagen 7 to patients with a more severe form of the disease, recessive dystrophic EB [146].

In contrast to the high number of trials focusing on biologicals, the investigation of drug substances for therapy of chronic wounds is still at early stages. Currently, only 12 pharmacological candidates are undergoing clinical investigation, covering various mechanisms of action (Suppl. material 1: table S2). While anti-inflammatory properties are a recurring theme, many compounds target distinct aspects of the wound-healing process. Among the substances focusing on the reduction of chronic inflammation are: i) the pan-JAK inhibitor MDI-1228 [147, 148]; ii) TCP-25, a thrombin-derived peptide with anti-inflammatory properties based on scavenging of pathogen-derived DAMPs [149]; iii) S42909, a NADPH oxidase inhibitor that dampens the production of reactive oxygen species (ROS), thereby alleviating chronic inflammation [150]; and iv) Melatonin, which exerts antioxidant and anti-inflammatory effects beyond its role in the circadian rhythm [151]. Substances with other diverse modes of action include: i) TR-987, a yeast glucan polymer which acts as an infection decoy and activates host immune cells to reboot the healing process [152]; ii) Esmolol and timolol, beta blockers with pleiotropic actions including promotion of keratinocyte-, fibroblast- and endothelial cell migration [153]; iii) Folinic acid, involved in biosynthetic pathways of amino acids and hence important for maintaining normal cell growth and replication [154]; iv) ENERGI-F703, an adenine-containing gel found to accelerate wound closure in an early clinical study with DFUs, presumably by increasing cellular energy [155]; v) Nitric oxide, an endogenously produced mediator that promotes vasodilation, angiogenesis and antimicrobial activity [156]; vi) Deferoxamine, an iron chelator that stabilizes HIF-1 $\alpha$  and induces hypoxia-responsive, pro-angiogenic gene expression, promoting angiogenesis and tissue regeneration [157]; and vii) Cilostazol, a PDE3 inhibitor and antiplatelet agent with vasodilatory properties [158].



**Figure 3.** Recent clinical studies with interventional biological and pharmacological therapies for chronic wounds. This figure summarizes trials active between 2020 and 2025, grouped by treatment category (left) and by subclasses of trials with biologics (right). Details of the trials are provided in Suppl. material 1: table S2. Abbreviations: Extracellular Vesicles (EV).

The advent of artificial intelligence is expected to improve the management of chronic wounds (reviewed in [159]) (Fig. 3). The application of AI is already leading to fast and efficient documentation of the wound with smartphone apps or dedicated 3D camera systems, encompassing many parameters of the WUHWS triangle of wound assessment, e.g., wound area, depth, and tissue composition [159–162]. By combining wound imaging documentation and information from electronic health records of >1.2 million wounds, wound healing trajectories can be predicted with high accuracy, aiding in early identification of patients at risk of developing a chronic wound [163]. With smart dressings containing electrochemical sensors, AI could also help monitor biological processes directly in the wound environment [159, 164] to inform the healthcare professional remotely when a change of bandage or therapy is necessary. However, these devices are still in the experimental stage. Future development is also focusing on engineering dressings that deliver medication upon specific triggers in the wound environment. Ideally, in the future, treatment could be continuously adapted to respond to actual changes in the wound environment without the stress of changing bandages [165].

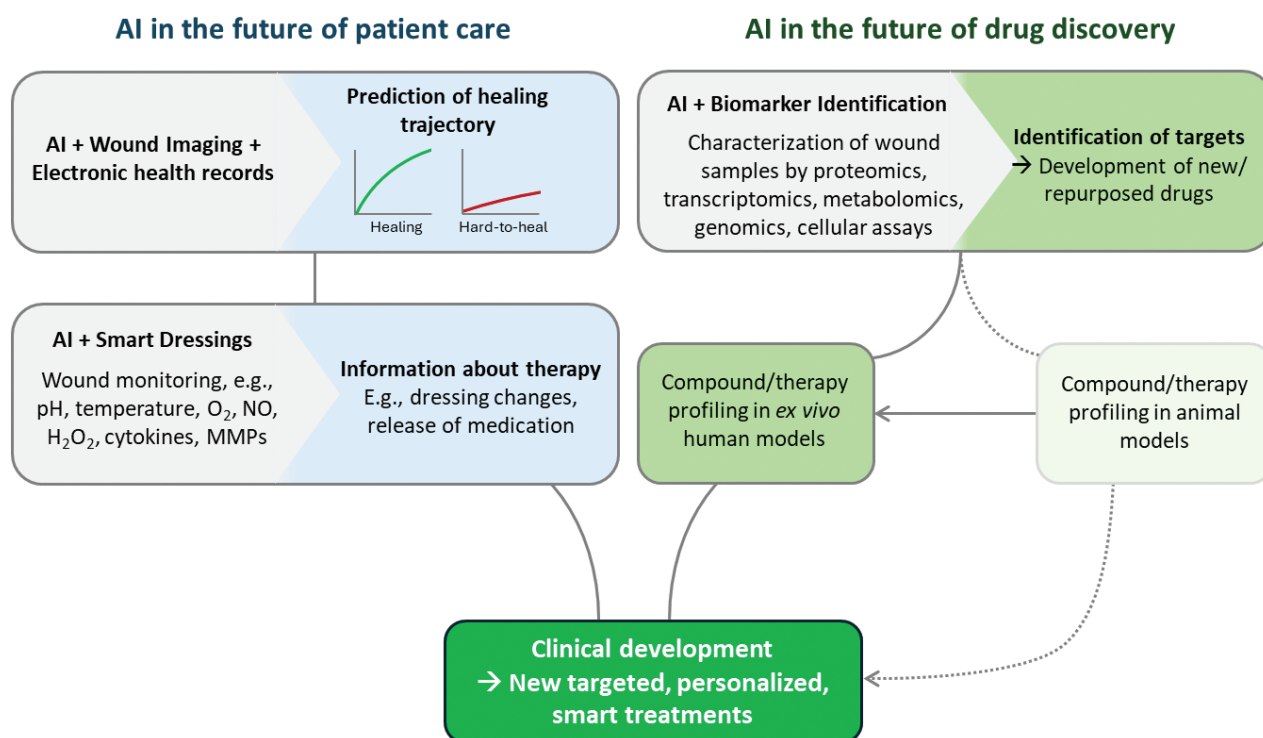


Figure 4. The use of artificial intelligence in wound care.

However, currently such strategies are severely hampered by the limited number of therapeutics in clinical use and registered for chronic wounds. Considering the complexity of chronic wounds, it is unlikely that targeting a single biological effect/process is sufficient to correct the entire pathology of a chronic wound. AI and machine learning can integrate large -omics datasets to identify biomarkers, new drug targets, or target combinations, as recently shown [166, 167]. The major challenge remains the validation of these targets for human therapy, since the predictive value of presently used animal models is limited [18, 168]. Therefore, test systems using human wound material are

desirable for the characterization of future therapeutics. This includes 3D models of human skin, either skin biopsies or *in vitro* models, such as skin-on-a-chip, organoids, and bioprinted skin equivalents [19], as well as personalized cellular assays of chronic wounds [44]. Doerfler et al. (2025) have recently shown that exudates from chronic wounds transfer their chronic phenotype to normal human fibroblasts grown in cell culture, leading to production of inflammatory mediators and impaired proliferation. The assay was used to test the rescue capacity of approved wound therapeutics in the context of individual wound exudates, paving the way for personalized pre-testing of drugs for chronic wound therapy, as well as its use as a companion diagnostic. This assay also has the potential to help identify and characterize new drugs or aid in the validation of targets identified by -omics approaches [44, 169]. The use of wound exudates as a source of biomarkers for personalized medicine is also being investigated by proteomics [45]. Clinical validation of wound exudate-based cellular and molecular biomarkers will be necessary to finally demonstrate their usefulness to improve translational medicine for chronic wounds.

A major challenge in translational science for chronic wounds is the regulatory framework. The current regulatory requirement of full and lasting wound closure for approval of a new drug or therapeutic device is unrealistic and represents a big hurdle. Wound healing societies such as the American WHS and the Wound Care Collaborative Community (WCCC) initiative (<https://www.woundcarecc.org/wp-content/uploads/2025/05/2025-WCCC-Combined-Summit-Deck-.pdf>, accessed 29.07.2025) are working together with the FDA on defining meaningful and patient-centric clinical endpoints. Suggestions include percent wound area reduction, reduced infection, reduced pain/analgesia use, increased function and ambulation, and improved quality of life. Hopefully, incorporating these measures will make it more attractive for pharma and device companies to conduct clinical studies that include patients with problematic wounds that are unlikely to close within the currently postulated time frame of 12 weeks.

## 6. Conclusions

Chronic wounds remain a major challenge in modern medicine, reflecting a convergence of complex pathophysiological mechanisms, comorbidities, and socioeconomic burdens. While significant progress has been made in understanding the cellular and molecular drivers of chronicity—such as persistent inflammation, ischemia, microbial dysbiosis, and cellular dysfunction [42, 170]—this knowledge has not yet translated into major treatment breakthroughs. This is due in part to the multifactorial nature of non-healing wounds and the marked heterogeneity of patients, who often present with multiple comorbidities and diverse medication regimens. The success of future therapeutic interventions will likely depend on the application of personalized medicine, using biomarkers to stratify patients during clinical development and/or companion diagnostics to predict the therapeutic success of specific treatments. Promising biomarker candidates [14, 45] and *ex vivo* models for new drug discovery [44] have been reported and await clinical validation. Another obstacle to clinical development is the limited predictive value of conventional preclinical animal models, which fail to fully replicate the chronic wound microenvironment [18].

Despite these challenges, the field is experiencing a surge of innovation. Multimodal therapies—such as placental-derived products, stem cell-based interventions, and engineered biologicals—are being developed to address the diverse cellular and molecular deficits in chronic wounds. Assuming clinical efficacy is demonstrated, these therapies still come with major challenges related to manufacturing and standardization, high costs, and low accessibility due to the need for specialized medical facilities. Therefore, there is a major need for the development of effective drugs to promote healing of chronic wounds. Drugs are manufactured with standardized and controlled processes, such as chemical synthesis and bioreactors, leading to low variability, which decreases costs and increases accessibility beyond specialized medical centers all the way to home-based care.

The integration of artificial intelligence offers powerful opportunities for real-time wound assessment, predictive modeling, and personalized therapy, particularly when combined with smart dressings and exudate-based biomarker assays. Moreover, the adoption of biologically relevant human preclinical models and more meaningful clinical endpoints as alternatives to complete wound closure promises to bridge the translational gap. Collectively, these developments mark a pivotal shift toward individualized, patient-centric care strategies that could redefine the therapeutic landscape for chronic wound management (Fig. 5).

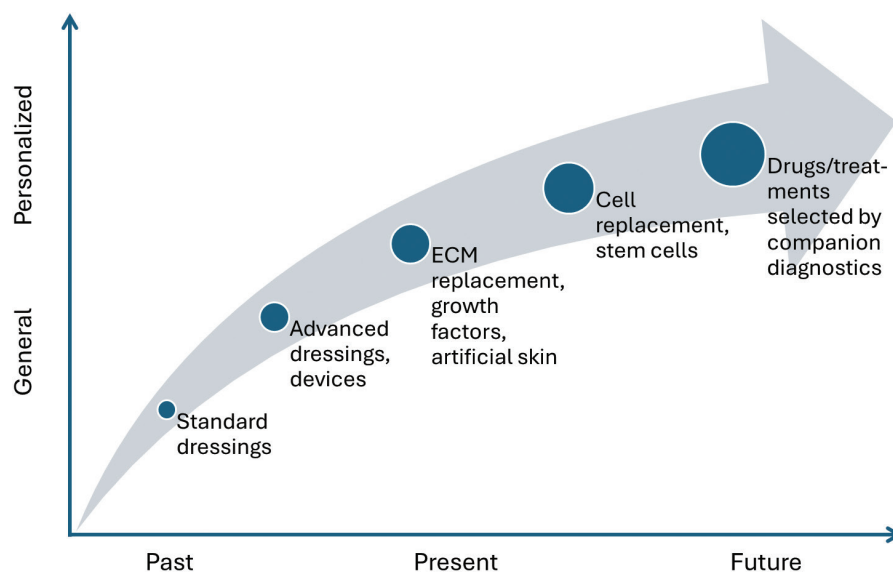


Figure 5. Development of wound care: from general to personalized therapies.

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## Additional information

### Conflict of interest

The authors have declared that no competing interests exist.

## Use of AI

AI was used in part to improve the flow of the text and make it more concise. The authors critically reviewed the AI suggestions.

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## Author contributions

Both authors reviewed the literature, conceptualized the manuscript, and generated figures. Both authors read and revised together the final manuscript version.

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## Data availability

All of the data that support the findings of this study are available in the main text or Supplementary Information.

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## Supplementary material 1

### Supplementary tables S1, S2

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Explanation note: This supplementary file contains two tables. The first table lists the recommendations from the official guidelines for advanced therapies for the four most common types of chronic wounds (DFU, VLU, ALU, and PU). The second table contains the results of a search of the [clinicaltrials.gov](https://clinicaltrials.gov) database, focusing on recent clinical studies with interventional pharmacological and biological therapies for chronic wounds.

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