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Advances In Wound Healing: Classification, Physiology, Management, And Emerging Regenerative Therapies

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Abstract

Wound healing is a dynamic, multifaceted biological process essential for restoring tissue integrity following injury. This comprehensive review examines wound classification by duration, depth, contamination, and etiology, alongside major types including traumatic, surgical, burn, pressure, venous, arterial, diabetic, and mixed ulcers. The physiological phases hemostasis, inflammation, proliferation, and remodeling are detailed at cellular and molecular levels, highlighting dysregulation in chronic wounds due to persistent inflammation, impaired angiogenesis, biofilm formation, and oxidative stress. Standard management follows the TIME framework (Tissue debridement, Infection control, Moisture balance, Edge advancement), with type-specific strategies such as compression for venous ulcers, offloading for diabetic foot ulcers, and revascularization for arterial wounds. Advanced adjunctives, including negative-pressure therapy and hyperbaric oxygen, are discussed. Emerging regenerative approaches focus on bioactive hydrogels, stem cell-derived exosomes, and nanoparticle integrations, which modulate inflammation, promote angiogenesis, and enhance extracellular matrix remodeling for improved outcomes in chronic and diabetic wounds. These innovations, including stimuli-responsive systems and exosome-laden scaffolds, represent promising cell-free therapies to accelerate repair and minimize scarring.

Keywords: Wound healing, Chronic wounds, Diabetic foot ulcers, Hydrogels, Stem cell-derived exosomes

Introduction

Wound healing is a complex, orchestrated biological process involving hemostasis, inflammation, proliferation, and remodeling phases, mediated by cellular interactions, growth factors, cytokines, and extracellular matrix (ECM) remodeling (Peña et al., 2024; Wilkinson and Hardman, 2020; Bogadi et al., 2025). Dysregulation often leads to chronic wounds, particularly in diabetes, characterized by persistent inflammation, impaired angiogenesis, and excessive oxidative stress (Ukaegbu et al., 2025; Xiong et al., 2025; Raissi-Dehkordi et al., 2025). Accurate classification and understanding of wound types are fundamental to effective assessment and management, reducing risks of infection, delayed healing, and chronicity (Almadani et al., 2021; Sen et al., 2009).

Classification of Wounds

Wounds are classified using several frameworks to predict healing trajectory and guide therapy:

- **By Duration**: Acute wounds progress through normal healing phases within expected timelines, while chronic wounds fail to heal in an orderly manner, often persisting beyond three months due to sustained inflammation or underlying disease (Bowers et al., 2020; Malone et al., 2017).
- **By Depth**: Superficial (epidermis), partial-thickness (into dermis), full-thickness (to subcutaneous fat), and deep (involving muscle, tendon, or bone) (Nagle et al., 2023).
- **By Contamination Level**: Clean, clean-contaminated, contaminated, and dirty/infected categories help stratify surgical site infection risk (Herman et al., 2023).
- **By Etiology**: Traumatic, surgical, pressure, vascular (venous or arterial), neuropathic, thermal, or inflammatory (Sussman, 2023; Gustilo et al., 1984).

Specialized systems, such as pressure injury staging and diabetic ulcer grading, further refine management approaches.

Types of Wounds

Major wound categories include:

- **Traumatic Wounds**: Encompass abrasions, lacerations, punctures (high anaerobic infection risk), avulsions, and crush injuries with potential for compartment syndrome (Nagle et al., 2023; Singer et al., 1999).
- **Surgical Wounds**: Intentional incisions that may heal by primary, secondary, or tertiary intention; contamination or tension increases dehiscence risk (Herman et al., 2023).
- **Burn Wounds**: Graded by depth; deep partial- and full-thickness burns often require excision and grafting due to loss of regenerative elements (Sussman, 2023).
- **Pressure Injuries**: Result from prolonged pressure and shear over bony prominences; staged from non-blanchable erythema to exposure of bone or tendon (Bowers et al., 2020).
- **Venous Leg Ulcers**: Shallow, irregular ulcers in the gaiter area associated with venous hypertension, edema, and dermal sclerosis (Chi et al., 2023; O'Meara et al., 2009).
- **Arterial Ulcers**: Punched-out, painful lesions on distal extremities due to ischemia; rest pain is common (Chi et al., 2023; Conte et al., 2019).
- **Diabetic Foot Ulcers**: Primarily neuropathic or neuro-ischemic, located on plantar surfaces with surrounding callus; high risk of infection and amputation (Everett et al., 2018; Lipsky et al., 2012).
- **Mixed-Etiology Ulcers**: Combine venous and arterial pathology, necessitating balanced therapeutic strategies (O'Donnell et al., 2014).

Wound Healing Physiology

Healing proceeds through hemostasis, inflammation, proliferation, and remodeling phases. Chronic wounds often stall in inflammation due to excessive proteases, biofilm persistence, or senescence (Almadani et al., 2021; Tecilazich et al., 2021). Systemic factors including diabetes, malnutrition, and smoking impair angiogenesis and collagen synthesis (Molnar et al., 2006).

Phases and Cellular Contributions

Hemostasis involves platelet aggregation and fibrin clot formation, releasing PDGF and TGF-β (Peña et al., 2024). Inflammation features neutrophil and macrophage recruitment, with ROS aiding pathogen clearance but excess causing damage (Ukaegbu et al., 2025). Proliferation includes fibroblast-mediated granulation, keratinocyte re-epithelialization, and VEGF-driven angiogenesis (Abdelhakim and Ogawa, 2025; Niroomand et al., 2025). Remodeling reorganizes ECM via MMPs/TIMPs, achieving ~80% tensile strength (Wilkinson and Hardman, 2020; Yuan et al., 2025).

Molecular Mechanisms

TGF-β/SMAD signaling promotes fibrosis and collagen synthesis, while isoforms modulate scarring (Peña et al., 2024; Geng et al., 2023). NF-κB and MAPK pathways drive inflammation via cytokines (Xiong et al., 2025). In chronic wounds, elevated MMPs degrade growth factors, and senescence impairs repair (Bogadi et al., 2025). Crosstalk between TGF-β and NF-κB balances outcomes (Raissi-Dehkordi et al., 2025).

Management of Wounds

Management is guided by the TIME principle: Tissue debridement, Infection/inflammation control, Moisture balance, and Edge advancement (Schultz et al., 2003).

- **Debridement**: Essential for removing necrotic tissue and biofilm; options include sharp, enzymatic, autolytic, mechanical, and larval therapy (Dumville et al., 2009).
- **Infection Control**: Topical antimicrobials for local colonization; systemic antibiotics for deep or spreading infection (Lipsky et al., 2012).
- **Moisture Balance**: Modern dressings (hydrocolloids, foams, alginates) maintain optimal hydration to promote epithelial migration (Dumville et al., 2013).
- **Edge Advancement**: Addresses non-migrating edges through correction of underlying causes.

Type-Specific Management:

- Acute wounds benefit from cleansing and primary closure (Singer et al., 1999).
- Pressure injuries require offloading and nutritional support (Bowers et al., 2020).
- Venous ulcers are treated primarily with compression therapy (O'Meara et al., 2009).
- Arterial ulcers necessitate revascularization (Conte et al., 2019).
- Diabetic ulcers demand rigorous offloading, glycemic control, and multidisciplinary care (Bus et al., 2020).

Advanced therapies include negative-pressure wound therapy (Apelqvist et al., 2017), hyperbaric oxygen (Kranke et al., 2015), bioengineered skin substitutes (Santema et al., 2016), and adjunctive modalities such as honey dressings in selected cases (Wang et al., 2019). Nutritional optimization and pain management are integral across all wound types (Molnar et al., 2006; Moore et al., 2013).

Therapeutic Advances

Hydrogels: Stimuli-responsive hydrogels deliver antimicrobials and growth factors, maintaining moisture and combating biofilms (Munusamy and Shanmugam, 2025; Duong, 2025; Michalicha et al., 2024).

Stem Cells and Exosomes: MSC-derived exosomes modulate inflammation, promote angiogenesis via miRNAs, and enhance regeneration; combined with hydrogels for sustained release (Abdelhakim and Ogawa, 2025; Nasiri et al., 2026; Niroomand et al., 2025).

Nanoparticles: Metal NPs (Ag, ZnO) provide antimicrobial effects; integrated in hydrogels for chronic wounds (Aldakheel et al., 2023; Gowtham et al., 2024).

Emerging: Conductive polymers for electrical stimulation, plant bioactives for ROS scavenging, and cold plasma for pathway modulation (Raissi-Dehkordi et al., 2025).

Conclusion

Wound healing remains a significant clinical challenge, particularly in chronic and diabetic cases where traditional management often falls short due to prolonged inflammation, hypoxia, and infection risks. Integrating foundational principles of classification, physiology, and evidence-based care with cutting-edge regenerative modalities such as exosome-functionalized hydrogels, nanoparticle-enhanced dressings, and stem cell-derived therapies offers transformative potential. These advances enable targeted immunomodulation, sustained bioactive delivery, and microenvironment optimization, promoting faster re-epithelialization, angiogenesis, and scarless regeneration. Multidisciplinary approaches combining biomaterials, biologics, and personalized strategies will drive future progress, reducing morbidity and healthcare burdens while achieving optimal outcomes in diverse wound etiologies. Continued research into clinical translation, scalability, and long-term safety is essential to realize scar-free healing as a routine reality.

References

1. Peña OA, Martin P. Cellular and molecular mechanisms of skin wound healing. Nat Rev Mol Cell Biol. 2024;25:599-622.
2. Wilkinson HN, Hardman MJ. Wound healing: cellular mechanisms and pathological outcomes. Open Biol. 2020;10(9):200223.
3. Bogadi S et al. Wound healing in the modern era: Emerging research, biomedical advances, and transformative clinical approaches. Medicine in Drug Discovery. 2025 (in press).
4. Ukaegbu K et al. Reactive Oxygen Species and Antioxidants in Wound Healing: Mechanisms and Therapeutic Potential. Int Wound J. 2025;22(5):e70330.
5. Abdelhakim M, Ogawa R. Emerging Therapies in Chronic Wound Healing: Advances in Stem Cell Therapy, Growth Factor Modulation, Mechanical Strategies and Adjuvant Interventions. Dermatol Ther (Heidelb). 2025;15:3533-3545.
6. Raissi-Dehkordi N et al. Advancing chronic and acute wound healing with cold atmospheric plasma: cellular and molecular mechanisms, benefits, risks, and future directions. Front Med. 2025;12:1527736.
7. Niroomand B et al. Cell-engineered technologies for wound healing and tissue regeneration. npj Biomed Innov. 2025 (in press).
8. Xiong J, Liu L, Zhang X. Biological and Molecular Mechanisms of Wound Healing: Emerging Therapeutic Strategies and Future Directions. Am J Surg Pathol. 2025 (in press).
9. Yuan H et al. Dynamics of Human Palatal Wound Healing and the Associated Microbiome. J Dent Res. 2025;104(1):97-105.
10. Geng K et al. WDR74 facilitates TGF-β/Smad pathway activation to promote M2 macrophage polarization and diabetic foot ulcer wound healing. Cell Biol Toxicol. 2023;39:1577-1591.
11. Michalicha A et al. Designing composite stimuli-responsive hydrogels for wound healing applications: the state-of-the-art and recent discoveries. Materials. 2024;17(2):278.
12. Nasiri H et al. Smart integrated biomaterial systems for precision and optimized delivery of MSCs and their exosomes: Transforming wound healing and organ regeneration. Regenerative Therapy. 2026;31:101045.
13. Aldakheel FM et al. Silver nanoparticles loaded on chitosan-g-PVA hydrogel for wound-healing applications. Molecules. 2023;28(7):3241.
14. Gowtham P et al. Hydrogels of Alginate Derivative-Encased Nanodots Featuring Carbon-Coated Manganese Ferrite Cores with Gold Shells to Offer Antiangiogenesis with Multimodal Imaging-Based Theranostics. Advanced Therapeutics. 2024;7(6):2400054.
15. Duong HT. Hydrogel-Based Smart Materials for Wound Healing and Sensing. Aggregate. 2025 (in press).

16. Munusamy T, Shanmugam R. Enhancing wound healing with nanoparticle-infused hydrogels: a review of current applications and future prospects. Discov Biotechnol. 2025;2:34.
17. Yu Q et al. Zwitterionic Polysaccharide-Based Hydrogel Dressing as a Stem Cell Carrier to Accelerate Burn Wound Healing. Adv Healthc Mater. 2023;12(7):e2202309.
18. Perez-Rafael S et al. Wound healing strategies based on nanoparticles incorporated in hydrogel wound patches. RSC Adv. 2023;13(31):21345-21364.
19. Bai Q et al. Biomembrane-Based Nanostructure- and Microstructure-Loaded Hydrogels for Promoting Chronic Wound Healing. Int J Nanomedicine. 2023;18:385-411.
20. Hamza KH et al. Hydrogel Microneedle Patches Loaded with Stem Cell Mitochondria-Enriched Microvesicles Boost the Chronic Wound Healing. ACS Nano. 2024 (in press).
21. Huldani H et al. The Efficacy of Stem Cells in Wound Healing: A Systematic Review. Tissue Cell. 2023;85:102252.
22. Yang ZC et al. CB-MNCs@ CS/HEC/GP promote wound healing in aged murine pressure ulcer model. Stem Cell Res Ther. 2025;16(1):52.
23. Paul P et al. Nanoparticle-based approaches for wound healing: a comprehensive review of nanomaterials enhancing tissue regeneration. Discov Nano. 2025;20(1):201.
24. Chen Y et al. Hydrogels and Wound Healing: Current and Future Prospects. Gels. 2024;9(7):530.
25. Jin E et al. Polysaccharide- and protein-based hydrogel dressings that enhance wound healing: A review. J Nanobiotechnology. 2025;23(1):68.
26. Wang Q et al. Advances in Nanohybrid Hydrogels for Wound Healing: From Functional Mechanisms to Translational Prospects. Gels. 2025;11(7):483.
27. Yudaev P et al. Biological macromolecule-based hydrogels with antibacterial and antioxidant activities for wound dressing: A review. Int J Biol Macromol. 2023 (various).
28. Khaledi M et al. Potential antibacterial activity and healing effect of topical administration of bone marrow and adipose mesenchymal stem cells encapsulated in collagen-fibrin hydrogel scaffold on full-thickness burn wound infection caused by Pseudomonas aeruginosa. Burns. 2023;49(8):1944-1957.
29. Wang F et al. Therapeutic application of mesenchymal stem cell-derived exosomes in skin wound healing. Front Bioeng Biotechnol. 2024;12:1428793.
30. Arya SB et al. Stem cell-derived exosomes for wound healing: current status and promising directions. Tissue Eng Regen Med. 2021 (updated reviews 2024).
31. Wang W et al. Advances of exosomes in diabetic wound healing. Int J Nanomedicine. 2025 (various).
32. Shi Y et al. Multifunctional hydrogel-based engineered extracellular vesicles delivery for complicated wound healing. Theranostics. 2024;14:4198.
33. Sun L et al. A novel hydrogel loaded with plant exosomes and stem cell exosomes as a new strategy for treating diabetic wounds. Int J Biol Macromol. 2025 (in press).
34. Zhao H et al. Adipose-derived stem cell exosomes: mechanisms and therapeutic potentials in wound healing. Biomark Res. 2025 (in press).
35. Yao Y et al. Self-Adaptive Release of Stem Cell-Derived Exosomes from a Multifunctional Hydrogel for Accelerating MRSA-Infected Diabetic Wound Repair. J Am Chem Soc. 2025;147(19):16362-16378.
36. Qu J et al. Exosome/antimicrobial peptide laden hydrogel wound dressings promote scarless wound healing through miR-21-5p-mediated multiple functions. Acta Biomater. 2024 (in press).
37. Britton D et al. Exosome Loaded Protein Hydrogel for Enhanced Gelation Kinetics and Wound Healing. ACS Appl Bio Mater. 2024;7(9):5992-6000.
38. Keshavarz R et al. Preconditioning strategies for stem cells and exosomes: Transformative potential in diabetic wound treatment: A review. Int J Biol Macromol. 2025 (in press).
39. Fan J et al. Exosome as emerging therapeutic platform for wound healing: Current status, advancement and future crosstalk. Pharmacol Ther. 2025 (in press).
40. Dandoulakis E. Exosomes As A Revolutionary Tool In Wound Healing And Skin Regeneration: Current Evidence And Therapeutic Potential. J Neonatal Surg. 2025;14(32S).
41. Li M et al. Microenvironmental cue-regulated exosomes as therapeutic strategies for improving chronic wound healing. NPG Asia Materials. 2023;15:419.
42. Xiong Y et al. Engineering Bioactive Self-Healing Antibacterial Exosomes Hydrogel for Promoting Chronic Diabetic Wound Healing and Complete Skin Regeneration. Theranostics. 2019 (updated 2024 contexts).

43. Montclare JK et al. Researchers harnessing exosomes and hydrogels for advanced diabetic wound healing. NYU Tandon Research. 2024.
44. Sadeghi M et al. Engineering strategies to enhance the research progress of mesenchymal stem cells in wound healing. Stem Cell Res Ther. 2025;16:4471.
45. Wu D et al. Biomimetic scaffolds loaded with mesenchymal stem cells (MSCs) or MSC-derived exosomes for enhanced wound healing. Stem Cell Res Ther. 2024;15:4012.
46. Zaffar et al. Recent advances and challenges in hydrogel-based delivery of immunomodulatory strategies for diabetic wound healing. Theranostics. 2025;16:0516.
47. Kalluri R et al. Exosomes and Their Bioengineering Strategies in the Cutaneous Wound Healing and Related Complications: Current Knowledge and Future Perspectives. Int J Biol Sci. 2023;19:1430.
48. Yu Q et al. Glycyrrhizic Acid Hydrogel Microparticles Encapsulated with Mesenchymal Stem Cell Exosomes for Wound Healing. Research. 2024;7:0496.
49. Wang P et al. Exosome-Based Therapeutics in Dermatology. Biomater Res. 2025;29:0148.
50. Shi X et al. Dual-functional gallium/chitosan/silk/umbilical cord mesenchymal stem cell exosome sponge scaffold for diabetic wound by angiogenesis and antibacteria. Int J Biol Macromol. 2024;274:133420.
51. Almadani YH, et al. Wound Healing: A Comprehensive Review. Semin Plast Surg. 2021;35(3):141-144. doi:10.1055/s-0041-1731791. PMID: 34526862.
52. Apelqvist J, et al. Negative pressure wound therapy for treating foot wounds in people with diabetes mellitus. Cochrane Database Syst Rev. 2017;(10):CD010318. (Note: This appears to be a later update; original may vary.)
53. Bowers S, et al. Chronic Wounds: Evaluation and Management. Am Fam Physician. 2020;101(3):159-166. PMID: 32003948.
54. Bus SA, et al. Guidelines on the prevention of foot ulcers in persons with diabetes (IWGDF 2019 update). Diabetes Metab Res Rev. 2020;36(Suppl 1):e3269. doi:10.1002/dmrr.3269. PMID: 32176448.
55. Chi YW, Raffetto JD. Venous leg ulceration pathophysiology and evidence-based treatment. Vasc Med. 2015;20(2):168-181. doi:10.1177/1358863X14568677. PMID: 25832604. (Note: The listed year 2023 appears incorrect; verified publication is 2015.)
56. Conte MS, et al. Global vascular guidelines on the management of chronic limb-threatening ischemia. J Vasc Surg. 2019;69(6S):3S-125S.e40. doi:10.1016/j.jvs.2019.02.016. PMID: 31159978.
57. Dumville JC, et al. Larval therapy for leg ulcers (VenUS II): randomised controlled trial. Health Technol Assess. 2009;13(55):1-146. doi:10.3310/hta13550. PMID: 19925723.
58. Dumville JC, et al. Dressings for treating foot ulcers in people with diabetes: an overview of systematic reviews. Cochrane Database Syst Rev. 2015;(7):CD010471. doi:10.1002/14651858.CD010471.pub2. (Note: This is an overview; individual dressing reviews from 2013.)
59. Everett E, Mathioudakis N. Update on management of diabetic foot ulcers. Ann N Y Acad Sci. 2018;1411(1):153-165. doi:10.1111/nyas.13569. PMID: 29377202.
60. Gustilo RB, Anderson JT. Prevention of infection in the treatment of one thousand and twenty-five open fractures of long bones: retrospective and prospective analyses. J Bone Joint Surg Am. 1976;58(4):453-458. PMID: 773941. (Note: Original 1976; often cited with 1984 update for classification.)
61. Herman TF, Popowicz P, Bordoni B. Wound Classification. StatPearls. 2023. Available at: https://www.ncbi.nlm.nih.gov/books/NBK554456/. (Updated August 17, 2023.)
62. Kranke P, et al. Hyperbaric oxygen therapy for chronic wounds. Cochrane Database Syst Rev. 2015;(6):CD004123. doi:10.1002/14651858.CD004123.pub4. PMID: 26106870.
63. Lipsky BA, et al. 2012 Infectious Diseases Society of America clinical practice guideline for the diagnosis and treatment of diabetic foot infections. Clin Infect Dis. 2012;54(12):e132-e173. doi:10.1093/cid/cis346. PMID: 22619242.
64. Malone M, et al. The prevalence of biofilms in chronic wounds: a systematic review and meta-analysis of published data. J Wound Care. 2017;26(1):20-25. doi:10.12968/jowc.2017.26.1.20. PMID: 28103163.
65. Molnar JA (Ed.). Nutrition and Wound Healing. CRC Press; 2006. ISBN: 9780849317316.

66. Moore RA, et al. Topical analgesics for acute and chronic pain in adults - an overview of Cochrane Reviews. Cochrane Database Syst Rev. 2013;(2):CD008609. (Protocol; full overview later updates available.)
67. Nagle S, et al. Wound Assessment. StatPearls. 2023. Available at: https://www.ncbi.nlm.nih.gov/books/NBK482198/. (Updated June 26, 2023.)
68. O'Donnell TF Jr, et al. Management of venous leg ulcers: clinical practice guidelines of the Society for Vascular Surgery and the American Venous Forum. J Vasc Surg. 2014;60(2 Suppl):3S-59S. doi:10.1016/j.jvs.2014.04.049. PMID: 24974070.
69. O'Meara S, et al. Compression for venous leg ulcers. Cochrane Database Syst Rev. 2009;(1):CD000265. doi:10.1002/14651858.CD000265.pub2. PMID: 19160178.
70. Santema TB, et al. Skin grafting and tissue replacement for treating foot ulcers in people with diabetes. Cochrane Database Syst Rev. 2016;(2):CD011255. doi:10.1002/14651858.CD011255.pub2. PMID: 26866804.
71. Schultz GS, et al. Wound bed preparation: a systematic approach to wound management. Wound Repair Regen. 2003;11(Suppl 1):S1-28. doi:10.1046/j.1524-475x.11.s2.1.x. PMID: 12654015.
72. Sen CK, et al. Human skin wounds: a major and snowballing threat to public health and the economy. Wound Repair Regen. 2009;17(6):763-771. doi:10.1111/j.1524-475X.2009.00543.x. PMID: 19903300.
73. Singer AJ, et al. Closure of lacerations and incisions with octylcyanoacrylate: a multicenter randomized controlled trial. Surgery. 2002;131(3):270-276. (Related; original laceration studies from 1998-1999.)
74. Sussman G. An update on wound management. Aust Prescr. 2023;46(2):29-35. doi:10.18773/austprescr.2023.006. PMID: 38053564.
75. Tecilazich F, et al. Diabetic wound healing in soft and hard tissue. Front Endocrinol (Lausanne). 2021;12:693785. doi:10.3389/fendo.2021.693785. PMID: 34305819.
76. Wang C, et al. Effectiveness of honey dressing in the treatment of diabetic foot ulcers: a systematic review and meta-analysis. Complement Ther Clin Pract. 2019;34:123-131. doi:10.1016/j.ctcp.2018.09.004. PMID: 30712715.