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Towards Accessible and Circular Wound Care: Integrating
Innovation, Education, and Evidence into Clinical Practice



Manifesto

International Journal of Wound Research (IJWR) is an international peer-reviewed scientific journal that promotes the development and exchange of knowledge in wound care research and clinical practice. IJWR supports evidence-based interventions and encourages critical reflection on the science and innovation of wound management.

The journal particularly welcomes studies that evaluate complex wound care strategies and health policies, using rigorous research designs appropriate to clinical and interdisciplinary inquiry. IJWR also aims to strengthen research quality by publishing methodological papers on clinical tools, treatment protocols, and investigative techniques. The journal publishes original peer-reviewed articles of interest to the global wound care community.

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The Granulation Tissue:

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A Dynamic Repair Interface

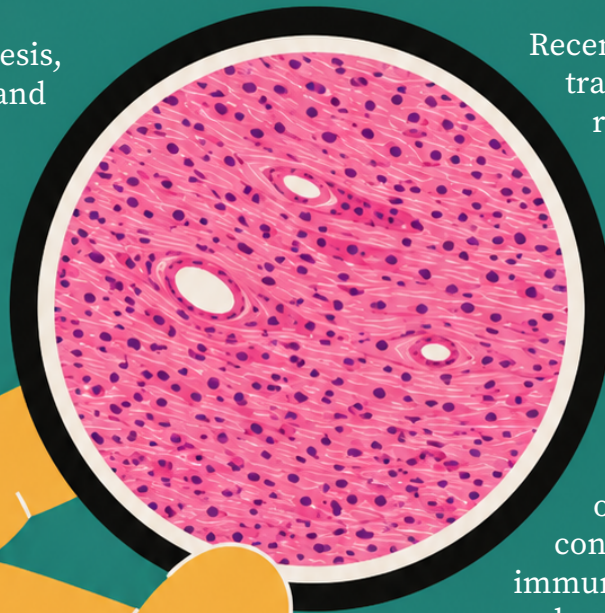
Once considered merely the “red bed” of healing wounds, granulation tissue is now recognized as a highly organized, transient repair organ that integrates extracellular matrix deposition, angiogenesis, immune resolution, and epithelial migration. During the proliferative phase, fibroblasts and endothelial cells build a provisional matrix rich

in collagen III, fibronectin, hyaluronan, and newly formed capillaries, creating the biological platform on which keratinocytes migrate to close the wound.^{1,2}

Recent single-cell and spatial transcriptomic studies have redefined this tissue as a coordinated multicellular niche rather than a uniform mass. Human wound maps show that inflammatory macrophages, fibroblasts, endothelial cells, and keratinocytes act sequentially, with fibroblast subtypes contributing not only to collagen deposition and contraction but also to immune-cell recruitment and vascular remodeling.^{2,3}

In chronic wounds, this program becomes uncoupled. Diabetic and venous ulcers show persistent inflammation, altered macrophage polarization, dysfunctional fibroblast states, excessive matrix degradation, impaired angiogenesis, and delayed re-epithelialization.^{1,4,5} These findings explain why clinically “poor” granulation tissue often appears pale, friable, overinflamed, or stalled.

Together, the latest evidence positions granulation tissue as a therapeutic target: improving its quality means restoring immune balance, vascular ingrowth, fibroblast function, extracellular matrix organization, and wound-bed readiness for epithelial closure.^{1,6,7}



The Regenerative Core

Key Scientific Highlights

Single-Cell Atlases Reveal Granulation Tissue as a Multicellular Repair Niche

Recent human wound-healing atlases using single-cell and spatial transcriptomics have mapped the transition from inflammation to proliferation and remodeling. These studies show that macrophages and fibroblasts support keratinocyte migration in a temporally coordinated sequence, while distinct fibroblast populations occupy specialized matrix and immune niches.^{2,3} This reframes granulation tissue as a dynamic cellular ecosystem rather than a passive connective tissue filler.

Fibroblast-Immune Crosstalk Drives Matrix Formation and Vascular Repair

Fibroblasts are now viewed as active immune organizers within granulation tissue. Experimental evidence shows that fibroblast-derived chemokine signaling supports macrophage recruitment, revascularization, and re-epithelialization.⁶ In diabetic ulcers, single-cell data reveal inflammatory fibroblast subsets, increased MMP expression, altered macrophage polarization, and impaired matrix remodeling, linking defective granulation to chronic wound persistence.^{4,5}

Angiogenesis and Matrix Quality Define Functional Granulation Tissue

Healthy granulation tissue depends on synchronized capillary growth, oxygen delivery, collagen deposition, and later remodeling. Recent reviews emphasize that diabetes and chronic inflammation impair angiogenesis, delaying granulation tissue maturation and epithelial closure.^{1,7} Myofibroblasts remain central to wound contraction and matrix organization, but their persistence or dysregulation can shift repair toward fibrosis, hypertrophic scarring, or non-healing tissue.⁸

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Towards Accessible and Circular Wound Care: Integrating Innovation, Education, and Evidence into Clinical Practice

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There are moments in which clinical practice must move beyond routine thinking and reconsider its own foundations. Chronic wound care is currently experiencing one of those moments. It can no longer be regarded merely as a problem of tissue integrity or as a technical challenge reserved for specialists. Its magnitude reflects one of the most pressing public health issues of our time, bringing together many of the tensions that characterize contemporary healthcare systems.

Population ageing, the increasing burden of non-communicable diseases, persistent pressure on healthcare systems, and inequalities in access to specialized care are converging in ways that can no longer be ignored. In this context, complex wounds are far more than persistent tissue defects; they represent a growing challenge for healthcare organizations, care models, and ultimately for the ethical quality of the assistance we provide.¹

One fundamental conviction underpins this reflection: the future of wound care will depend on our ability to overcome fragmentation and build a more integrated, critical, and ambitious

vision of care.²

As the prevalence of chronic wounds steadily increases among vulnerable populations, so too do suffering, functional dependence, the risk of complications, and the human and economic burden that healthcare systems are required to bear.³ This discussion becomes even more compelling in pediatrics and neonatology, where skin fragility and dependence on medical devices – together with other conditions of vulnerability – make skin integrity a direct indicator of the quality and safety of care. An avoidable skin injury in a newborn or a child represents pain, an increased risk of infection, prolonged hospitalization, and an unnecessary burden for families during a developmentally sensitive period.⁴

Recognizing this reality requires both clinical responsibility and ethical honesty: excellence in healthcare can only be claimed when the most vulnerable individuals are effectively protected.⁵

Responding to these challenges with inherited formulas or with excessive reliance on methodological frameworks that, although

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valuable, are no longer sufficient to capture the complexity of real-world practice would be a mistake. The field of wound care must reconsider the way it interprets evidence. The objective is not to abandon methodological rigor but to rescue it from an overly restrictive interpretation that risks excluding the complexity of everyday clinical practice.⁶

The unquestioned dominance of a linear hierarchy of evidence – where only selected study designs are perceived as legitimate sources of knowledge – has left insufficient room for the realities of routine care. In the management of people living with chronic wounds, context is not a secondary element but an essential component of clinical decision-making. Patients frequently present with multiple comorbidities, limited social and economic resources, fragmented care pathways, and clinical decisions that cannot wait for perfect evidence to emerge.⁶

Advocating for a circular model of evidence means promoting a science that is less dogmatic and more clinically useful – one capable of integrating randomized clinical trials with high-quality registries, observational research, and systematically collected professional experience.⁶ Such an approach does not seek to replace traditional hierarchies of evidence but rather to enrich them by incorporating forms of knowledge that are essential in complex clinical environments. In wound care, where patient heterogeneity, contextual factors, organizational constraints, and implementation challenges all influence outcomes, the integration of different sources of knowledge can provide a more complete understanding of clinical effectiveness.⁶

Within this evolving perspective, technological innovation occupies a central position. However, technology should not be celebrated simply because it is new. It possesses no intrinsic value. Its significance lies in its ability to improve clinical decision-making, reduce uncertainty, expand access to care, and ultimately produce better patient outcomes.⁷

The digital transformation of wound care offers an extraordinary opportunity to move in this direction. Artificial intelligence applied to image analysis, tissue segmentation, automated wound measurement, and longitudinal comparison of lesion evolution represents an important step toward more objective and reproducible assessment, reducing interobserver variability

and improving standardization.⁷

Nevertheless, the sophistication of an algorithm matters only if it improves clinical practice. Improving the ability to see is the first step toward improving the ability to prevent and to treat. In wound care, where every delay, omission, or misinterpretation may translate into prolonged healing or preventable complications, this distinction has profound clinical significance.⁸

Recent evidence suggests that AI-based systems can improve diagnostic accuracy and support clinical decision-making. However, further validation across diverse healthcare settings remains necessary before their widespread implementation.⁸

Similarly, telemedicine and remote monitoring should be viewed not merely as technological solutions but as instruments of health equity, capable of decentralizing expertise and reducing unnecessary patient displacement, particularly for individuals with limited mobility or restricted access to specialized services. Technological progress deserves its name only when it reduces inequalities rather than deepening them.⁹

The same principle applies to smart sensors and advanced biomaterials designed to monitor the wound microenvironment. Although many of these technologies still require further validation and clinical maturation, their direction of development signals an important paradigm shift. Moving from episodic assessment toward continuous, sensitive, and contextualized monitoring means envisioning a model of care that is less reactive, less delayed, and considerably more capable of anticipating deterioration before it becomes clinically evident.¹⁰

Regenerative medicine and photobiomodulation occupy this same frontier of innovation. These fields deserve enthusiasm – but enthusiasm disciplined by evidence rather than driven by expectations alone. A fundamental conceptual shift has occurred: the skin is no longer viewed simply as a passive physical barrier but as an immunologically active organ that plays a dynamic role in tissue repair and regeneration. Within this framework, photobiomodulation, including blue-light therapy, emerges as a promising option for difficult-to-heal wounds, although robust scientific evidence remains necessary to establish its definitive clinical role.^{11,12}

Yet it would be naive to believe that innovation

alone can solve the challenges facing wound care. No technology can generate sustainable value without an organizational model capable of adopting it, evaluating it, and integrating it into routine clinical practice for the benefit of patients, families, and healthcare systems.

As care increasingly shifts from hospitals to homes and community settings, our understanding of efficiency must also evolve. Success should no longer be measured solely by the number of procedures performed but by the amount of suffering avoided, the complications prevented, the reduction in healing time achieved, and the quality of life preserved.

From this perspective, sustainability should not be presented as a constraint on innovation but rather as the ultimate demonstration of its maturity. An innovation that fails to improve outcomes or cannot be realistically integrated into healthcare systems is not a genuine solution; it is simply a promise that has not yet fulfilled its purpose.¹³

The second major pillar – and perhaps the most decisive – is specialized education. There is a persistent illusion, particularly during periods of rapid technological advancement, that devices and algorithms will compensate for weaknesses in clinical care. They will not.

No technological innovation can substitute for clinical judgment, trained observation, contextual interpretation, or the prudence required to make decisions in complex situations while considering the needs of both patients and their families.^{14,15}

For this reason, continuing professional education should never be regarded as an optional complement but rather as the structural foundation of any serious strategy for improving care. Education in wound care extends far beyond technical instruction; it requires the development of clinical reasoning, ethical judgment, interdisciplinary collaboration, educational competence, and critical appraisal of scientific evidence.¹⁶

Within this process, specialized nursing represents the backbone of prevention, longitudinal follow-up, therapeutic education, and effective coordination of care. The progress achieved by highly skilled teams can rapidly disappear if education is reduced to isolated training events or if institutions fail to develop a culture capable of sustaining continuous professional growth. High staff turnover,

heterogeneity of experience, and the daily pressures of healthcare delivery mean that excellence is always a fragile and dynamic equilibrium.¹⁷

This is why translating evidence into practical tools, shared consensus documents, clear algorithms, and effective educational strategies is essential. Scientific knowledge that does not reach the point of care in a language that clinicians can readily apply risks becoming academic prestige without meaningful clinical consequences.¹⁸

Recent advances in device-related pressure injury prevention, skin integrity monitoring, family-centered care, and specialized nursing competencies have further highlighted the need for approaches specifically tailored to newborns and children. As healthcare systems increasingly pursue safer and more personalized models of care, pediatric populations represent not only a challenge but also an extraordinary opportunity for innovation, interdisciplinary collaboration, and future research.¹³

The third pillar, clinical documentation, deserves even greater attention than it usually receives. In an era increasingly fascinated by artificial intelligence, it is worth recalling a simple truth: no intelligent system can compensate for poor, fragmented, or inconsistent clinical data. Clinical documentation remains the fundamental substrate upon which continuity of care, outcome evaluation, applied research, and the visibility of professional practice are built.¹⁹

When essential variables such as pain, nutritional status, wound progression, or performed interventions are inadequately documented, patient safety is compromised. Equally important, the opportunity to learn from experience and generate meaningful knowledge from routine practice is substantially weakened.¹⁹

Defending the quality of clinical documentation is therefore not merely defending an administrative requirement. It is defending an ethic of care that recognizes that every good future decision depends, at least in part, on the seriousness with which we document what we observe and what we do today.

Ultimately, the future of wound care will not be defined exclusively in laboratories, scientific congresses, or specialized units. It will also depend on our ability to build a scientific and clinical community that is less fragmented,

more collaborative, and more willing to share knowledge without transforming it into a privilege.⁶

In this regard, the commitment to accessible publishing models and more democratic systems of knowledge dissemination is not an ideological aspiration but a matter of coherence. If wound care seeks to address a global burden of disease, the knowledge it generates cannot remain accessible only to those with the resources to obtain it.⁶

Likewise, if we genuinely aspire to person-centered care, patients, families, and caregivers must no longer be considered passive recipients of healthcare but active partners in defining therapeutic priorities, care goals, and meaningful outcomes.

Ultimately, the future of wound care will not be determined by a single technological breakthrough or by an isolated scientific discovery. It will depend on our collective capacity to integrate meaningful innovation, robust education, plural forms of evidence, rigorous clinical documentation, and open collaboration into a coherent model of care. What is at stake is more than the evolution of a clinical discipline – it is the opportunity to build a healthcare system that is more intelligent, more equitable, and more faithful to the dignity of every person living with a wound. Faced with this responsibility, observing change is no longer sufficient. The time has come to decide what kind of difference we are willing to make.

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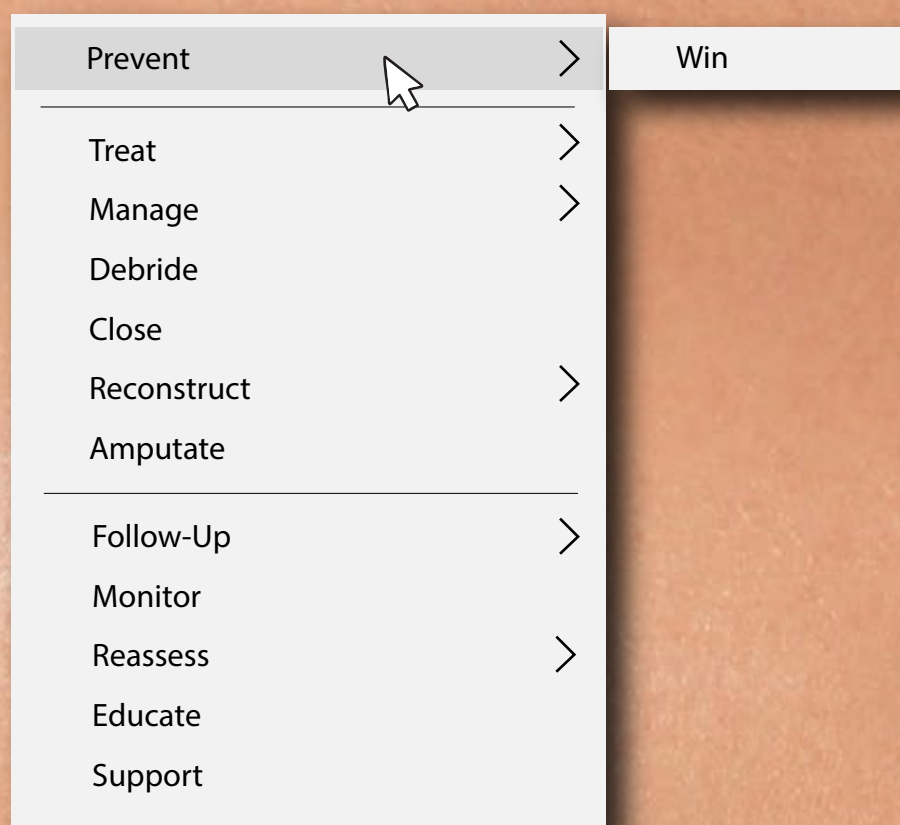
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SPECIAL ISSUE ON WOUND PREVENTION

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CLINICAL WINDOWS START WITH PREVENTION

Hacia un Cuidado de Heridas Accesible y Circular: Integrando Innovación, Educación y Evidencia en la Práctica Clínica

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Existen momentos en los que la práctica clínica debe ir más allá del pensamiento rutinario y reconsiderar sus propios fundamentos. El cuidado de las heridas crónicas atraviesa actualmente uno de esos momentos. Ya no puede considerarse simplemente un problema de integridad tisular ni un desafío técnico reservado a especialistas. Su magnitud refleja uno de los problemas de salud pública más urgentes de nuestro tiempo, reuniendo muchas de las tensiones que caracterizan a los sistemas sanitarios contemporáneos.

El envejecimiento de la población, el creciente peso de las enfermedades no transmisibles, la presión constante sobre los sistemas de salud y las desigualdades en el acceso a la atención especializada convergen de una manera que ya no puede ignorarse. En este contexto, las heridas complejas representan mucho más que defectos tisulares persistentes; constituyen un desafío creciente para las organizaciones sanitarias, los modelos asistenciales y, en última instancia, para la calidad ética de la atención que ofrecemos.¹

Una convicción fundamental sustenta esta

reflexión: el futuro del cuidado de las heridas dependerá de nuestra capacidad para superar la fragmentación y construir una visión de la atención más integrada, crítica y ambiciosa.²

A medida que la prevalencia de las heridas crónicas aumenta de forma constante entre las poblaciones vulnerables, también lo hacen el sufrimiento, la dependencia funcional, el riesgo de complicaciones y la carga humana y económica que los sistemas sanitarios deben afrontar.³ Este debate adquiere aún mayor relevancia en pediatría y neonatología, donde la fragilidad cutánea y la dependencia de dispositivos médicos, junto con otras condiciones de vulnerabilidad, convierten la integridad de la piel en un indicador directo de la calidad y la seguridad asistencial. Una lesión cutánea evitable en un recién nacido o en un niño implica dolor, un mayor riesgo de infección, hospitalizaciones prolongadas y una carga innecesaria para las familias durante una etapa especialmente sensible del desarrollo.⁴

Reconocer esta realidad exige tanto responsabilidad clínica como honestidad ética:

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solo puede hablarse de excelencia sanitaria cuando se protege de manera efectiva a las personas más vulnerables.⁵

Responder a estos desafíos mediante fórmulas heredadas o confiando excesivamente en marcos metodológicos que, aunque valiosos, ya no son suficientes para captar la complejidad de la práctica real sería un error. El ámbito del cuidado de las heridas debe replantearse la manera en que interpreta la evidencia científica. El objetivo no es abandonar el rigor metodológico, sino rescatarlo de una interpretación excesivamente restrictiva que corre el riesgo de excluir la complejidad de la práctica clínica cotidiana.⁶

El dominio incuestionado de una jerarquía lineal de la evidencia – en la que solo determinados diseños de estudio se consideran fuentes legítimas de conocimiento – ha dejado poco espacio para las realidades de la atención diaria. En el manejo de las personas que viven con heridas crónicas, el contexto no es un elemento secundario, sino un componente esencial de la toma de decisiones clínicas. Los pacientes presentan con frecuencia múltiples comorbilidades, recursos sociales y económicos limitados, itinerarios asistenciales fragmentados y situaciones clínicas que no pueden esperar a que aparezca una evidencia perfecta.⁶

Defender un modelo circular de la evidencia significa promover una ciencia menos dogmática y más útil desde el punto de vista clínico, capaz de integrar los ensayos clínicos aleatorizados con registros de alta calidad, estudios observacionales y experiencia profesional recopilada de manera sistemática.⁶ Este enfoque no pretende sustituir las jerarquías tradicionales de la evidencia, sino enriquecerlas incorporando formas de conocimiento esenciales en entornos clínicos complejos. En el cuidado de las heridas, donde la heterogeneidad de los pacientes, los factores contextuales, las limitaciones organizativas y los desafíos de implementación influyen en los resultados, la integración de diferentes fuentes de conocimiento puede ofrecer una comprensión más completa de la efectividad clínica.⁶

Dentro de esta perspectiva en evolución, la innovación tecnológica ocupa una posición central. Sin embargo, la tecnología no debe celebrarse simplemente porque sea nueva. No posee un valor intrínseco. Su verdadera importancia reside en su capacidad para mejorar la toma de decisiones clínicas, reducir la incertidumbre, ampliar el acceso a la atención y,

en última instancia, generar mejores resultados para los pacientes.⁷

La transformación digital del cuidado de las heridas ofrece una oportunidad extraordinaria para avanzar en esta dirección. La inteligencia artificial aplicada al análisis de imágenes, la segmentación tisular, la medición automatizada de las heridas y la comparación longitudinal de su evolución representa un paso importante hacia una evaluación más objetiva y reproducible, reduciendo la variabilidad entre observadores y mejorando la estandarización.⁷

No obstante, la sofisticación de un algoritmo solo tiene sentido si mejora la práctica clínica. Mejorar la capacidad de observar constituye el primer paso para mejorar la capacidad de prevenir y tratar. En el cuidado de las heridas, donde cada retraso, omisión o interpretación errónea puede traducirse en una cicatrización prolongada o en complicaciones evitables, esta diferencia posee una enorme relevancia clínica.⁸

La evidencia reciente sugiere que los sistemas basados en inteligencia artificial pueden mejorar la precisión diagnóstica y apoyar la toma de decisiones clínicas. Sin embargo, sigue siendo necesaria una validación adicional en diferentes contextos sanitarios antes de su implementación generalizada.⁸

Del mismo modo, la telemedicina y la monitorización remota no deben considerarse únicamente soluciones tecnológicas, sino instrumentos de equidad en salud, capaces de descentralizar la experiencia especializada y reducir los desplazamientos innecesarios de los pacientes, especialmente de aquellos con movilidad limitada o acceso restringido a servicios especializados. El progreso tecnológico solo merece realmente ese nombre cuando reduce las desigualdades en lugar de profundizarlas.⁹

El mismo principio se aplica a los sensores inteligentes y a los biomateriales avanzados diseñados para monitorizar el microambiente de la herida. Aunque muchas de estas tecnologías aún requieren mayor validación y maduración clínica, su dirección de desarrollo señala un importante cambio de paradigma. Pasar de una evaluación episódica a una monitorización continua, sensible y contextualizada significa imaginar un modelo asistencial menos reactivo, menos tardío y mucho más capaz de anticipar el deterioro antes de que este se haga clínicamente evidente.¹⁰

La medicina regenerativa y la fotobiomodulación ocupan esta misma frontera de innovación. Estos campos merecen entusiasmo, pero un entusiasmo disciplinado por la evidencia y no impulsado únicamente por las expectativas. Se ha producido un cambio conceptual fundamental: la piel ya no se considera simplemente una barrera física pasiva, sino un órgano inmunológicamente activo que desempeña un papel dinámico en la reparación y regeneración tisular. En este contexto, la fotobiomodulación, incluida la terapia con luz azul, emerge como una opción prometedora para las heridas de difícil cicatrización, aunque aún se requieren evidencias científicas sólidas para definir su papel clínico definitivo.^{11,12}

Sin embargo, sería ingenuo pensar que la innovación, por sí sola, resolverá los desafíos del cuidado de las heridas. Ninguna tecnología puede generar un valor sostenible sin un modelo organizativo capaz de adoptarla, evaluarla e integrarla en la práctica clínica cotidiana en beneficio de los pacientes, sus familias y los sistemas sanitarios.

A medida que la atención se desplaza progresivamente del hospital al domicilio y a la comunidad, también debe evolucionar nuestra comprensión de la eficiencia. El éxito ya no debería medirse únicamente por el número de procedimientos realizados, sino por la cantidad de sufrimiento evitado, las complicaciones prevenidas, la reducción del tiempo de cicatrización conseguida y la calidad de vida preservada.

Desde esta perspectiva, la sostenibilidad no debe presentarse como una limitación para la innovación, sino como la demostración definitiva de su madurez. Una innovación que no mejora los resultados o que no puede integrarse de forma realista en los sistemas sanitarios no constituye una solución auténtica; es simplemente una promesa que aún no ha cumplido su propósito.¹³

El segundo gran pilar – y quizá el más decisivo – es la educación especializada. Existe una ilusión persistente, especialmente en épocas de rápido desarrollo tecnológico, según la cual los dispositivos y los algoritmos compensarán las debilidades de la atención clínica. No lo harán.

Ninguna innovación tecnológica puede sustituir el juicio clínico, la observación entrenada, la interpretación contextual ni la prudencia necesaria para tomar decisiones en situaciones complejas considerando las necesidades tanto

de los pacientes como de sus familias.^{14,15}

Por ello, la formación continua nunca debería considerarse un complemento opcional, sino el fundamento estructural de cualquier estrategia sería destinada a mejorar la atención. La educación en el cuidado de las heridas va mucho más allá de la enseñanza técnica; requiere desarrollar razonamiento clínico, juicio ético, colaboración interdisciplinaria, competencias educativas y capacidad crítica para evaluar la evidencia científica.¹⁶

Dentro de este proceso, la enfermería especializada constituye el eje central de la prevención, el seguimiento longitudinal, la educación terapéutica y la coordinación efectiva de los cuidados. Los avances alcanzados por equipos altamente capacitados pueden desaparecer rápidamente si la formación se reduce a eventos aislados o si las instituciones no desarrollan una cultura capaz de sostener un crecimiento profesional continuo. La elevada rotación del personal, la heterogeneidad de la experiencia y las presiones cotidianas de la asistencia sanitaria hacen que la excelencia sea siempre un equilibrio frágil y dinámico.¹⁷

Por ello, resulta esencial traducir la evidencia científica en herramientas prácticas, documentos de consenso compartidos, algoritmos claros y estrategias educativas eficaces. El conocimiento científico que no llega al punto de atención en un lenguaje fácilmente aplicable por los profesionales corre el riesgo de convertirse en prestigio académico sin consecuencias clínicas reales.¹⁸

Los avances recientes en la prevención de lesiones por presión relacionadas con dispositivos médicos, la monitorización de la integridad cutánea, la atención centrada en la familia y las competencias especializadas de enfermería han puesto aún más de manifiesto la necesidad de enfoques específicamente adaptados a los recién nacidos y a los niños. A medida que los sistemas sanitarios avanzan hacia modelos asistenciales más seguros y personalizados, la población pediátrica representa no solo un desafío, sino también una extraordinaria oportunidad para la innovación, la colaboración interdisciplinaria y la investigación futura.¹³

El tercer pilar, la documentación clínica, merece una atención aún mayor de la que habitualmente recibe. En una época cada vez más fascinada por la inteligencia artificial, conviene recordar una verdad sencilla: ningún sistema

inteligente puede compensar datos clínicos deficientes, fragmentados o inconsistentes. La documentación clínica constituye el fundamento sobre el que se construyen la continuidad asistencial, la evaluación de resultados, la investigación aplicada y la visibilidad de la práctica profesional¹⁹

Cuando variables esenciales como el dolor, el estado nutricional, la evolución de la herida o las intervenciones realizadas se documentan de manera insuficiente, la seguridad del paciente se ve comprometida. Del mismo modo, la oportunidad de aprender de la experiencia y generar conocimiento útil a partir de la práctica cotidiana se debilita considerablemente.¹⁹

Defender la calidad de la documentación clínica no significa únicamente defender un requisito administrativo. Significa defender una ética del cuidado que reconoce que toda buena decisión futura depende, al menos en parte, del rigor con el que documentamos hoy lo que observamos y lo que hacemos.

En última instancia, el futuro del cuidado de las heridas no se definirá exclusivamente en laboratorios, congresos científicos o unidades especializadas. También dependerá de nuestra capacidad para construir una comunidad científica y clínica menos fragmentada, más colaborativa y más dispuesta a compartir el conocimiento sin convertirlo en un privilegio.⁶

En este sentido, el compromiso con modelos de publicación accesibles y con sistemas más democráticos de difusión del conocimiento no constituye una aspiración ideológica, sino una cuestión de coherencia. Si el cuidado de las heridas pretende afrontar una carga mundial de enfermedad, el conocimiento que genera no puede permanecer accesible únicamente para quienes disponen de los recursos necesarios para obtenerlo.⁶

Del mismo modo, si realmente aspiramos a una atención centrada en la persona, los pacientes, las familias y los cuidadores ya no deben ser considerados receptores pasivos de la asistencia sanitaria, sino socios activos en la definición de las prioridades terapéuticas, los objetivos asistenciales y los resultados verdaderamente significativos.

En definitiva, el futuro del cuidado de las heridas no estará determinado por un único avance tecnológico ni por un descubrimiento científico aislado. Dependerá de nuestra capacidad colectiva para integrar una innovación

con sentido, una educación sólida, formas plurales de evidencia, una documentación clínica rigurosa y una colaboración abierta dentro de un modelo asistencial coherente. Lo que está en juego es mucho más que la evolución de una disciplina clínica: es la oportunidad de construir un sistema sanitario más inteligente, más equitativo y más fiel a la dignidad de toda persona que vive con una herida. Frente a esta responsabilidad, observar el cambio ya no es suficiente. Ha llegado el momento de decidir qué tipo de diferencia estamos dispuestos a generar.

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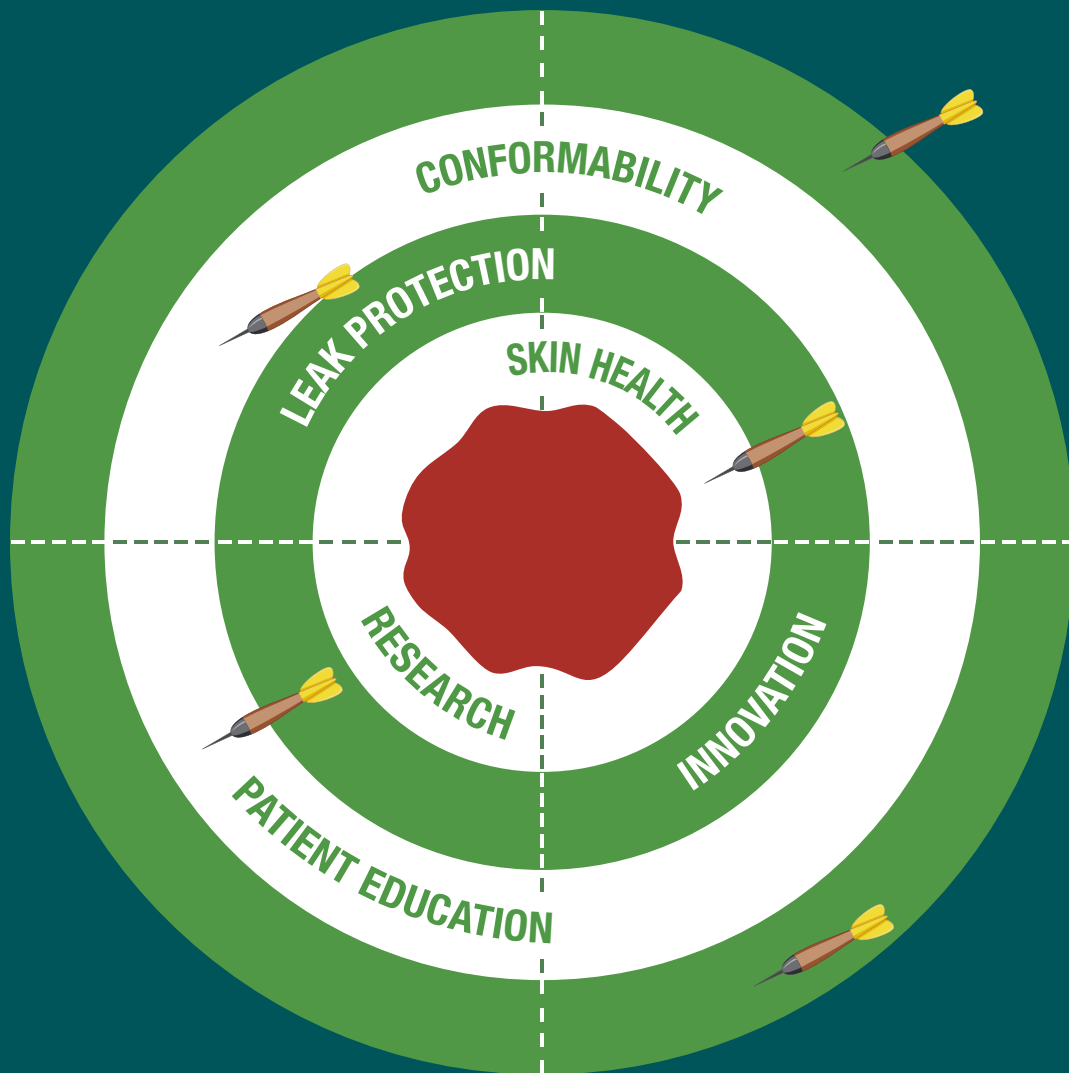
SPECIAL ISSUE ON
ADVANCES IN
PERISTOMAL
SKIN CARE

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DON'T MISS THE TARGET!

DIFFERENT PERSPECTIVES. ONE COMMON GOAL: BETTER PATIENT CARE.

Neonatal Skin Care to Maintain Skin Integrity: A Scoping Review

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Abstract

Introduction. Neonatal skin is essential for maintaining physiological homeostasis; however, its structural and functional immaturity - particularly in preterm infants - makes it highly susceptible to dehydration, infection, thermal instability, and environmental damage. Maintaining skin integrity is therefore a critical component of neonatal and early pediatric care to reduce morbidity and support healthy development.

Methods. A scoping review was conducted following the PRISMA-ScR guidelines to synthesize current global evidence on neonatal and pediatric skin care practices. Five electronic databases were systematically searched for studies published between 2014 and 2025 in English, Italian, or Spanish. Eligible studies addressed skin care interventions in neonates and children, including bathing practices, emollient use, perineal care, prevention of atopic dermatitis and management of skin lesions. A total of 38 studies met the inclusion criteria, encompassing randomized controlled trials, observational and quasi-experimental studies, qualitative research, and expert consensus documents.

Results. The reviewed evidence indicates that delayed bathing after birth, gentle cleansing routines, and careful selection of skin care products contribute to improved skin barrier function. Early and regular use of emollients containing physiological lipids was associated with enhanced hydration, reduced transepidermal water loss, and a lower incidence of irritant and atopic dermatitis. Structured perineal care protocols were shown to reduce diaper-related skin breakdown. Preterm infants emerged as a particularly vulnerable group, requiring highly cautious

and individualized approaches due to their markedly underdeveloped skin barrier. The review also highlights substantial global disparities in skin care practices, especially in low-resource settings, where access to appropriate products and standardized protocols is limited.

Discussion. Overall, the findings underscore the importance of evidence-based, standardized, and culturally sensitive skin care guidelines tailored to neonatal and pediatric populations. Implementing consistent practices across diverse clinical settings may improve skin integrity, reduce preventable complications, and support optimal neonatal outcomes, particularly among high-risk neonates.

Keywords: Infant, Newborn, Neonates, Premature Infants, Skin Care, Skin Integrity

Introduction

The skin of the newborn represents one of the most dynamic and vulnerable organs during the early phases of life. It is responsible for essential physiological functions including protection against pathogens, regulation of body temperature and maintenance of hydro-electrolytic balance. Although the epidermal structure of term infants already resembles that of adults, complete functional maturation continues throughout childhood and is not achieved until late infancy.¹

The comparison between human fetal and adult skin is shown in Figure 1.²

Preterm infants, whose epidermal and dermal layers remain incompletely developed, are

significantly more susceptible to mechanical injury, dehydration and infection.¹

During embryogenesis, skin maturation begins with the formation of the periderm at around the seventh week of gestation. This temporary cellular layer disappears between the twenty-fourth and twenty-fifth week, allowing the maturation of epidermal cell populations such as melanocytes, Merkel cells and Langerhans cells. The dermal-epidermal junction is markedly immature in preterm infants because its anchoring structures, including hemidesmosomes and collagen fibrils, are fewer and less cohesive than in term newborns and adults.^{1,3,4}

The stratum corneum, consisting of corneocytes embedded in a lipid matrix, is the primary physical barrier against trans epidermal

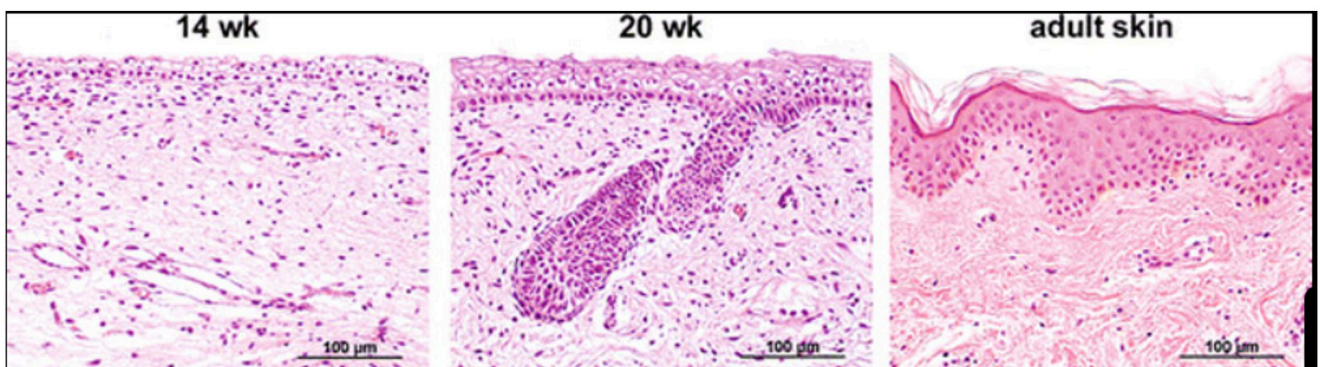


Figure 1. Histological progression of human skin development from fetal to adult stages. Representative histological sections of human integument showing skin development at 14 weeks of gestation, 20 weeks of gestation, and adult skin. Early fetal skin (14 weeks) is characterized by a thin, poorly stratified epidermis and a loosely organized dermis. At 20 weeks of gestation, increased epidermal stratification and early formation of adnexal structures can be observed. Adult skin displays a fully differentiated, multilayered epidermis and a well-organized dermis. Scale bar: 100 µm.

(Image available under the terms of the creative commons attribution-noncommercial- no derives license (CC BY-NC-ND 4.0))²

water loss and external insults. Its development begins around the fifteenth week of gestation. Term infants typically possess multiple corneocyte layers, whereas extremely preterm infants may have only a few layers or none at all in those born at the limits of viability.^{4,5}

At approximately twenty-four weeks, the skin appears red, gelatinous and translucent, reflecting profound immaturity.³

Sebaceous glands become active during late gestation and contribute to the formation of vernix caseosa, a hydrophobic, lipid-rich biofilm composed of water, sebaceous lipids, epidermal

lipids, proteins, cytokines and antimicrobial peptides.⁶⁻⁸

Vernix provides barrier protection in utero, prevents maceration from amniotic fluid and supports thermoregulation and innate immunity immediately after birth. Preterm infants, particularly those born before twenty-eight weeks, often lack vernix coverage, which further compromises their skin barrier.⁷

Key structural and functional characteristics of neonatal and pediatric skin, with clinical implications for wound prevention and integrity management, are summarized in Table 1.¹

Table 1. Structural and functional characteristics of neonatal and pediatric skin and their associated clinical implications for wound prevention and skin integrity management.

This table represents a reworked synthesis and academic reinterpretation of data derived from previously published literature (IMAG, 2004; White and Butcher, 2006; Visscher et al., 2013; Kanti et al., 2014)¹

Neonatal skin characteristics	Physiological and functional implications	Clinical considerations
The stratum corneum is composed of approximately 2–3 cell layers, compared with 20–30 layers in adult skin	Immature barrier function increases vulnerability to mechanical injury, chemical penetration, microbial colonization, and infection. Trans epidermal water loss is elevated, potentially compromising fluid balance, particularly in extremely preterm infants.	Topical exposure to substances known to exert irritant or cytotoxic effects, including iodine, alcohol, and high-concentration chlorhexidine, should be minimized or avoided. Maintain strict hand hygiene Monitor hydration status and consider humidity-controlled environments. Reduce pressure-related skin damage.
Reduced number and wider spacing of dermal–epidermal junction fibrils in preterm infants; dermis is poorly developed and less dense during the early postnatal period	Increased susceptibility to skin stripping, particularly during adhesive removal, and to shear forces associated with handling, movement, jewelry, and contact with medical devices	Limit the use of adhesives and prefer sterile silicone-based adhesive removers. Minimize handling. Remove jewelry and maintain short fingernails. Prevent device-related pressure injuries through regular repositioning and frequent skin inspection.
Reduced or absent subcutaneous fat in very preterm infants	Limited energy reserves, reduced shock absorption, and impaired thermoregulation	Ensure adequate caloric intake in accordance with dietetic guidance . Reposition infants regularly to prevent pressure injuries. Minimize exposure to cold stress during care procedures.
Increased expression of type III collagen	Potential influence on tissue remodeling and mechanical properties during skin development.	Potential implications for tissue repair, although clinical relevance remains uncertain and influenced by multiple local and systemic factors.
Immature acid mantle in term and preterm newborns, developing during the first weeks of life.	Increased vulnerability to biochemical and microbiological insults and higher risk of irritant-associated dermatitis	Emphasize rigorous hand hygiene to reduce healthcare-associated infections. Perform frequent nappy changes and apply appropriate barrier products to protect skin integrity
Increased sebaceous gland activity in newborn infants	Transient development of facial or nasal skin lesions	Reassure parents that this is a physiological and self-limiting condition that typically resolves within a few weeks as postnatal hormonal activity stabilizes

Hydration of the stratum corneum is essential for elasticity, proper desquamation and protection against mechanical stress. Natural Moisturizing Factors (NMF), composed of hydrophilic amino acids and derivatives, contribute to moisture retention and are present at lower levels in preterm infants than in term newborns.⁴

Skin surface pH plays a critical role in microbial colonization, enzymatic lipid processing and lipid organization. While term infants rapidly transition from a neutral to acidic skin surface during the first two weeks of life, preterm infants experience delayed acidification, which increases their vulnerability to infection.^{5,9,10}

Trans Epidermal Water Loss (TEWL) is one of the most sensitive indicators of skin barrier maturity. However, the time it takes for TEWL to

stabilize can vary depending on gestational age, environmental humidity, clinical condition, and skin care practices. Extremely preterm infants typically have significantly elevated TEWL at birth due to the immaturity of the stratum corneum and may require a prolonged postnatal adjustment period before achieving more stable barrier function parameters.

Term newborns gradually reach stable TEWL values within four to six weeks after birth, whereas extremely preterm infants display dramatically elevated TEWL levels at birth due to the absence of an adequate stratum corneum.⁷

They may require one to two weeks of postnatal life to achieve TEWL levels comparable to term infants.⁹

Figure 2 shows the TEWL difference between newborn and adult skin.¹⁰

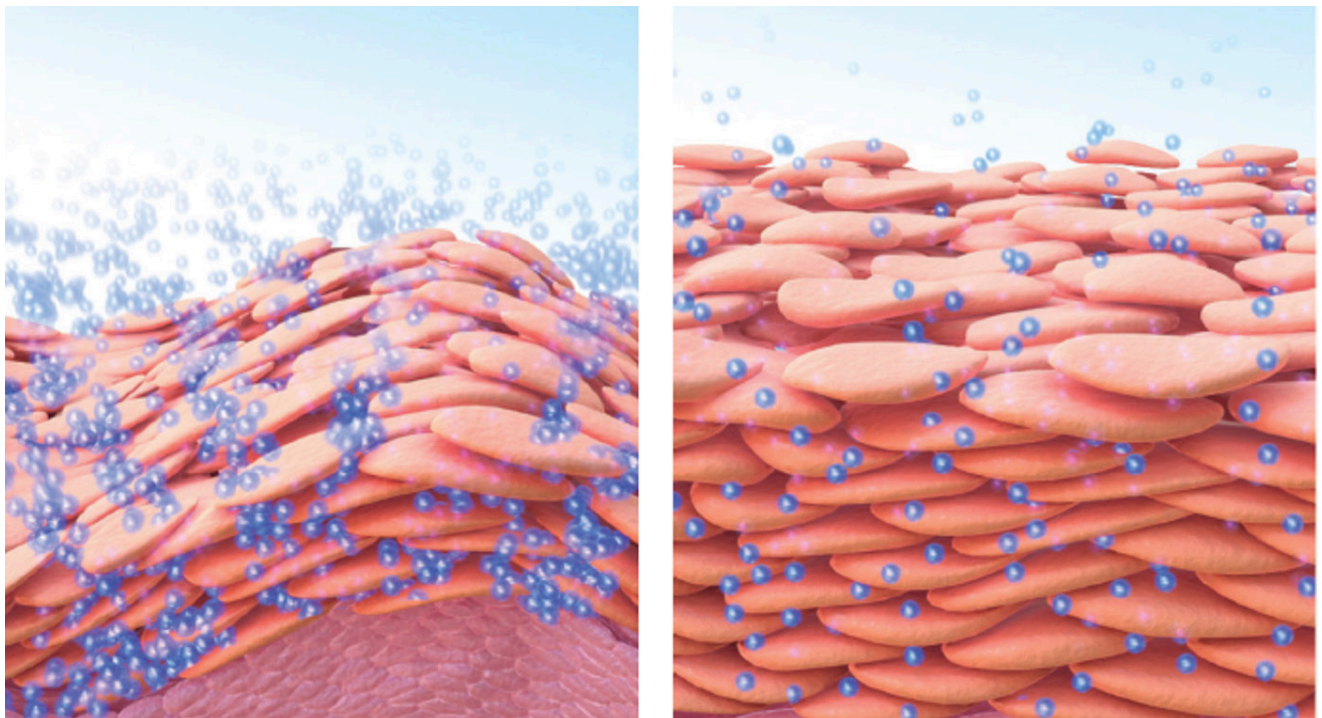


Figure 2. Infant and adult skin: stratum corneum (SC) hydration and water transport properties. The SC of infant skin (a) and adult skin (b) is hydrated (small blue spheres) under normal conditions. Infant SC is more hydrated but also loses water at higher rates than adult SC.

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At the same time, skin microbiota colonization begins immediately after delivery and is shaped by the mode of birth, environmental exposure and healthcare practices.⁵

Vaginally delivered newborns show a predominance of *Lactobacillus* and *Prevotella* species, whereas cesarean-delivered infants display early colonization by *Staphylococcus* and *Corynebacterium*.^{5,6}

Preterm infants, especially those requiring intensive care, show restricted microbial diversity and increased susceptibility to colonization by pathogenic bacteria.^{4,7,11}

This biological immaturity, combined with frequent handling, invasive procedures and exposure to medical devices, explains why neonatal skin care is a critical component of overall clinical management.¹²⁻¹⁴

Evidence-based practices are essential to preserve skin integrity, prevent complications and promote healthy development.¹⁵

In this context, this scoping review aims to map the available literature on neonatal and pediatric skin care, with particular attention to bathing routines, emollient therapy, perineal care, prevention of atopic dermatitis, management of cutaneous lesions, microbiota-related aspects and global disparities in care.

Methods

This scoping review followed the methodological framework of the PRISMA-ScR guidelines to ensure transparency, reproducibility and methodological rigor. The research question was developed using the Population-Concept-Context (PCC) framework, as recommended for scoping reviews, with the aim of mapping the breadth of existing literature rather than evaluating the superiority of specific interventions.¹⁶

The population of interest comprised neonates, infants, preterm and extremely preterm infants, children and adolescents, including patients cared for in hospital settings and in neonatal and pediatric intensive care units. The concept of interest encompassed skin care practices and methods aimed at maintaining skin integrity and preventing skin damage, including cleansing routines, bathing practices, use of emollients, perineal care, prevention of dermatitis and management of cutaneous injuries such as pressure injuries (PIs), incontinence associated dermatitis (IAD), diaper rash, wounds and skin tears.

The context included hospital environments, with particular focus on neonatal and pediatric intensive care units, across different healthcare systems and geographical contexts. Maintenance of skin integrity was considered the overarching outcome of interest and was explored through reported measures of skin hydration, skin surface pH, trans epidermal water loss, incidence of dermatitis or cutaneous lesions, and patterns of microbial colonization.

The literature was mapped using a structured approach. The search was conducted from September 2024 to May 2025 across five electronic databases: PubMed, CINAHL, Cochrane Library, Trip Database and Embase. Keywords and MeSH terms related to infants, children, skin care, emollients, pressure ulcers,

diaper dermatitis and wounds were combined using Boolean operators AND and OR. The search strategies are presented in Appendix 1.

Studies were included if published between 2014 and 2025 in English, Italian or Spanish and if they addressed skin care in neonatal or pediatric populations. Literature reviews were excluded to avoid redundancy in the synthesis of evidence.

Two independent reviewers screened all titles and abstracts identified by the search strategy. When disagreements arose, a third reviewer evaluated the article to reach consensus. Full texts of potentially eligible studies were reviewed in detail to confirm eligibility and relevance to the scope of the review. Extracted data included study design, population characteristics, type of intervention, outcome measures and main findings.

Because of the clinical and methodological heterogeneity among the included studies, statistical pooling was not appropriate. The findings were therefore synthesized narratively and organized thematically into key domains: bathing practices, emollient therapy, perineal care, prevention of atopic dermatitis, cutaneous lesions and wound management and global disparities in neonatal and pediatric skin care.

The PRISMA-ScR flow diagram for the selection process is shown in Figure 3.

Results

The search yielded thirty-eight studies that met the inclusion criteria. The selected articles were geographically diverse, originating from the United States, Turkey, Brazil, South Korea, the United Kingdom, Zambia, Egypt, Japan, Ireland, Spain and multinational collaborations. They encompassed randomized controlled trials, quasi-experimental research, qualitative studies, observational cohorts, expert consensus statements and quality improvement initiatives. This diversity reflects the global interest in neonatal and pediatric skin care and the range of clinical questions explored.

The included articles are presented in Table 2 and Summary Table 1 which provide an overview of bibliographic details, country, study design, sample characteristics, intervention components, outcomes, and a narrative summary of the findings.

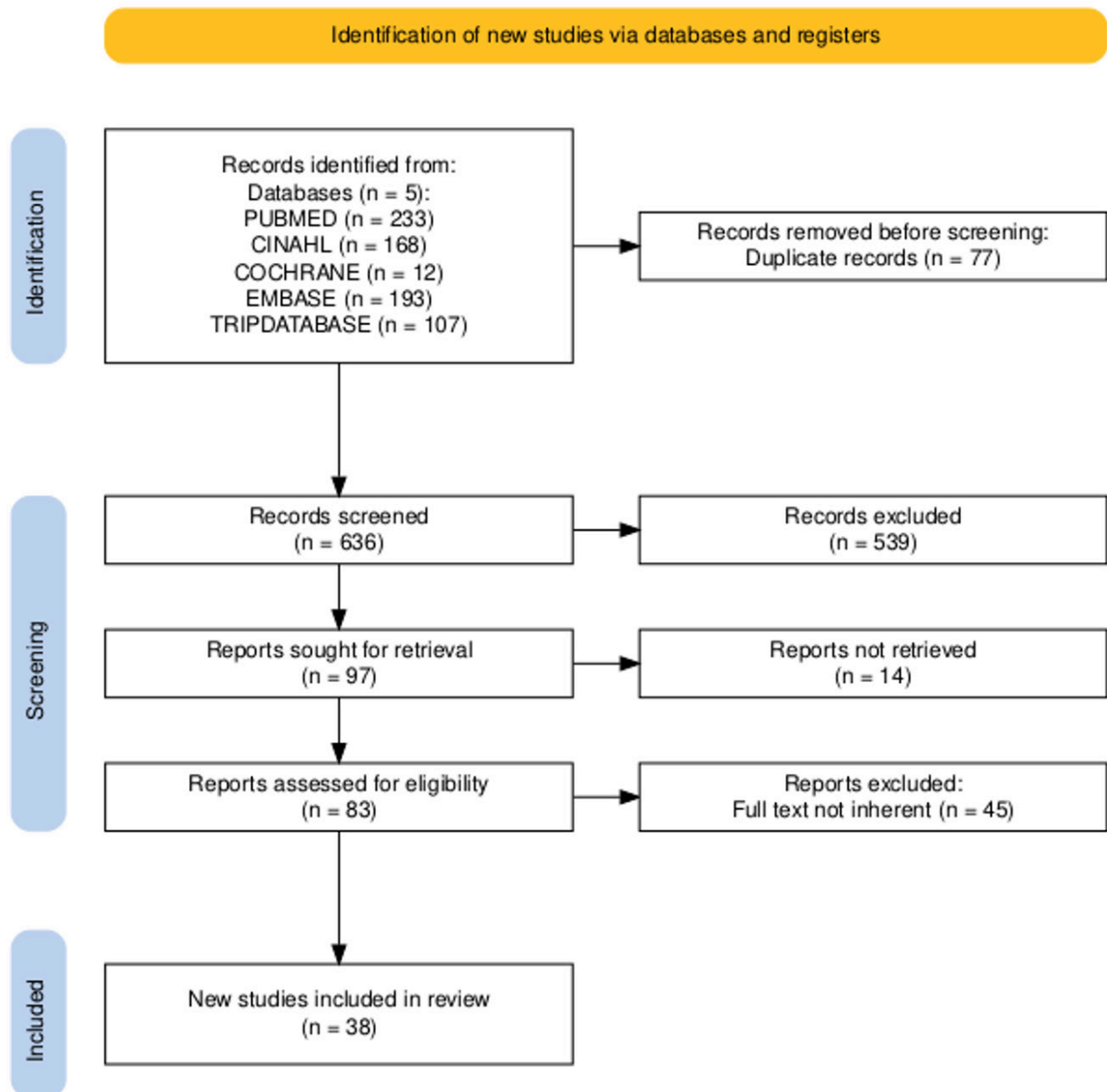


Figure 3. PRISMA-ScR flow diagram showing the selection of sources of evidence included in the scoping review.^{16,17}

Table 2. Included studies in the scoping review (N = 38): publication years, study types, and geographic distribution.

Total number of articles	38
Publication years	2014: 2 (5.3%); 2015: 4 (10.5%); 2017: 3 (7.9%); 2018: 2 (5.3%); 2019: 5 (13.2%); 2020: 7 (18.1%); 2021: 2 (5.3%); 2022: 3 (7.9%); 2023: 3 (7.9%); 2024: 5 (13.2%); 2025: 2 (5.3%).
Study types (% of total)	Randomized studies (RCT/crossover): 14 (36.8%); Quasi-experimental / pre-post studies: 6 (15.8%); Observational studies (cohort): 3 (7.9%); Consensus statements / guidelines: 4 (10.5%); Qualitative studies: 3 (7.9%); Quality improvement: 3 (7.9%); Survey: 2 (5.3%); Descriptive study: 1 (2.6%); Methodological study: 1 (2.6%); Case series: 1 (2.6%).
Geographic origin (% by continent)	Asia: 14 (36.8%); North America: 12 (31.6%); Europe: 4 (10.5%); Africa: 3 (7.9%); South America: 3 (7.9%); Global / Multicontinental: 2 (5.3%).

Regarding bathing practices, studies suggested considerable variation in timing, frequency and cleansing methods. Evidence indicated that delaying the first bath supported thermoregulation, stabilized vital parameters and improved parental involvement in routine care.^{13,14,18}

Infants who received delayed immersion baths were less prone to hypothermia than those bathed early with sponge methods.¹⁹

In preterm infants, extending the interval between baths from two to four days did not worsen skin condition or increase bacterial colonization, supporting the practice of reduced bathing frequency to minimize stress and heat loss.²⁰

Comparisons between water-only baths and baths using mildly acidic, soap-free cleansers revealed no significant differences in trans epidermal water loss or skin surface pH reduction. Nevertheless, the timing and nature of post-bath care influenced hydration in the hours following bathing. Infants receiving emollients ten minutes after bathing appeared to maintain more sustained hydration levels than those treated immediately after the bath, suggesting that a short interval may favor better absorption and barrier support.²¹

Studies on emollient therapy revealed substantial variability in effectiveness depending on lipid composition and neonatal maturity.²²⁻³⁰

While sunflower seed oil is widely used across different settings, one randomized trial showed that its application in extremely preterm infants increased TEWL and reduced hydration, suggesting adverse effects on barrier maturation.^{22,23,25,27}

In contrast, topical coconut oil consistently enhanced barrier function, reduced TEWL and limited pathogenic colonization.^{26,27}

Almond and olive oils improved hydration and skin condition without causing irritation, and no major adverse events were reported.²⁴

Qualitative studies conducted in African and other low-resource settings highlighted substantial variability in cultural skincare practices. In many regions, traditional oils such as coconut, olive or shea butter were commonly used, sometimes accompanied by vigorous massage that risked damaging fragile neonatal skin. Harmful substances, including motor oil, were also reported.²⁸⁻³⁰

Ceramide-containing moisturizers were associated with beneficial effects. Their lipid

profile resembles the physiological composition of the stratum corneum, supporting lipid organization and reducing the frequency of dermatitis episodes. Infants treated with ceramide-rich emollients experienced fewer relapses of atopic dermatitis and required less frequent use of topical corticosteroids.^{31,32}

Perineal care emerged as another critical domain. Regimens combining emollient-infused diapers with acid-buffered wipes produced lower perianal pH levels and reduced erythema compared with standard products.³³

Zinc oxide barrier creams seem to perform better than topical human milk in moderate to severe diaper dermatitis, although human milk showed partial benefits in mild cases.³⁴

The introduction of standardized perineal care guidelines appeared to significantly decrease the incidence and severity of diaper dermatitis and shortened healing time.³⁵

Studies focusing on atopic dermatitis prevention emphasized that early skin care plays a pivotal role in high-risk infants. Consensus recommendations highlighted gentle cleansing with mildly acidic products, brief lukewarm baths two to three times per week and daily use of ceramide-enriched emollients.³⁶

A prospective cohort study from Japan suggested that structured skincare protocols may have season-dependent effectiveness, with infants born in winter benefiting most from proactive moisturizing routines that enhance barrier development.³⁷

Research conducted in neonatal and pediatric intensive care settings revealed a high incidence of cutaneous lesions, particularly among preterm infants. These lesions included hematomas, abrasions, erythema, candidiasis, diaper dermatitis and moisture-associated skin damage.³⁸

Cyanoacrylate-based skin protectants may represent a promising intervention for the management of moisture-associated skin damage and device-related irritation. Their application formed a flexible, breathable barrier that adhered effectively to moist areas, supporting rapid healing of granulomatous tissue around tracheostomies, peri-stomal irritation and superficial lacerations.³⁹

PIs were frequently associated with medical devices, especially in younger infants whose facial and scalp skin is particularly fragile.⁴⁰⁻⁴²

Implementation of pressure injury prevention bundles incorporating regular repositioning,

risk assessments, protective products and staff education successfully reduced both incidence and severity of PIs.^{1,43,44}

These findings highlight the potential importance of culturally sensitive educational interventions that integrate evidence-based recommendations with respect for local traditions.⁴⁵⁻⁵²

Discussion

Our mapping underscores the breadth of evidence on neonatal and pediatric skin care, spanning bathing and cleansing routines, emollient therapy, perineal care, strategies to prevent atopic dermatitis, management of skin lesions and international variation in care practices.

Bathing practices suggest that delaying the first bath may support thermal stability, preserve vernix caseosa, and facilitate parent–infant bonding, in line with international recommendations.⁵³

In preterm infants, reduced bathing frequency appears safe and may minimize physiological stress by limiting handling and temperature fluctuations.⁵³

The evidence on emollient therapy highlights the importance of selecting products appropriate to neonatal maturity and skin physiology. Although sunflower seed oil is widely available and inexpensive, data suggesting increased TEWL in extremely preterm infants urge caution in its use in this vulnerable population.²⁵

In contrast, coconut oil appears to offer advantages in improving hydration, promoting barrier maturation, and reducing colonization with potentially pathogenic organisms.^{26,27} Almond and olive oils can also be considered safe options when used under appropriate clinical supervision.²²

Ceramide-containing products are of interest because they closely resemble the natural lipid composition of the stratum corneum. Their early use not only improves hydration but also appears to reduce the incidence and severity of atopic dermatitis, with a consequent reduction in the need for topical corticosteroids.³¹

These findings support the proactive use of ceramide-rich emollients in infants with a family history of atopy or other risk factors for barrier dysfunction.³²

Perineal care studies highlight the potential importance of maintaining an acidic skin

surface to inhibit pathogenic colonization and reduce irritant damage. Structured protocols incorporating pH-buffered wipes and barrier creams based on zinc oxide or other protective agents have been associated with reductions in the incidence and severity of diaper dermatitis.³³

Such protocols may be particularly relevant for hospitalized neonates and preterm infants, who are frequently exposed to prolonged moisture and irritants.^{34,35}

Cutaneous lesions, especially pressure injuries in neonatal and pediatric intensive care settings, remain a significant clinical problem. Several studies suggested that multidisciplinary bundles including systematic risk assessment, repositioning strategies, appropriate support surfaces, and careful device management may help reduce the incidence and severity of pressure injuries.^{40,43,44}

Younger infants, and particularly those with complex cardiac or respiratory conditions, appear to be at greatest risk, emphasizing the need for consistent preventive strategies.⁴¹

Global disparities in skin care practices reflect differences in cultural traditions, resource availability and educational support.^{49,50}

While certain traditional practices, such as the use of natural oils and delayed bathing, may align with evidence-based recommendations, others pose significant risks and require modification. Educational interventions that respect cultural norms while promoting safe and effective practices are essential to improving outcomes in low-resource settings.⁵⁴

This review has several strengths, including its broad international scope and the use of a structured methodological approach. However, it is limited by variability in study design, sample size and outcome measures across the included articles. Few randomized controlled trials are available for some interventions, and long-term outcomes are rarely reported. Further high-quality clinical research is needed to clarify optimal product selection, frequency of interventions and tailored strategies for different subgroups of neonates and children.

Conclusions

Neonatal and pediatric skin care requires an approach that acknowledges the unique vulnerability and physiological immaturity of early life. Across the literature synthesized in this scoping review, evidence supports delayed

bathing, careful use of emollients tailored to developmental stage, structured perineal care, preventive strategies for atopic dermatitis and targeted interventions for wound management. Preterm infants, particularly those born at extremely low gestational age, require highly individualized care and access to specialized products that support rapid yet safe maturation of the skin barrier.

Significant disparities persist between high- and low-resource settings, where economic constraints, infrastructural limitations and cultural practices influence the feasibility of implementing standardized protocols. Developing and disseminating culturally sensitive, evidence-based guidelines is therefore essential. Educational initiatives for healthcare professionals and parents, as well as the integration of skin care bundles into routine clinical practice, can contribute to improved outcomes and to the recognition of neonatal skin health as a fundamental component of the right to health for all infants.

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Therapeutic Application of hUC-MSC-derived Exosomes in Diabetic Wounds: A Scoping Review

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Abstract

Introduction. Diabetic foot ulcers (DFUs) represent a severe and debilitating complication of diabetes mellitus, often proving refractory to conventional therapies due to a persistent pro-inflammatory state that delays granulation tissue formation and re-epithelialization. While stem cell therapies offer potential, challenges regarding tumorigenicity, cell survival, and regulatory hurdles have spurred interest in cell-free approaches, specifically nanometric vesicles known as exosomes derived from human umbilical cord mesenchymal stem cells (hUC-MSCs). This scoping review aimed to map the extent and nature of evidence regarding the therapeutic application of hUC-MSC-derived exosomes in diabetic wound management across preclinical and clinical settings.

Methods. Conducted according to the Joanna Briggs Institute (JBI) methodology and PRISMA-ScR guidelines, systematic searches were performed in PubMed, Embase, CINAHL, Lilacs, and grey literature (Google Scholar and Research Square) through January 31, 2026.

Results. Nineteen studies met the inclusion criteria, primarily comprising preclinical investigations (n=15) alongside two randomized clinical trials. Preclinical evidence consistently demonstrates that hUC-MSC-derived exosomes accelerate wound closure by enhancing angiogenesis (CD31 and VEGF upregulation), modulating macrophage polarization toward the anti-inflammatory M2 phenotype, and promoting extracellular matrix restructuring. Clinical trials involving 130 participants reported favorable outcomes, including complete ulcer closure and a documented safety profile over a 24-month

follow-up period. Technological advancements include the use of biomaterial carriers, such as hydrogels and scaffolds, to ensure sustained release and localized retention within the wound bed.

Discussion. While evidence is consistent in the preclinical domain, a significant translational gap remains due to mechanistic differences between rodent contraction-based healing and human re-epithelialization. Standardizing dose-response protocols and conducting multicenter randomized trials are essential to bridge the gap toward real-world clinical implementation.

Keyword: Wound Care Innovation, hUC-MSC, Diabetic Foot, Exosomes, Healing, Scoping Review

Introduction

Wounds in individuals with diabetes, particularly diabetic foot ulcers (DFUs), are considered the most debilitating and burdensome complications of diabetes mellitus (DM). They frequently result in hard-to-heal wounds and partial or total amputation of lower limb segments, imposing significant social and economic burdens.^{1,2} Although traditional wound care based on dressings and other adjuvant therapies is improving these outcomes,³ a substantial proportion of DFUs remains refractory to these approaches due to a persistent inflammatory state.⁴ This state is sustained by hyperglycemia, advanced glycation end-products (AGEs), and reactive oxygen species (ROS), which impair the proliferation of fibroblasts and keratinocytes, thereby delaying granulation tissue formation and re-epithelialization.⁵⁻⁸

Stem cell therapies have garnered considerable attention from researchers. However, due to challenges regarding cell survival, potential tumorigenic risks, pharmacodynamic limitations, and regulatory hurdles imposed by health authorities, alternative approaches to harness biologically active molecules are being investigated, such as the use of exosomes.⁹⁻¹¹ Extracellular vesicles, specifically exosomes derived from human umbilical cord mesenchymal stem cells (hUC-MSCs), have emerged as a promising tool due to their ability to transfer molecules such as microRNAs, growth factors, and cytokines. These nanometric vesicles have demonstrated the potential to modulate tissue repair processes by promoting

angiogenesis, attenuating oxidative stress, favoring extracellular matrix (ECM) remodeling, and regulating macrophage polarization from pro-inflammatory to anti-inflammatory phenotypes.¹²⁻¹⁴

Preclinical evidence indicates that hUC-MSC-derived exosomes possess a potential therapeutic impact on the repair of diabetic wounds.¹⁵⁻¹⁷ Experimental studies have shown that these vesicles exert multifunctional actions, including the promotion of fibroblast migration, angiogenesis, and modulation of local inflammation critical components for effective healing.^{18,19} Research across various animal models has shown accelerated re-epithelialization and ECM restructuring when treated with hUC-MSC-derived exosomes, either alone or in combination with carriers such as hydrogels.^{20,21}

Early-phase clinical trials have begun to translate these findings to human samples. In a phase I/II trial involving patients with DFUs non-responsive to standard care, participants received local injections of allogeneic preparations rich in hUC-MSC-derived exosomes. The result was complete ulcer closure in all participants, and no adverse events or recurrence over a 24-month follow-up period.²² Similarly, another randomized clinical trial involving individuals with DFUs showed that the topical application of an exosome gel derived from Wharton's jelly led to complete healing in 62% of patients by the sixth week, compared to markedly longer healing times in control groups.²³ These outcomes were accompanied by a favorable safety profile, suggesting not only clinical efficacy but also viability in a real-world practice setting.

Despite this encouraging progress, the current body of literature remains fragmented. Experimental designs differ considerably between studies, including the source and characterization of exosomes, administration routes (topical vs. injectable), frequency and duration of application, and the incorporation of delivery vehicles like hydrogels. Furthermore, although some clinical studies suggest robust signs of efficacy, sample sizes are small, and the regulatory landscape governing exosome-based therapies remains immature. Considering these limitations, a scoping review is justified to map the existing evidence on the application of hUC-MSC-derived exosomes in the treatment of diabetic wounds.

Accordingly, this review addressed the following research question: What is the extent and nature of the evidence on the therapeutic application of hUC-MSC-derived exosomes in the management of diabetic wounds across clinical and preclinical settings?

Methods

Study Design

This scoping review was conducted in accordance with the Joanna Briggs Institute (JBI) methodology for evidence synthesis, which advocates for a rigorous and transparent process to map the extent, range, and characteristics of literature in complex or emerging fields.²⁴ The review was reported in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR), and the PRISMA-ScR checklist was used to guide reporting.²⁵

The protocol was developed using the Population, Concept, and Context (PCC) framework. The review addressed the following research question: What is the extent and nature of the evidence on the therapeutic application of hUC-MSC-derived exosomes in the management of diabetic wounds across clinical and preclinical settings?

Literature Selection

Eligibility criteria were defined according to the PCC framework. The population comprised: (i) individuals with diabetes mellitus presenting with cutaneous wounds, including DFUs; (ii) *in vivo* diabetic wound models; and (iii) relevant *in vitro* models reproducing diabetes-related

conditions. The concept of interest was the therapeutic application of exosomes derived specifically from hUC-MSCs, used either alone or in combination with biomaterials or delivery vehicles. The context included any clinical care setting for human studies and any laboratory setting for preclinical studies, without geographic restriction.

Evidence sources considered eligible encompassed primary quantitative research such as randomized clinical trials, quasi-experimental studies, cohort analyses, and animal experiments. In addition, *in vitro* experimental studies, as well as relevant secondary studies for evidence mapping, were included. Studies evaluating mesenchymal stromal/stem cells from sources other than the human umbilical cord were excluded, as were studies on non-diabetic wounds without a clearly diabetes-related component, editorials, comments, letters, and conference abstracts without accessible full text.

Information Sources and Search Strategy

The databases PubMed (MEDLINE), Embase, CINAHL, and Lilacs were searched, along with Google Scholar and Research Square for grey literature, without a lower date limit, including studies published up to January 31, 2026. Inclusion was restricted to publications in English, Portuguese, or Spanish. The search strategy was built using controlled vocabulary and free terms related to diabetic foot ulcers and exosomes.

The final PubMed strategy included combinations of: ((“Exosomes”[Mesh] OR “Extracellular Vesicles”[Mesh] OR “exosom*”[TiAb] OR “extracellular vesicle*”[TiAb])) AND ((“Umbilical Cord”[Mesh] OR “Wharton Jelly”[Mesh] OR “umbilical cord”[TiAb] OR “Wharton*”[TiAb])) AND ((“Mesenchymal Stem Cells”[Mesh] OR “mesenchymal”[TiAb] OR “MSC”[TiAb] OR “MSCs”[TiAb])) AND ((“Diabetes Mellitus”[Mesh] OR “Diabetic Foot”[Mesh] OR “diabetic wound*”[TiAb] OR “diabetic ulcer*”[TiAb])). The PubMed strategy was developed first and then adapted to the syntax and controlled vocabulary of each database. The complete search strings for all sources are provided in Supplementary Table S1. Reference lists of included studies and relevant reviews were also manually screened to identify additional eligible records.

Study Selection

All retrieved citations were exported to Zotero reference management software (version 7.0.X, Corporation for Digital Scholarship, Virginia, USA) for duplicate removal and then transferred to the Rayyan systematic review platform (Rayyan Systems Inc., Cambridge, MA, USA) for blind screening. Titles and abstracts were reviewed independently by two reviewers (VFC and MRK), followed by full-text evaluation. Discrepancies were resolved by consensus or a third reviewer (AOP). The selection process followed PRISMA-ScR guidelines²⁶ and is summarized in a official PRISMA flow diagram format.

Data Extraction and Synthesis

Data were charted independently by two reviewers using a standardized extraction form developed in accordance with JBI recommendations for scoping reviews.²⁷ The form captured bibliographic information (author, year, country, journal), study characteristics (design, methods, population or model, wound type, intervention, comparator, and outcomes), and the principal findings relevant to the review question. The charting process was iterative, and the extraction form could be refined when necessary to ensure that all relevant information was consistently captured across heterogeneous sources of evidence.

To support structured interpretation of the mapped evidence, results were synthesized using the PAGER framework, which allowed the findings to be organized according to recurring Patterns, Advances, Gaps, Evidence for practice, and Research recommendations.²⁸ This approach was used to summarize major biological effects, technological approaches, methodological limitations, and priorities for future translational development.

Results

Study Selection Process

As shown in Figure 1, the search identified 1,799 records across the selected databases and sources. After duplicate removal, 924 records were screened by title and abstract. Thirty-seven reports were sought for retrieval, three of which were inaccessible. Of the 34 full-text reports assessed for eligibility, 15 were excluded because

they did not meet the predefined population, context, or concept criteria. Therefore, 19 studies were included in the final evidence map.

Characteristics of Included Studies

The evidence found in the 19 studies regarding hUC-MSC-derived exosome (hUC-MSC-Exos) application in DM wounds is primarily preclinical. There is a wide variety of study designs, from animal models^{20,21,29–34} and *in vitro* experiments^{16,18,19,35–38} (conducted exclusively in Chinese institutions) to clinical trials and secondary research. Clinical trials originated in Jordan²² (a randomized controlled trial (RCT) with 110 participants over 24 months) and Egypt²³ (20 patients followed for 12–16 weeks). Overall, the body of evidence indicates rapid growth in publications over the last decade, alongside increasing diversification in exosome engineering, delivery platforms, and mechanistic targets. Further characteristics of the studies are presented in Table 1.

Diabetic Wound Models and Clinical Populations

Preclinical studies employed two main diabetes induction strategies, streptozotocina (STZ) injection, sometimes combined with a high-fat diet,^{21,30,32,34,36,38} and genetically diabetic models using db/db mice.^{18,19} All preclinical models used full-thickness excisional wounds on rodent dorsal skin (8 mm to 2 cm).

The clinical evidence focused on chronic diabetic foot ulcers. One phase I/II trial evaluated local administration of hUC-MSC derivatives in patients with University of Texas grade II–III ulcers and reported complete closure in the treated cohort over follow-up, with favorable long-term safety observations.²² Another randomized clinical trial assessed a Wharton's jelly MSC-derived exosome gel in chronic DFUs and reported faster healing and a higher proportion of complete recovery than the comparator group.²³

Exosome Characterization

Isolation methods varied, with ultracentrifugation being most common, followed by commercial kits^{21,32,37} or polyethylene glycol (PEG) precipitation combined with ultracentrifugation.²⁹

Delivery strategies ranged from direct

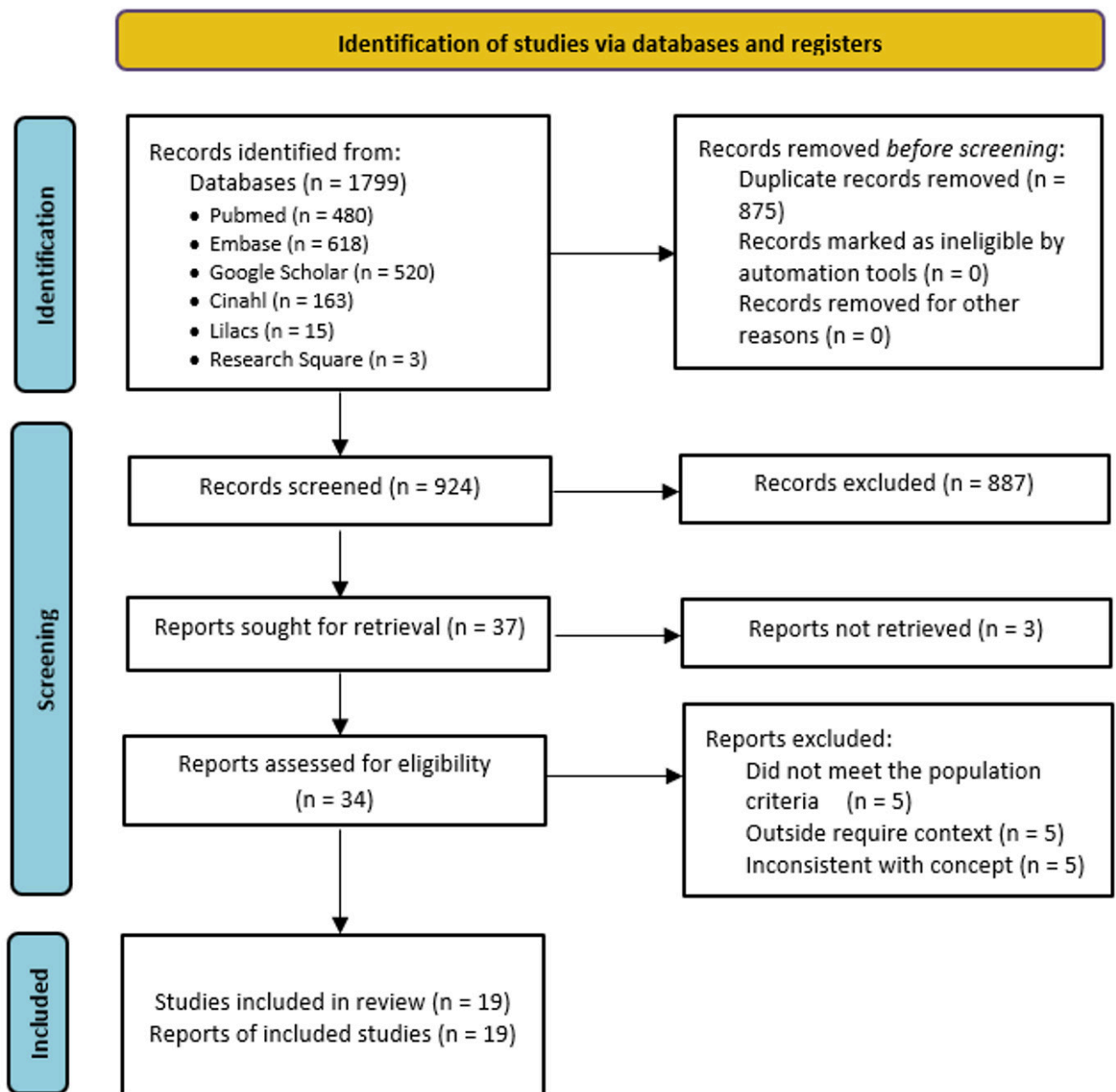


Figure 1. Search results and study selection and inclusion process.

injection^{18,19,22,30,35} to biomaterial-based systems such as chitosan hydrogels²⁹, Pluronic F-127²¹, decellularized porcine ECM³⁴, and gallium/chitosan/silk scaffolds.²³ Biomaterials address the issue of rapid exosome clearance at wound sites.

Biological Effects

Wound Closure and Healing Outcomes

Despite variability, studies converged on

the benefits of wound closure and improved repair markers. Preclinical closure rates ranged from near-complete by day 12 to 97.4% by day 1430. Hydrogel/biomaterial carriers showed superior performance compared to free exosomes.^{21,23,29,32,34} Clinically, Kishta et al.²³ reported a 62% recovery rate (mean 6 weeks vs. 20 weeks in control), and Jafar et al.²² reported 100% closure (mean 4.2 weeks) with a favorable long-term safety profile. Chen L et al.³⁹ found a significant standardized mean difference (SMD) of 4.03 (95% CI: 3.29–4.76) favoring exosomes in

Table 1. Characteristics of Included Studies.

Study	Country	Evidence Category	Design	Population / Model	Target Wound Type
Zhang B et al. (2015)	China	Primary preclinical	<i>In vivo</i>	STZ-induced diabetic SD rats	Burn wounds
Yang J et al. (2020)	China	Primary preclinical	<i>In vivo</i> and <i>in vitro</i>	STZ-induced diabetic SD rats	Full-thickness excisional wounds
Wei Q et al. (2021 preprint) – miR-221-3p	China	Primary preclinical	<i>In vivo</i> and <i>in vitro</i>	db/db diabetic mice; HUVECs	Full-thickness excisional wounds
Wei Q et al. (2022) – miR-17-5p	China	Primary preclinical	<i>In vivo</i> and <i>in vitro</i>	db/db diabetic mice; HUVECs	Full-thickness excisional wounds
Yan C et al. (2022)	China	Primary preclinical	<i>In vivo</i> and <i>in vitro</i>	STZ-induced diabetic C57BL/6 mice; HUVECs	Full-thickness excisional wounds
Teng L et al. (2022)	China	Primary preclinical	<i>In vivo</i>	STZ-induced diabetic SD rats	Full-thickness excisional wounds
Yang S et al. (2023)	China	Primary preclinical	<i>In vivo</i>	STZ-induced diabetic SD rats	Full-thickness excisional wounds
Zhao X et al. (2023)	China	Primary preclinical	<i>In vivo</i> and <i>in vitro</i>	db/db diabetic mice; fibroblasts	Full-thickness excisional wounds
Ge L et al. (2023)	China	Primary preclinical	<i>In vivo</i> and <i>in vitro</i>	Diabetic mice; HUVECs	Full-thickness skin wounds
Yang J et al. (2024)	NR	Primary preclinical	<i>In vivo</i>	Diabetic mice	Full-thickness excisional wounds
Wu S et al. (2024)	China	Primary preclinical	<i>In vivo</i>	STZ-induced diabetic SD rats; fibroblasts	Full-thickness excisional wounds
Yang R et al. (2024)	China	Primary preclinical	<i>In vivo</i> and <i>in vitro</i>	db/db diabetic mice; keratinocytes	Full-thickness skin wounds
Shi X et al. (2024)	China	Primary preclinical	<i>In vivo</i> and <i>in vitro</i>	STZ-induced diabetic SD rats	Full-thickness skin wounds
Chen X et al. (2025)	China	Primary preclinical	<i>In vivo</i>	STZ-induced diabetic C57BL/6 mice	Not clearly specified in source spreadsheet
Zhang X et al. (2026)	NR	Primary preclinical	<i>In vivo</i> and <i>in vitro</i>	STZ-induced diabetic SD rats	Full-thickness skin wounds
Jafar H et al. (2025)	Jordan	Primary clinical	Phase I/II open-label clinical trial (single arm)	Adults with T2DM and chronic DFUs (n=110)	Diabetic foot ulcers
Kishta MS et al. (2025)	Egypt	Primary clinical	Randomized controlled clinical trial	Adults with T2DM and persistent DFUs (n=20)	Diabetic foot ulcers
Dehghani L et al. (2024)	NR	Secondary evidence	Narrative review	Review of diabetic wound studies	Various diabetic wound types
Chen L et al. (2025)	NR	Secondary evidence	Systematic review and meta-analysis	Meta-analysis of animal diabetic wound studies	Full-thickness excisional wounds

animal models. The variables related to wound healing outcomes and inflammatory markers are presented in Table 2A and Table 2B, for preclinical and clinical studies, respectively.

Markers of Angiogenesis, Inflammation, and Tissue Regeneration

Secondary outcomes favored tissue repair. Angiogenesis increased across all studies

Table 2. Preclinical efficacy outcomes and biological signals.

Study	Model	Exosome Preparation / Strategy	Delivery Strategy	Main Wound-Healing Outcome	Key Biological Markers	Safety Note
Zhang B et al. (2015)	STZ-induced diabetic SD rats	Serial centrifugation; native exosomes	Subcutaneous injection	Accelerated wound closure versus control; complete closure reported	↑ Collagen deposition; ↑ re-epithelialization	Not reported
Yang J et al. (2020)	STZ-induced diabetic SD rats	ExoQuick/commercial kit; native exosomes	Pluronic F127 hydrogel; topical application	Significantly accelerated healing versus control with near-complete closure	↑ CD31; ↑ VEGF; ↑ vessel density; ↑ collagen deposition; ↑ re-epithelialization; ↑ Ki67; ↑ TGF-β	No significant adverse events reported
Wei Q et al. (2021 preprint) – miR-221-3p	db/db diabetic mice; HUVECs	Ultracentrifugation; native exosomes	Peri wound injection (every other day)	Accelerated wound closure; complete healing reported by day 21	↑ VEGF; ↑ vessel density; ↑ blood perfusion; ↑ tube formation; ↑ collagen deposition; ↑ re-epithelialization	Not reported
Wei Q et al. (2022) – miR-17-5p	db/db diabetic mice; HUVECs	Serial/differential centrifugation; native exosomes	Peri wound injection (every other day)	Accelerated wound closure with complete healing reported by day 12	↑ CD31; ↑ VEGF; ↑ vessel density; ↑ blood perfusion	Not reported
Yan C et al. (2022)	STZ-induced diabetic C57BL/6 mice; HUVECs	Ultracentrifugation; native exosomes	Subcutaneous injection	Significantly accelerated healing versus control	↑ CD31; ↑ blood perfusion; ↓ oxidative stress	Not reported
Teng L et al. (2022)	STZ-induced diabetic SD rats	Ultracentrifugation; native exosomes	Subcutaneous injection	~98% closure reported within 7 days; accelerated healing versus control	↑ CD31; ↑ VEGF; ↑ vessel density; ↓ TNF-α; ↑ M2 macrophages/CD206; ↑ collagen deposition; ↑ re-epithelialization	Not reported
Yang S et al. (2023)	STZ-induced diabetic SD rats	Ultracentrifugation + PEG precipitation; native extracellular vesicles	Chitosan hydrogel	Statistically significant improvement in closure versus controls	↑ Tube formation; ↑ collagen deposition	Not reported
Zhao X et al. (2023)	db/db diabetic mice; fibroblasts	Ultracentrifugation; optogenetic eNOS loading	Subcutaneous injection	Accelerated wound closure versus control	↑ CD31; ↑ vessel density; ↑ eNOS; ↓ TNF-α/IL-6/IL-1β; ↑ collagen deposition; ↑ re-epithelialization	No local irritation reported
Ge L et al. (2023)	Diabetic mice; HUVECs	Ultracentrifugation/commercial kit; miR-132 overexpression	Subcutaneous injection	Complete closure/improved healing reported	↑ Blood perfusion; ↓ TNF-α/IL-6; ↑ M2 macrophages; ↑ collagen deposition	Not reported
Yang J et al. (2024)	Diabetic mice	Ultracentrifugation; native exosomes	Subcutaneous injection	Accelerated wound closure versus control	↑ VEGF; ↑ N2 neutrophils	Not reported
Wu S et al. (2024)	STZ-induced diabetic SD rats; fibroblasts	Ultracentrifugation; quercetin pretreatment	Subcutaneous injection	Statistically significant improvement in closure versus control	↑ VEGF; ↑ vessel density; ↑ blood perfusion; ↑ collagen deposition; ↑ re-epithelialization	Not reported
Yang R et al. (2024)	db/db diabetic mice; keratinocytes	Serial centrifugation; coenzyme Q10 pretreatment	Not specified	Statistically significant improvement in closure versus control	↑ Collagen deposition; ↓ ferroptosis	Not reported
Shi X et al. (2024)	STZ-induced diabetic SD rats	ExoQuick kit; native exosomes	Gallium/chitosan/silk sponge scaffold	Accelerated healing versus control with statistically significant improvement	↑ Vessel density; ↓ TNF-α/IL-6; ↑ collagen deposition; ↑ re-epithelialization	Not reported
Chen X et al. (2025)	STZ-induced diabetic C57BL/6 mice	Differential centrifugation; native exosomes	Intraperitoneal injection	Sheet reports improved healing, but wound-healing outcomes are not clearly documented	Macrophage polarization; INS/SOD1; PI3K/AKT signaling	Not reported
Zhang X et al. (2026)	STZ-induced diabetic SD rats	Ultracentrifugation; native exosomes	pADM/PF-127 thermosensitive hydrogel; topical application	~96–97% closure within 14 days; statistically superior to comparators	↑ CD31; ↑ vessel density; ↑ M2 macrophages/CD206; ↓ CD68; ↑ collagen deposition; ↑ re-epithelialization	No cytotoxicity observed; >80% cell survival; no organ damage reported

Table 2B. Clinical studies: efficacy and safety.

Study	Design / population	Intervention	Comparator	Main efficacy outcome	Safety findings
Jafar H et al. (2025)	Phase I/II open-label clinical trial (single arm); Adults with T2DM and chronic DFUs (n=10)	Perilesional injection once weekly, up to 10 sessions	None reported	All participants achieved complete ulcer closure; mean healing time 4.2 weeks; no recurrence during 24-month follow-up	No significant adverse events; mild transient local reactions only
Kishta MS et al. (2025)	Randomized controlled clinical trial; Adults with T2DM and persistent DFUs (sample size reported as 20 in study-design field)	Weekly topical exosome gel for 4 weeks + standard care	Standard care / control group	62% complete recovery; mean time to full recovery 6 weeks versus 20 weeks in control	Adverse-event frequency did not differ significantly between groups; events included fever, wound infection, osteomyelitis, and blisters

(higher CD31+ density and VEGF expression). Meta-analysis confirmed significant neovascular density increase (SMD = 3.66).³⁹ Collagen deposition increased 1.6-fold by day 7 in Zhang et al.²⁰, supported by Chen et al.³⁹ (SMD = 3.72). Re-epithelialization increased (SMD = 5.05) and scar width decreased (SMD = -5.75). Anti-inflammatory effects involved M2 macrophage polarization (increased CD206, decreased TNF- α) and N2 neutrophil polarization (increasing from <10% to 80.37% post-treatment). Significant reductions in IL-6 and TNF- α were reported by Zhang et al.³⁴, Yang et al.²⁹, and Teng et al.³⁰

Safety Profile

Safety data remain scarce. Preclinical studies reported no adverse events and favorable biocompatibility. Clinical studies provided the most robust data, Kishta et al.²³ found no significant difference in adverse events between groups, and Jafar et al.²² documented only mild, transient reactions (local pain, erythema, mild fever) over 24 months.

Study Limitations

Methodological limitations include small samples, lack of explicit animal counts, and poor reporting of randomization or blinding.³⁹ Technical heterogeneity in isolation methods and incomplete characterization of functional molecules persist. Jafar et al.²² acknowledged their open, uncontrolled design as a limitation, while Kishta et al.²³ emphasized the need for large-scale validation.

Discussion

This scoping review addressed the proposed research question by mapping the extent and nature of the evidence on the therapeutic application of hUC-MSC-derived exosomes in diabetic wounds across preclinical and clinical settings. Overall, the evidence base is expanding rapidly but remains predominantly preclinical. Across animal and cell-based models, the findings consistently suggest that hUC-MSC-derived exosomes can enhance wound closure, stimulate angiogenesis, modulate inflammation, and improve extracellular matrix remodeling. Clinical translation has begun, but the current human evidence remains limited to a small number of early studies.^{18–23,29–32,34–39}

These findings are clinically relevant because DFUs remain among the most severe complications of diabetes mellitus. They are associated with recurrent ulceration, infection, hospitalization, amputation, and excess mortality, even after apparent healing.^{40–44} In Brazil, diabetic foot disease also represents a substantial burden for the health system and requires structured prevention, timely diagnosis, and multidisciplinary management.^{45,46} The biological rationale for exosome-based therapy is therefore compelling, particularly in cases that remain refractory to standard care because of persistent inflammatory dysregulation, impaired angiogenesis, oxidative stress, and defective tissue regeneration.^{3,5–8}

The mapped evidence presents a coherent mechanistic pattern. hUC-MSC-Exos tend to accelerate diabetic wound closure and restore repair parameters like angiogenesis, collagen deposition, and inflammatory reduction,

showing consistency across animal models and converging mechanisms^{18,30,36}, meta-analysis reinforces this direction.³⁹ However, the translation gap between rodent dorsal wounds and human DFUs remains a crucial concern. Rodents heal primarily by contraction rather than re-epithelialization, and animal models may not fully replicate the chronic inflammatory microenvironment and comorbidities present in humans. Thus, positive results must be interpreted with caution.

Evidence is mechanistic, with studies exploring exosomes as intercellular signaling vectors capable of reprogramming the diabetic wound microenvironment. In DFUs, local retention is critical; thus, biomaterial systems functioning as sustained-release reservoirs are preferable to repeated manipulations.^{21,23,34}

The evidence base has notable gaps. The lack of dose-response data hinders therapeutic optimization. Dependence on short-term rodent models and small clinical samples leaves long-term efficacy and safety uncertain. Furthermore, the geographic concentration of preclinical work in China raises questions about generalizability.

Using the PAGER framework, the mapping indicates an urgent need to standardize dose-response protocols and molecular characterization. Without this, reproducibility remains a challenge for large-scale clinical practice. Transitioning from direct injections to biomaterial carriers like hydrogels is a viable path.^{21,34}

The primary gap is the biological distance between models and humans (contraction vs. re-epithelialization), requiring models that better mimic chronic inflammation and metabolic complexity.⁴⁷ While preclinical evidence is consistent³⁹, future priority must be given to multicenter RCTs with larger samples and prolonged follow-up to ensure that accelerated healing translates into safe, durable tissue repair.^{22,23}

This review has several strengths. It used a broad multi-database search strategy, including grey literature sources, and mapped both preclinical and clinical evidence in an emerging translational field. The review was structured using the PCC framework, conducted according to JBI methodology, and synthesized through the PAGER framework, which supported a coherent interpretation of patterns, advances, gaps, and research priorities.²⁸

However, some limitations of this review should

be acknowledged. The available evidence is heavily weighted toward preclinical studies, and the included studies were highly heterogeneous in design, exosome preparation, dosing, delivery strategy, and outcome reporting. The review also depended on the quality and completeness of reporting in the primary studies, which was variable. In addition, because the evidence base remains small and methodologically diverse, the mapped findings should not be interpreted as equivalent to a definitive assessment of clinical effectiveness. Finally, before resubmission, the final corpus should be rechecked to eliminate any potential duplicate study records across preprint and peer-reviewed versions.

Conclusions

The current evidence on the therapeutic application of hUC-MSC-derived exosomes in diabetic wound management is characterized by a burgeoning, yet predominantly preclinical, landscape. Regarding the extent of the evidence, this scoping review mapped 19 pivotal studies, reflecting an exponential growth in publications over the last decade, with a significant geographical concentration of experimental work in China and emerging clinical trials in Egypt and Jordan.

The nature of this evidence is multifaceted: preclinical findings consistently demonstrate that these exosomes act as potent intercellular signaling vectors that reprogram the diabetic microenvironment by enhancing angiogenesis, modulating macrophage polarization toward an anti-inflammatory M2 phenotype, and accelerating extracellular matrix remodeling. Clinically, the evidence has recently transitioned from mechanistic theory to human application, with randomized controlled trials, reporting favorable clinical outcomes in chronic DFU closure and a favorable safety profile over a 24-month period. Despite encouraging results, current research highlights the need for standardized dose-response protocols and validation across multiple centers.

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Oxidized Regenerated Cellulose/ Collagen Dressings With Silver Rebalance Protease Activity in Venous Ulcer Fibroblasts: Translational Implications for Clinical Practice

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Abstract

Introduction. Chronic venous leg ulcers disproportionately affect older adults and are characterized by delayed healing, high recurrence rates, and substantial impacts on quality of life and healthcare costs. Persistent inflammation and an imbalance between matrix metalloproteinases and their tissue inhibitors contribute to healing failure, maintaining the wound in an inflammatory state. Oxidized regenerated cellulose/collagen dressings, with and without silver, accelerate healing in venous ulcers, but the cellular mechanisms linking these outcomes to changes in the wound microenvironment are not fully understood. This study evaluated how oxidized regenerated cellulose/collagen and oxidized regenerated cellulose/collagen/silver modulate venous ulcer fibroblasts, focusing on proteases, their endogenous inhibitors and key growth factors, to connect *in vitro* findings to potential clinical applications.

Methods. Fibroblasts were isolated from chronic venous

leg ulcers and cultured for 72 hours in control medium, oxidized regenerated cellulose/collagen (2.8 mg/mL) or oxidized regenerated cellulose/collagen/silver (4.2 mg/mL). Cell metabolic activity was assessed by MTT assay. MMP 1, MMP 2, MMP 3, MMP 10, MMP 13, TIMP 1, TIMP 2, TIMP 3 and TGF β 1, TGF β 2, TGF β 3 were quantified in conditioned media using bead based multiplex immunoassays. Vimentin, collagen type I and collagen type III expression were evaluated by immunofluorescence. Statistical analysis used the paired Wilcoxon signed rank test ($p < 0.05$).

Results: Both dressings maintained venous leg ulcer fibroblast metabolic activity at levels comparable to, or slightly higher than, control medium, without evidence of overt cytotoxicity. Oxidized regenerated cellulose/collagen alone did not significantly alter MMPs, TIMPs or TGF β isoforms. Oxidized regenerated cellulose/collagen/silver significantly increased MMP 1 ($p = 0.0002$) and reduced MMP 13 ($p = 0.0155$) versus control, while decreasing TIMP 2 and TIMP 3 and preserving TIMP 1. TGF β 1, TGF β 2, TGF β 3 and collagen type I and III expression remained unchanged across groups, and vimentin expression was preserved.

Discussion. In this *in vitro* model, oxidized regenerated cellulose/collagen and oxidized regenerated cellulose/collagen/silver preserved fibroblast viability and did not overtly interfere with TGF β signaling or collagen type I and III expression. The silver free matrix did not modify the analyzed protease inhibitor levels, supporting a predominantly extracellular protease sequestering mechanism. The silver containing matrix induced a shift in the fibroblast derived protease inhibitor profile, characterized by increased MMP 1, decreased MMP 13 and reduced TIMP 2 and TIMP 3 with preserved TIMP 1, a pattern that may rebalance protease activity toward matrix remodeling under non cytotoxic conditions. These findings offer a mechanistic, hypothesis generating framework with translational implications for the clinical use of silver-containing oxidized regenerated cellulose/collagen dressings in venous leg ulcers.

Keywords: Oxidized Cellulose, Silver, Venous Ulcer, Wound Healing, Metalloproteinases

Introduction

Chronic venous ulcers are a major clinical and public health problem, affecting approximately 1% of the population and becoming frequent with advancing age. They account for up to 80% of all chronic ulcers and are characterized by prolonged healing times, frequent episodes of recurrence and a tendency to become long-

standing lesions. The recurrence rate is high, ranging from 40% to 70% within five years of initial healing, creating a cycle of chronic morbidity that profoundly impacts patient quality of life.¹⁻³

Beyond the physical burden, venous ulcers impose substantial psychological distress, social isolation and economic hardship on affected individuals. Healthcare systems bear

considerable financial costs, with treatment expenses reaching billions annually in developed countries, encompassing direct medical costs, lost productivity, and long-term disability management.¹⁻³

Despite advances in wound care, venous ulcer management remains challenging. Standard compression therapy, while effective for venous hypertension control, does not directly address the molecular imbalances within the wound bed.^{2,4} Persistent inflammation and protease dysregulation are central features of venous ulcer pathophysiology. Excessive activity of matrix metalloproteinases, not adequately counterbalanced by tissue inhibitors, leads to degradation of the newly formed extracellular matrix and key growth factors, perpetuating the inflammatory phase and preventing transition to effective tissue repair. A better understanding of these molecular mechanisms has supported the development of targeted strategies to modulate the wound microenvironment.⁴⁻⁶

Among these strategies, bioactive dressings that interact with components of wound exudate have gained prominence in recent years.⁶ Dressings composed of oxidized regenerated cellulose and collagen, with or without silver addition, have demonstrated clinical benefits in accelerating healing.^{5,7-9} These bioactive materials have been proposed to interact directly with proteases and other signaling molecules present in wound exudate, which may reduce local inflammatory burden and help create a more favorable environment for tissue repair. The oxidized regenerated cellulose component has been proposed, based on *ex vivo* chronic wound fluid studies, to bind and sequester excessive proteases, while the collagen matrix provides a provisional scaffold that supports cell migration and tissue organization.^{10,11} When supplemented with silver, these dressings acquire antimicrobial properties that may help prevent or treat wound infection, a common complication in chronic venous ulcers that further delays healing and increases morbidity.^{9,12} Despite clinical evidence supporting the efficacy of oxidized regenerated cellulose/collagen dressings with and without silver^{10,13-19}, important gaps remain in understanding how specific cellular components are modulated in chronic venous ulcers.

Understanding how these dressings influence the expression of matrix metalloproteinases,

tissue inhibitors of metalloproteinases, growth factors, and extracellular matrix components in venous ulcer-derived fibroblasts is important for elucidating mechanisms of action and may help identify potential biomarkers associated with treatment response in clinical practice. This knowledge gap represents a critical barrier to optimizing clinical application and to developing more personalized treatment strategies based on individual wound characteristics.

Therefore, this study aimed to evaluate the *in vitro* behavior of venous ulcer fibroblasts in the presence of oxidized regenerated cellulose/collagen and oxidized regenerated cellulose/collagen/silver by monitoring the expression levels of matrix metalloproteinases, tissue inhibitors of metalloproteinases, transforming growth factor beta isoforms and collagen I and III. This translational approach seeks to bridge the gap between clinical observations and cellular mechanisms, providing an evidence based rationale to inform treatment selection and to advance understanding of how bioactive dressings may influence the wound microenvironment in chronic venous ulcers.

Methods

The study protocol was reviewed and approved by the Ethics and Research Commission of the Hospital das Clínicas, Medical School, Universidade de São Paulo (CAAE #21868413.5.0000.0068). This was an *in vitro*, prospective, controlled, non randomized, non blinded study. Venous ulcer fibroblasts (VUFs) were collected from 12 female patients aged 40–65 years with chronic lower limb ulcers (> 6 months) due to venous insufficiency (CEAP C6), without arterial insufficiency. No patient identifiable data or sensitive medical record information were used in this study, and all analyses were performed on anonymized cell cultures derived from donated tissue samples.

Optimal concentrations of oxidized regenerated cellulose/collagen (2.8 mg/mL) and oxidized regenerated cellulose/collagen/silver (4.2 mg/mL) were defined in preliminary MTT assays as those maintaining fibroblast metabolic activity without evidence of marked cytotoxicity. For main experiments, VUFs were seeded at 4×10^3 cells per well in 24 well plates and cultured for 48 hours to allow adhesion. Cells were then exposed for 72 hours to control medium (D10), oxidized regenerated cellulose/collagen (2.8

mg/mL) or oxidized regenerated cellulose/collagen/silver (4.2 mg/mL). After this period, conditioned media were collected, centrifuged ($378 \times g$, for 5 minutes) and analyzed by bead-based multiplex immunoassay (Millipore, St. Louis, MO) for MMP-1, MMP-2, MMP-3, MMP-10, MMP-13, TIMP1, TIMP2, TIMP3, and TGF- β isoforms, according to the manufacturer's protocol. For MTT and multiplex immunoassays, each experimental condition was performed in technical triplicates for each of the 12 patient derived fibroblast cultures.

For immunofluorescence analyses, VUFs from three independent patients (biological replicates) were seeded in black, flat bottom 96 well plates at 4×10^3 cells per well (technical triplicates per condition), allowed to adhere for 48 hours and then exposed for 72 hours to control medium (D10), oxidized regenerated cellulose/collagen (2.8 mg/mL) or oxidized regenerated cellulose/collagen/silver (4.2 mg/mL). Cells were fixed with 4% paraformaldehyde, permeabilized with 0.1% Triton X 100 and blocked with 5% bovine serum albumin in PBS. Primary antibodies against collagen type I (rabbit polyclonal, Rockland, 1:100, #600.401.103-0.5), collagen type III (rabbit polyclonal, Rockland, 1:100, #600-401-105-0.1) and vimentin (mouse monoclonal, Dako Flex clone 9, ready to use, #IR630) were applied overnight at 4°C. Detection was performed using Alexa Fluor 488 goat anti rabbit IgG (H+L) secondary antibody (1:1000, Invitrogen/Thermo Fisher Scientific, #A11008) for collagen types I and III and R phycoerythrin labeled anti mouse secondary antibody (1:1000, Invitrogen, #P852) for vimentin. Fluorescence was quantified using the ImageXpress system (Molecular Devices), and the number of positive cells and their fluorescence intensity were determined with MetaXpress software (Molecular Devices). Results are expressed as fluorescence intensity.

Statistical analyses were performed using IBM SPSS Statistics, version 24.0 (IBM, USA). Numerical variables are expressed as mean and standard deviation (SD). For all outcomes (MTT absorbance, MMPs, TIMPs, TGF β isoforms and immunofluorescence intensity), paired comparisons were conducted using the Wilcoxon signed rank test, considering each patient derived fibroblast culture as its own control. The following contrasts were assessed: control medium versus oxidized regenerated cellulose/collagen, control medium versus oxidized regenerated cellulose/collagen/silver,

and oxidized regenerated cellulose/collagen versus oxidized regenerated cellulose/collagen/silver. Z values are reported, and statistical significance was set at $p < 0.05$.

Results

After 72 hours, venous ulcer fibroblasts exposed to ORC/Collagen (mean = 1.141; SD = 0.058) or ORC/Collagen/Ag (mean = 1.119; SD = 0.066) showed higher MTT absorbance values compared with cells cultured in control medium (mean = 1.005; SD = 0.067). These differences were statistically significant for both formulations when compared with control ($p < 0.05$, Wilcoxon signed rank test), indicating preserved mitochondrial activity and absence of overt cytotoxicity under the tested conditions (Figure 1).

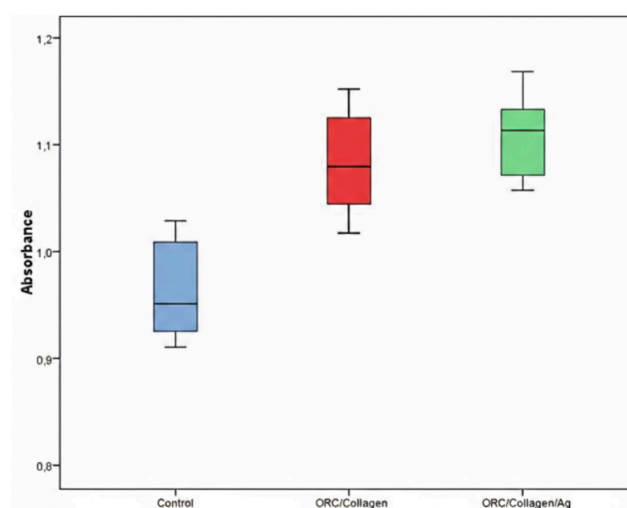


Figure 1. MTT assay of venous ulcer fibroblasts (VUFs) after 72 hours in control medium (blue), ORC/Collagen (red) and ORC/Collagen/Ag (green). Bars represent mean $\pm$ SD of 12 patient derived cultures. Statistical comparisons were performed using the paired Wilcoxon signed rank test; $p < 0.05$.

VUF-Specific Expression of Metalloproteinases, TIMPs, and Growth Factors

The secretion of MMP 1, MMP 2, MMP 3, MMP 10 and MMP 13 by venous leg ulcer fibroblasts after 72 hours of exposure is shown in Figure 2. When compared with the control medium, ORC/Collagen did not induce significant changes in MMP 1, MMP 2, MMP 3, MMP 10 or MMP 13 concentrations ($p > 0.05$, Wilcoxon signed rank test). In cultures treated with ORC/Collagen/Ag, MMP 1 levels were significantly increased,

showing an approximately 1.9 fold upregulation relative to control medium ($p = 0.0002$), whereas MMP 13 levels were significantly reduced, with an approximately 1.62 fold downregulation

($p = 0.0155$). No significant differences were observed for MMP 2, MMP 3 or MMP 10 in the ORC/Collagen/Ag group compared with control medium ($p > 0.05$).

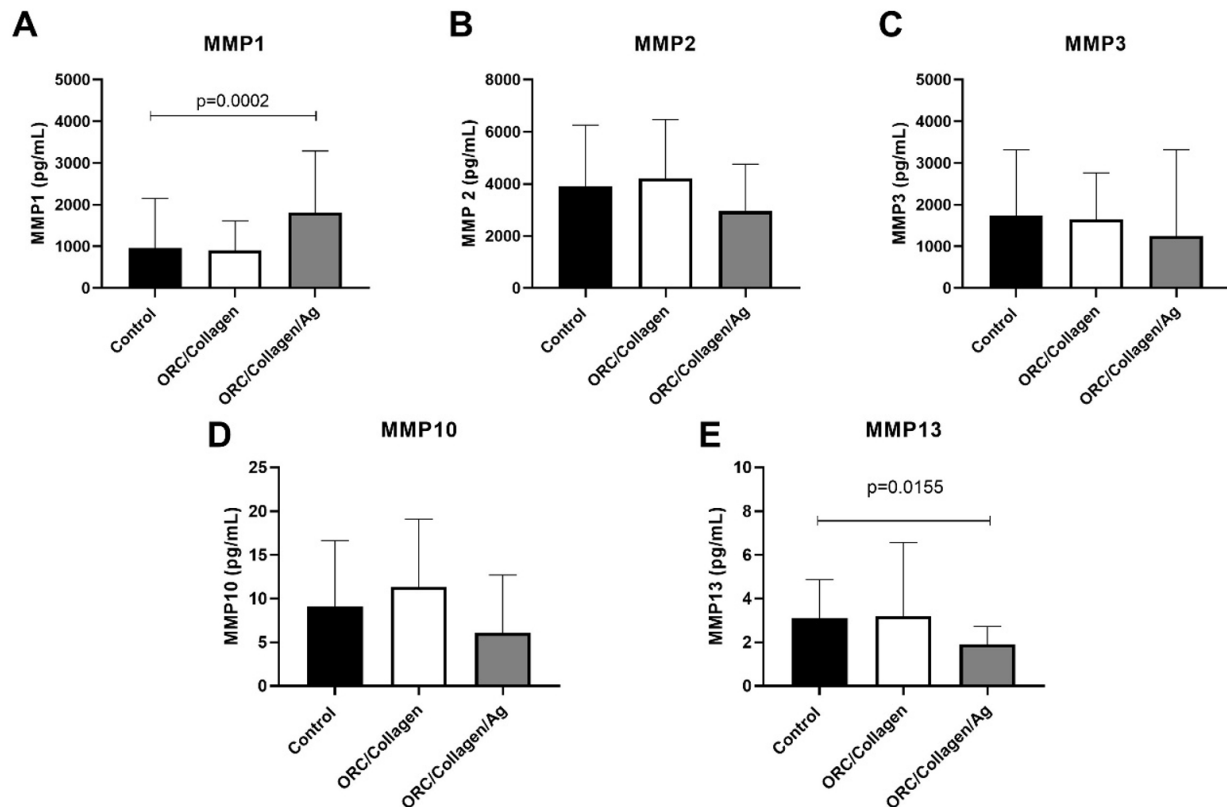


Figure 2. Secretion of MMP 1 (A), MMP 2 (B), MMP 3 (C), MMP 10 (D) and MMP 13 (E) by venous ulcer fibroblasts after 72 hours in control medium, ORC/Collagen and ORC/Collagen/Ag. Protein concentrations in conditioned media were measured by bead based multiplex immunoassay. Bars represent mean $\pm$ SD. Statistical comparisons were performed using the paired Wilcoxon signed rank test; $p < 0.05$ versus control medium.

The treatment with ORC/Collagen and ORC/Collagen/Ag did not significantly change TGF β 1,

TGF β 2 or TGF β 3 levels compared with control medium, as shown in Figure 3.

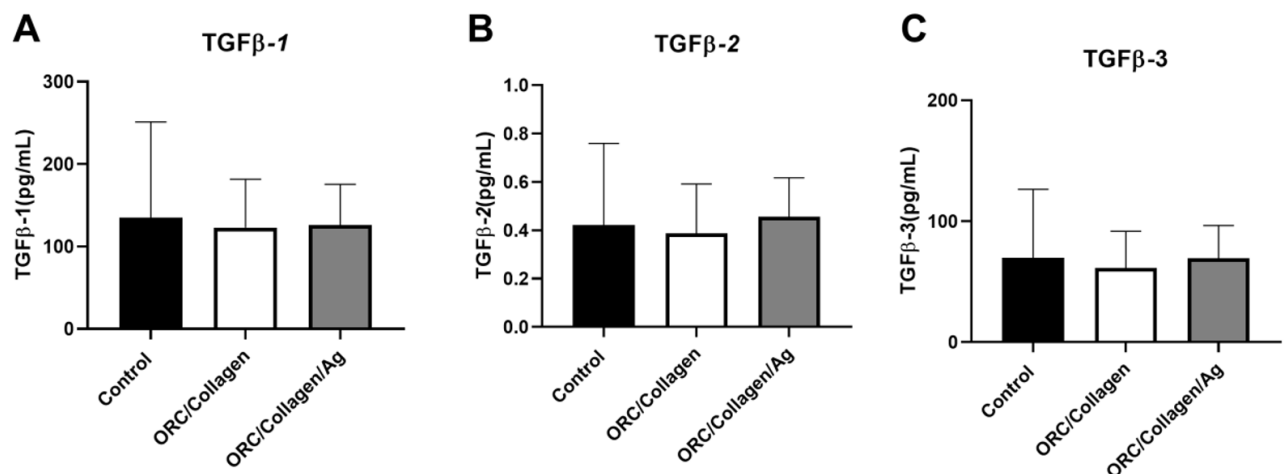


Figure 3. TGF β 1, TGF β 2 and TGF β 3 secretion by venous ulcer fibroblasts after 72 hours in control medium, ORC/Collagen and ORC/Collagen/Ag. Protein concentrations in conditioned media were measured by bead based multiplex immunoassay. Bars represent mean $\pm$ SD. Statistical comparisons were performed using the paired Wilcoxon signed rank test; no significant differences were detected between treatments and control medium ($p > 0.05$).

TIMP 1, TIMP 2 and TIMP 3 levels in venous ulcer fibroblast conditioned media after 72 hours are shown in Figure 4. Compared with control medium, ORC/Collagen did not induce significant changes in TIMP 1, TIMP 2 or TIMP 3 concentrations ($p > 0.05$, Wilcoxon signed rank

test). In contrast, VUFs exposed to ORC/Collagen/Ag showed reduced TIMP 2 (≈ 1.65 fold decrease; $p = 0.0048$) and TIMP 3 (≈ 6 fold decrease; $p < 0.0001$) levels relative to control medium, while TIMP 1 secretion remained unchanged.

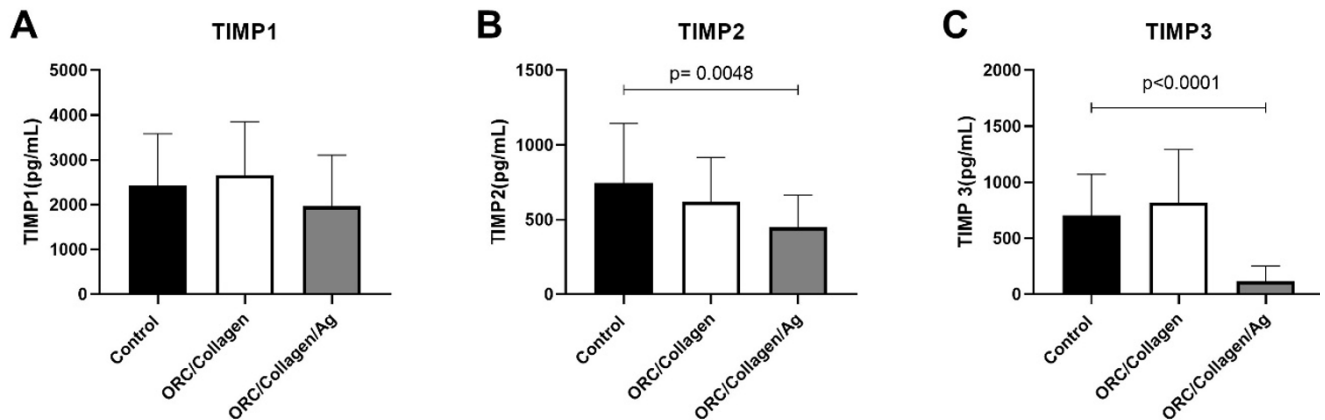


Figure 4. Secretion of TIMP 1, TIMP 2 and TIMP 3 by venous ulcer fibroblasts after 72 hours in control medium, ORC/Collagen and ORC/Collagen/Ag. Protein concentrations in conditioned media were measured by bead based multiplex immunoassay. Bars represent mean $\pm$ SD. Statistical comparisons were performed using the paired Wilcoxon signed rank test; $p < 0.05$ versus control medium.

VUF-specific quantification of vimentin, type I and III collagen by Immunofluorescence

Immunofluorescence analysis showed that vimentin, collagen type I and collagen type III expression in venous ulcer fibroblasts exposed for 72 hours to ORC/Collagen or ORC/Collagen/

Ag did not differ significantly from cells cultured in control medium ($p > 0.05$ for all comparisons, Wilcoxon signed rank test), as illustrated in Figures 5–8. Vimentin expression remained stable under all conditions, confirming preservation of the fibroblast phenotype.

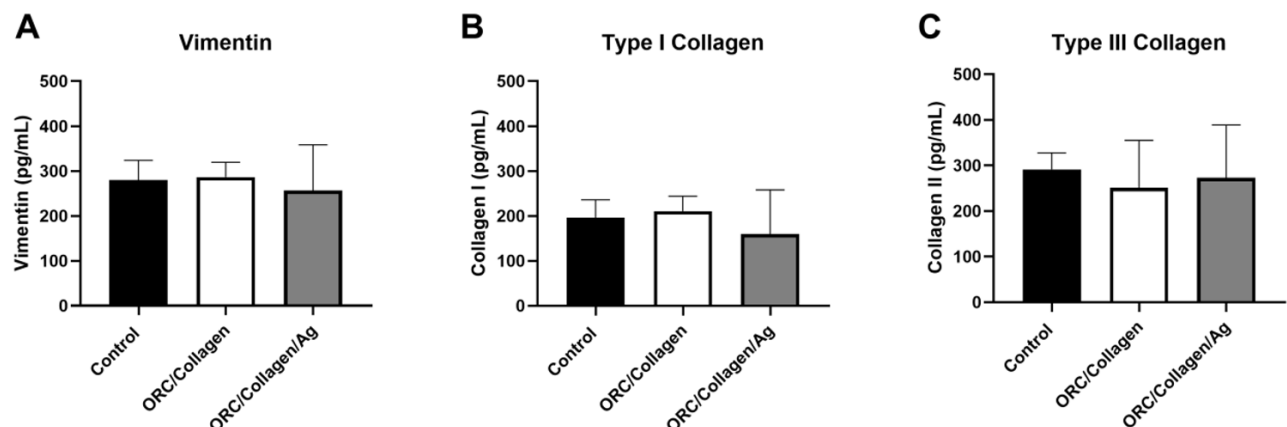


Figure 5. Quantification of vimentin, collagen type I and collagen type III expression in venous ulcer fibroblasts by immunofluorescence. Cells were cultured for 72 hours in control medium, ORC/Collagen or ORC/Collagen/Ag, and fluorescence intensity for vimentin, collagen type I and collagen type III was measured. Bars represent mean $\pm$ SD. Statistical comparisons were performed using the paired Wilcoxon signed rank test; no significant differences were detected between treatments and control medium ($p > 0.05$).

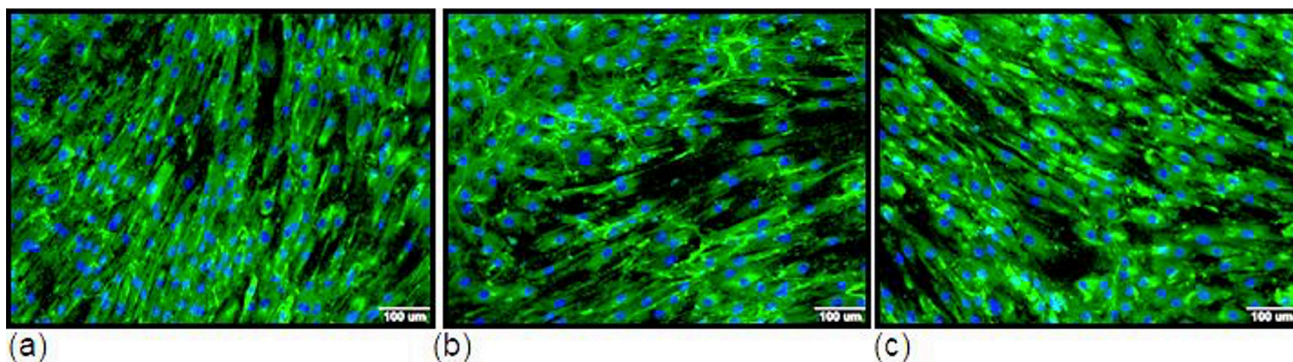


Figure 6. Representative images of collagen type I immunofluorescence in venous ulcer fibroblasts cultured for 72 hours in (a) control medium, (b) ORC/Collagen and (c) ORC/Collagen/Ag. Scale bar = 100 μ m.

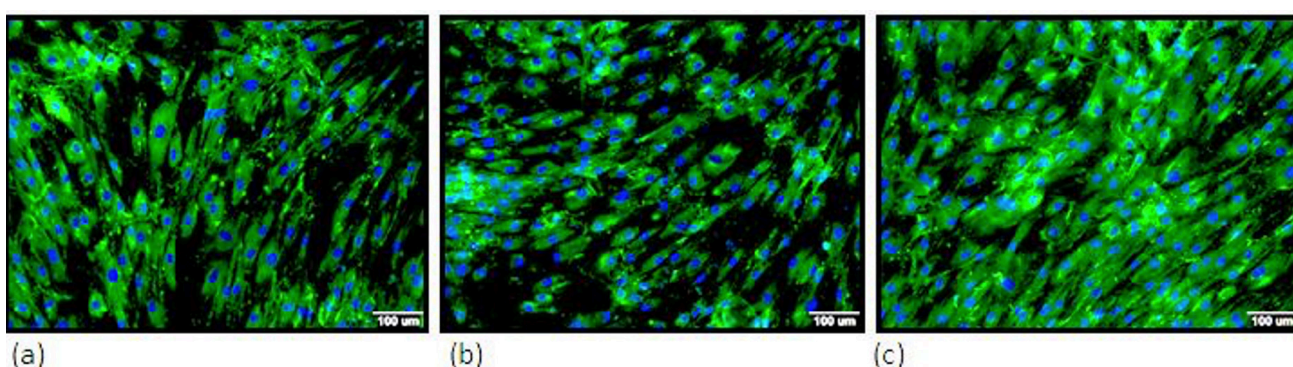


Figure 7. Representative images of collagen type III immunofluorescence in venous ulcer fibroblasts cultured for 72 hours in (a) control medium, (b) ORC/Collagen and (c) ORC/Collagen/Ag. Scale bar = 100 μ m.

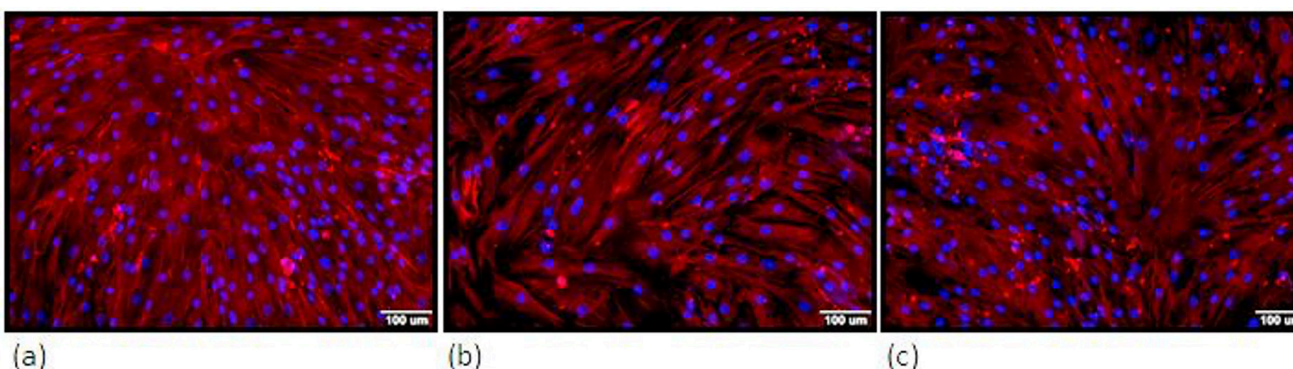


Figure 8. Representative images of vimentin immunofluorescence in venous ulcer fibroblasts cultured for 72 hours in (a) control medium, (b) ORC/Collagen and (c) ORC/Collagen/Ag. Scale bar = 100 μ m.

Discussion

In this study, the effects of oxidized regenerated cellulose/collagen dressings, with and without silver, on proteases, their inhibitors and key growth factors were evaluated in fibroblasts derived from chronic venous leg ulcers. Both formulations preserved venous ulcer fibroblast viability *in vitro*, without evidence of overt cytotoxicity at the concentrations tested, which supports their use in subsequent

molecular analyses. Importantly, the silver containing dressing induced specific changes in the fibroblast protease profile, whereas the formulation without silver produced minimal direct modulation of fibroblast secretory behavior, findings that are consistent with the concept of predominantly extracellular protease sequestration for the silver free matrix.

The MTT assays showed that oxidized regenerated cellulose/collagen at 2.8 mg/mL and oxidized regenerated cellulose/collagen/silver at

4.2 mg/mL maintained venous ulcer fibroblast metabolic activity at levels comparable to, or slightly higher than, control conditions, with MTT indices of 1.141 ± 0.058 and 1.119 ± 0.066 respectively, versus 1.005 ± 0.067 in control medium. These findings indicate the absence of an acute reduction in cell metabolic activity under the tested conditions and support the use of these concentrations for subsequent molecular analyses.²⁰ This pattern is in line with previous investigations reporting preserved fibroblast viability in culture systems exposed to oxidized regenerated cellulose/collagen based dressings, without evidence of overt toxicity at therapeutic concentrations.²¹ Although the MTT assay does not distinguish between increased cell number and enhanced mitochondrial activity, the maintenance of metabolic activity and fibroblast phenotype in our model suggests preservation of fundamental cellular functions required for tissue repair, while highlighting the need for additional assays to fully characterize long term proliferative and biocompatibility responses.

In the skin, matrix metalloproteinases degrade elements of the extracellular matrix, including collagen, elastin, proteoglycans and other structural glycoproteins, and play essential roles in the activation of growth factors such as transforming growth factor beta and vascular endothelial growth factor. These proteolytic enzymes are produced by multiple cell types, including keratinocytes, fibroblasts, macrophages, endothelial cells, mast cells, eosinophils and neutrophils. Matrix metalloproteinase mediated proteolytic degradation of the extracellular matrix is an essential component of tissue remodeling and repair during normal wound healing.²²

Matrix metalloproteinases are classified based on substrate specificity and structural organization into collagenases, gelatinases, stromelysins, matrilysins, metalloelastases, membrane type MMPs and other subgroups. In this study, venous ulcer fibroblasts exposed to oxidized regenerated cellulose/collagen/silver showed a significant increase in MMP 1 secretion compared with control medium, whereas the silver free formulation did not modify MMP 1 levels. MMP 1 is a key interstitial collagenase involved in the initial cleavage of fibrillar collagens, which enables subsequent degradation and replacement by newly synthesized matrix. In chronic venous ulcers,

persistent inflammation and disorganized collagen deposition contribute to a rigid, fibrotic wound bed that impairs cell migration and re epithelialization. A moderate upregulation of MMP 1 under non cytotoxic conditions, as observed in our model, may therefore facilitate removal of disorganized collagen fibers and support the transition toward a more structured matrix, provided that this occurs within a controlled proteolytic environment.²³ The preservation of venous ulcer fibroblast viability and the maintenance of type I and III collagen expression in our experiments suggest that this increase in MMP 1 is not associated with overt degradation of newly formed matrix.

In contrast, the reduction in MMP 13 levels observed in venous ulcer fibroblasts exposed to the silver containing dressing may represent a protective effect on nascent granulation tissue. MMP 13 has been reported to be upregulated in chronic wounds and is associated with extensive degradation of extracellular matrix components. Excessive MMP 13 activity can compromise granulation tissue stability and contribute to a persistent non healing state. In our model, the combination of increased MMP 1 and decreased MMP 13 in response to oxidized regenerated cellulose/collagen/silver is compatible with a shift from a more destructive proteolytic profile toward a pattern that may favor matrix remodeling. This interpretation remains hypothetical but provides a biologically plausible framework to reconcile the need for collagen degradation to remove damaged tissue with the preservation of structural support required for cell migration and proliferation.

The changes observed in tissue inhibitors of metalloproteinases further suggest that the action of the silver-containing dressing on the protease system is more nuanced than a simple suppression of proteolytic activity. In our experiments, TIMP 2 and TIMP 3 levels were reduced in venous ulcer fibroblasts exposed to oxidized regenerated cellulose/collagen/silver, whereas TIMP 1 secretion remained relatively stable across conditions. TIMP 1 is a major inhibitor of several MMPs and is often decreased in chronic venous ulcers, contributing to the predominance of proteolytic activity.²³ The preservation of TIMP 1 in our model may help maintain a basal level of control over matrix degradation, while the reduction in TIMP 2 and TIMP 3 may permit a degree of proteolytic activity that could be necessary for matrix

remodeling. Taken together, these observations indicate that the silver-containing dressing does not induce a generalized blockade of proteases but rather promotes a reconfiguration of the protease inhibitor balance that is compatible with controlled matrix turnover, although functional assays of protease activity would be required to confirm this hypothesis.

Neither formulation significantly altered the concentrations of TGF β 1, TGF β 2 or TGF β 3 in culture supernatants, nor the expression of type I and III collagen by venous ulcer fibroblasts. TGF β signaling is central to fibroblast activation, myofibroblast differentiation and extracellular matrix synthesis, and therapies that markedly suppress TGF β or collagen production could impair granulation tissue formation and long term wound strength. In this context, the maintenance of TGF β isoforms and collagen type I and III expression in our experiments suggests that the oxidized regenerated cellulose/collagen matrix, with or without silver, does not overtly interfere with these core reparative pathways in this *in vitro* model. From a translational perspective, this is consistent with the notion that protease modulating effects of the silver containing dressing can occur without obvious detrimental inhibition of fibroblast synthetic capacity, although *in vivo* studies are required to confirm this balance.

The absence of significant changes in MMPs, TIMPs and TGF β isoforms in cultures exposed to oxidized regenerated cellulose/collagen without silver is also informative. These results are consistent with the concept that this formulation acts primarily at the extracellular level, by binding and sequestering proteases and other soluble mediators present in the wound exudate, rather than by directly reprogramming fibroblast secretion. Experimental work with oxidized regenerated cellulose/collagen has shown that this biomaterial can rapidly adsorb proteases and other reactive species from wound fluid, thereby limiting proteolytic and oxidative damage to the extracellular matrix and growth factors.^{10,11} In this context, the lack of major changes in the secretory profile of fibroblasts exposed to the non silver formulation *in vitro* is compatible with its proposed mechanism of action as a protease absorbing scaffold, particularly in wounds with a moderate protease burden.

By contrast, the addition of silver appears to confer a more active influence on venous ulcer fibroblast protease profiles, beyond its well

known antimicrobial effect. Silver containing dressings are widely used in chronic wounds with heavy bioburden or clinical signs of local infection, and clinical studies have reported improved healing trajectories when they are used in appropriately selected venous ulcers.^{9,12} In our *in vitro* model, oxidized regenerated cellulose/collagen/silver increased MMP 1 and decreased MMP 13, while reducing TIMP 2 and TIMP 3, without affecting TGF β isoforms or collagen type I and III expression. This pattern is compatible with a reorganization of fibroblast derived protease and inhibitor levels toward a profile that may favor matrix remodeling under non-cytotoxic conditions. Although the precise molecular pathways linking silver exposure to these protease changes were not investigated in this study, the data are compatible with a broader concept in which antimicrobial activity and modulation of the inflammatory proteolytic milieu act in synergy to support restoration of a healing trajectory.

These *in vitro* results need to be interpreted in the context of important limitations. First, the study used isolated fibroblasts derived from chronic venous leg ulcers, cultured in a controlled environment. Chronic wounds *in vivo* comprise a complex interplay of keratinocytes, endothelial cells, immune cells, microbial communities and a dynamic exudate rich in cytokines, proteases and degradation products. The dressing concentrations and exposure time used here were chosen to avoid acute toxicity *in vitro* and may not fully replicate the kinetics of interaction between the materials and the wound bed in clinical practice. Second, the sample consisted only of female patients within a restricted age range and with a specific etiology (venous insufficiency, CEAP C6), which may limit generalizability to other patient groups or wound types. Third, the analysis focused on a selected panel of MMPs, TIMPs and TGF β isoforms; other proteases, cytokines and signaling pathways that are relevant to chronic wound pathophysiology were not assessed.

The absence of bacterial contamination or biofilm in the culture system represents another relevant limitation, particularly given the role of silver containing dressings in managing wounds with high bioburden. Infection and biofilm profoundly influence the wound microenvironment and can modulate both protease activity and fibroblast behavior. The interaction between antimicrobial action and

protease modulation in the presence of biofilm therefore requires further investigation through co culture models incorporating bacteria and fibroblasts.²¹

Despite these limitations, the study offers insights that may be relevant for the translational use of oxidized regenerated cellulose/collagen based dressings. The observation that oxidized regenerated cellulose/collagen/silver modulated the balance between MMP 1 and MMP 13, while preserving TGF β isoforms and collagen type I and III expression, provides a plausible biological rationale that is consistent with reports of improved granulation quality and accelerated closure in venous leg ulcers treated with this dressing.^{9,12} Conversely, the essentially extracellular mode of action suggested for oxidized regenerated cellulose/collagen without silver is in line with its use as a protease absorbing matrix in wounds with elevated proteolytic activity and without clear signs of critical colonization or infection.

Future translational research should correlate the molecular markers identified in this study with clinical healing outcomes through prospective trials incorporating serial measurements of MMP 1, MMP 13, TIMP 2 and TIMP 3 alongside standardized wound assessment. The development of point of care biomarker assays enabling real time protease status determination could guide more personalized dressing selection. Investigation of optimal silver concentrations, formulation characteristics, application frequencies and combination therapies with other advanced modalities warrants systematic study to maximize therapeutic benefits while minimizing potential adverse effects. Although combination therapies incorporating oxidized regenerated cellulose/collagen/silver with negative pressure wound therapy have demonstrated promising results in complex lower extremity wounds with exposed critical structures²⁴, further investigation is required to elucidate the molecular mechanisms underlying these synergistic effects and to establish optimal protocols for combined use with other advanced modalities such as growth factor supplementation or cellular therapies.

Conclusion

In this *in vitro* model using fibroblasts derived from chronic venous leg ulcers, oxidized

regenerated cellulose/collagen and oxidized regenerated cellulose/collagen/silver preserved cell viability at the tested concentrations and did not overtly interfere with TGF β isoforms or collagen type I and III expression. The silver free formulation did not induce significant changes in the secretion of the analyzed MMPs, TIMPs or TGF β isoforms, which is compatible with a predominantly extracellular protease sequestering mechanism. By contrast, the silver containing matrix increased MMP 1 and decreased MMP 13, while reducing TIMP 2 and TIMP 3 without affecting TIMP 1, suggesting a shift in the fibroblast derived protease-inhibitor profile toward a pattern that may favor matrix remodeling under non cytotoxic conditions. These findings provide a mechanistic hypothesis that is consistent with clinical observations of improved granulation and healing in venous leg ulcers treated with oxidized regenerated cellulose/collagen/silver dressings, but they should be interpreted as preliminary and hypothesis generating, requiring confirmation in more complex *in vitro* models and prospective clinical studies that integrate molecular markers with wound healing outcomes.

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Clinical Nursing Management of a Complex Vulvoperineal Wound in a Patient with Hidradenitis Suppurativa and Crohn's Disease: A Case Report

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Abstract

Introduction. Hidradenitis suppurativa (HS) is a chronic inflammatory skin disease that may lead to recurrent abscesses, sinus tracts, scarring, and complex wounds in anatomically and functionally challenging areas. Vulvoperineal involvement may be particularly difficult to manage because of severe pain, high exudate, risk of contamination, and major impact on quality of life.

Case presentation. We report the case of a 38-year-old woman with hidradenitis suppurativa, Crohn's disease, insulin-dependent diabetes mellitus, and rheumatoid arthritis, who presented with a complex post-surgical vulvoperineal wound following drainage of purulent fistulas. At initial assessment, the wound was deeply cavitated, highly exudative, fibrinous, painful, and at high risk of local infection. Pain during wound care was severe Visual Analog Scale (VAS 8/10), and the patient showed marked psychological distress.

Intervention and Management. A personalized multidisciplinary management plan was established, including multimodal analgesic support, wound cleansing with saline solution and PHMB-based antiseptics, application of an oxygen-enriched oleic matrix dressing, atraumatic secondary dressings, urinary catheter placement to reduce local contamination, and shared hospital-home follow-up. Nursing management focused on pain control, atraumatic local care, infection prevention, patient education, and continuity of care.

Results. Progressive wound improvement was observed over time, with reduction in pain, exudate, fibrin burden, and wound size. After 3 weeks, the wound area was significantly

reduced, and complete healing was achieved within 3 months. Treatment tolerance progressively improved, allowing regular outpatient and home-based wound care.

Conclusion. This case highlights the clinical value of individualized nursing management within a multidisciplinary pathway for complex vulvoperineal wounds in patients with HS and multiple comorbidities. Pain control, atraumatic dressing strategies, and continuity of care were key elements in supporting wound healing and treatment adherence.

Keywords: Hidradenitis Suppurativa, Crohn's Disease, Vulvoperineal Wound, Wound Care Nursing, Advanced Dressing, Case Report

Introduction

Hidradenitis suppurativa (HS) is a chronic, recurrent, inflammatory skin disease characterized by painful nodules, abscesses, and sinus tract formation, typically affecting intertriginous areas. The condition is associated with a significant physical and psychosocial burden and often requires long-term, multimodal management strategies.¹

In patients with severe disease and multiple comorbidities, such as Crohn's disease and diabetes, HS may lead to complex and difficult-to-heal wounds, particularly in anatomically challenging regions such as the vulvoperineal area. These lesions are frequently associated with high exudate levels, risk of bacterial contamination, and significant procedure-related pain, all of which may negatively impact healing and quality of life.^{2,3}

Despite the growing availability of medical and surgical treatment options for HS, the management of associated wounds remains insufficiently standardized. In particular, local wound care strategies, including the selection of appropriate dressings and the optimization of the wound microenvironment, play a crucial role but are still underrepresented in the literature.²⁻⁴

Recent evidence highlights the importance of advanced wound management approaches in HS, including the use of atraumatic dressings capable of reducing pain during dressing changes, controlling exudate, and supporting tissue repair.^{2,4} In this context, the choice of dressing should be tailored to wound characteristics, anatomical location, and patient tolerance, particularly in fragile and highly sensitive areas.³

This case report aims to describe the clinical course, nursing management, and wound healing

outcomes of a complex vulvoperineal wound in a patient with hidradenitis suppurativa and Crohn's disease, highlighting the role of individualized, atraumatic, and multidisciplinary care.

This case report was prepared in accordance with the CARE (CAsE REport) guidelines.

Ethical considerations

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Case presentation

A 38-year-old woman with hidradenitis suppurativa and multiple comorbidities, including insulin-dependent diabetes mellitus, Crohn's disease, and rheumatoid arthritis, was referred to the stoma care clinic after recently undergoing ileostomy creation because of Crohn's disease recurrence. She had also undergone surgical drainage of purulent vulvoperineal fistulas at another hospital. At the time of referral, no structured local wound care plan had been established, and no effective analgesic strategy had been prescribed for dressing-related pain.

At initial assessment, the patient reported severe perineal pain, particularly during wound cleansing and dressing procedures. Pain intensity was assessed by the wound care team using the Visual Analog Scale (VAS)⁵ and was rated as 8/10, indicating marked impairment in tolerance of local care.

Clinical examination revealed an extensive vulvoperineal wound with irregular margins, a predominantly fibrinous and hyperemic wound bed, and heavy exudate. The overall wound surface area was estimated at approximately

75 cm², with a maximum depth of about 5 cm. A strongly adherent fibrinous area extended for approximately 25 cm² toward the proximal thigh. Some wound areas appeared particularly fragile and at risk of bleeding during local manipulation. Overall, the lesion showed clinical features associated with a high risk of local infection.

In addition to the local clinical burden, the patient presented with marked psychological distress. She expressed concern regarding the effect of the wound on her privacy and dignity and showed limited confidence in the instructions previously received from healthcare professionals. The intimate anatomical location of the lesion, persistent pain, and uncertainty regarding the healing process appeared to further compromise her emotional well-being and engagement with treatment.

Management and Treatment Protocol

Therapeutic priorities and initial approach

Initial management focused primarily on pain control, as adequate analgesia was considered essential to enable atraumatic wound assessment and local treatment. At baseline, pain intensity assessed using the VAS was 8/10, significantly impairing tolerance to wound care procedures. A multimodal analgesic strategy was therefore implemented to improve procedural tolerability and facilitate subsequent interventions.

Clinical reassessment and diagnostic evaluation

Following partial pain control, a comprehensive wound reassessment was performed. This included evaluation of wound depth, extension, presence of undermining, and residual fistulous tracts. Vital signs were recorded, showing low-grade fever (37.2°C) and sinus tachycardia (110 beats per minute), while blood pressure and peripheral oxygen saturation remained within normal limits. Microbiological cultures were obtained to guide targeted antimicrobial therapy.

Local wound management

Local treatment included gentle cleansing with sterile saline solution and antiseptics using polyhexamethylene biguanide (PHMB)-based solutions. An oxygen-enriched oleic matrix dressing was applied to the wound bed.

This dressing was selected for its ability to conform to irregular and partially undermined wound surfaces, maintain a favorable moist microenvironment, support control of bacterial burden and odor, and minimize trauma during removal.

A secondary dressing was applied using hypoallergenic fixation systems with low-trauma silicone adhesives, combined with multiple layers of sterile gauze. This approach aimed to protect the wound from mechanical stress, reduce friction with clothing, and improve patient comfort during daily activities.

Contamination control strategies

Given the anatomical location of the lesion and the high risk of local contamination, temporary urinary catheterization was introduced. This intervention aimed to reduce urine exposure to the wound area and facilitate safer and more controlled dressing changes during the acute phase. The indication for catheterization was regularly reassessed, considering the potential risk of catheter-associated infection.

Systemic management

Systemic treatment included targeted antibiotic therapy guided by microbiological culture results, as well as analgesic and anti-inflammatory medications for pain control. A midline catheter (MC) was inserted to facilitate the administration of intravenous therapies. The potential initiation or optimization of immunosuppressive or biologic therapy was evaluated in collaboration with the multidisciplinary team, considering the patient's underlying inflammatory conditions.

Multidisciplinary care and patient education

The management plan was developed within a multidisciplinary framework involving surgeons, dermatologists, gastroenterologists, and nurses specialized in stoma care and wound management. In parallel, patient education was initiated, focusing on stoma care, basic wound management principles, and strategies to support adherence and self-care during the transition to home-based management.

Nursing management perspective

From a nursing perspective, the main priorities included pain reduction, atraumatic wound care, protection of fragile perilesional tissues, prevention of local contamination, and continuous reassessment of wound evolution and treatment tolerance. Particular attention was also given to patient and caregiver education

and to ensuring continuity of care across hospital and home settings. These elements were considered essential to support adherence, reduce psychological distress, and promote progressive wound healing.

The main nursing interventions adopted in this case, focusing on pain control, atraumatic

Table 1. Key nursing interventions in the management of complex vulvoperineal wounds.

Domain	Intervention
Pain management and procedural tolerance	1. Systematic pain assessment using the VAS 2. Implementation of multimodal analgesic strategies prior to wound care procedures 3. Continuous monitoring of pain response to treatment and dressing changes
Atraumatic wound care	4. Gentle cleansing with sterile saline solution 5. Selection of advanced dressings with low-trauma removal properties 6. Minimization of mechanical stress during dressing application and removal
Exudate and infection control	7. Regular assessment of exudate quantity and characteristics 8. Use of PHMB-based antiseptics 9. Microbiological sampling to guide targeted antibiotic therapy 10. Use of dressings supporting bacterial burden control and odor management
Protection of the perilesional area	11. Use of hypoallergenic fixation systems with low-trauma silicone adhesives 12. Application of secondary dressings to reduce friction and external contamination 13. Prevention of skin maceration and additional tissue damage
Contamination risk reduction	14. Temporary urinary catheterization to limit urine exposure in vulvoperineal wounds 15. Careful hygiene management in an anatomically high-risk area 16. Ongoing reassessment of catheter indication to balance benefits and risks
Patient and caregiver education	17. Training in basic wound care and dressing management 18. Education on stoma care and hygiene 19. Support for progressive involvement in self-care
Continuity of care	20. Integration of hospital-based and home-based wound management 21. Structured follow-up and regular reassessment 22. Coordination within a multidisciplinary team
Psychological support and engagement	23. Recognition of emotional distress related to wound location and chronicity 24. Supportive communication to improve trust and adherence 25. Promotion of patient involvement in the care process

wound care, contamination prevention, and continuity of care, are summarized in Table 1.

Follow-up and clinical outcomes

After the acute phase, the patient entered a structured outpatient follow-up pathway, progressively integrated with home-based care supported by the multidisciplinary team. Dressing changes were scheduled twice weekly, alternating between hospital and home management in order to reduce the burden of care while ensuring regular reassessment. Follow-up visits focused on wound size, depth, tissue quality, exudate amount, pain during dressing changes, signs of local contamination

or infection, dressing tolerability, and the patient's ability to participate in care. Periodic reassessment of the stoma site and previously drained perineal fistulas was also performed.

Results

Progressive clinical improvement of the vulvoperineal wound was observed throughout the follow-up period. The clinical course and response to treatment over time are summarized in Table 2

Table 1. Key nursing interventions in the management of complex vulvoperineal wounds.

Time	Clinical findings and management
Day 0	Extensive, highly exudative, painful vulvoperineal wound with fibrinous wound bed and signs of local infection risk. Initial pain score: VAS 8/10. Analgesic optimization and local wound care plan initiated (Figure 1)
Day 7	Improved tolerance of dressing changes. Reduced pain and exudate. Early activation of wound edges. Urinary catheter and vascular access device in place to support management. VAS 4/10. (Figure 2)
Day 30	Significant reduction in wound size. Cleaner wound bed with active margins and reduced exudate. Continued outpatient follow-up and shared home-based care. VAS 3/10.
Day 60	Progressive granulation tissue formation and further wound contraction. Good tolerance of dressing changes. VAS 2/10 (Figure 3).
Day 90	Near-complete/complete healing achieved. Urinary catheter removed. Return to usual daily activities reported. VAS 0/10 (Figure 4).



Figure 1. Day 0. Baseline appearance of an extensive, highly exudative and painful vulvoperineal wound with a fibrinous wound bed and clinical signs of infection risk.



Figure 2. Day 7. Improved tolerance to dressing changes with reduced pain and exudate and early wound edge activation



Figure 3. Day 60. Granulation and wound contraction with good dressing tolerance.



Figure 4. Day 90. Near-complete/complete wound healing, urinary catheter removal, and restoration of usual daily activities.

After three weeks of treatment, a marked reduction in wound size was observed, with the surface area decreasing from approximately 75 cm² to 30 cm². This reduction was associated with a progressive decrease in exudate, fibrin burden, and local inflammation, along with the appearance of active wound margins and early granulation tissue. Continued improvement was documented at subsequent follow-up assessments, leading to near-complete and then complete wound healing within three months.

Pain reduction represented a key outcome of the treatment pathway. At baseline, pain assessed using the VAS was 8/10 and significantly limited tolerance to wound care procedures. Following the introduction of a structured multimodal analgesic strategy and atraumatic dressing techniques, a progressive reduction in pain was observed over time, with VAS scores decreasing to 3/10 within the first weeks and reaching 0/10 at the end of the follow-up period. Improved pain control allowed regular dressing changes to be performed without the marked distress observed at presentation.

Local management strategies also contributed to improved control of contamination and exudate. The use of temporary urinary catheterization reduced urine exposure to the wound area, facilitating safer and more controlled dressing changes in a highly sensitive anatomical site. In parallel, the selected dressing strategy supported bacterial burden control and local microenvironment stabilization.

From a functional perspective, the patient progressively improved her tolerance to wound care and daily activities. The combination of effective pain control, atraumatic dressing techniques, and continuity of care enabled the transition from predominantly hospital-based management to a shared hospital-home care pathway, with regular follow-up in stoma therapy and gastroenterology clinics.

Patient engagement in the care process also improved over time. Initially, the patient experienced significant distress and difficulty in adhering to daily wound care. However, through ongoing nursing support, therapeutic education, and psychological support, she progressively gained confidence in the care team and improved her ability to cope with her condition and participate in treatment.

No major dressing-related complications or adverse events were documented during the follow-up period.

Discussion

The present case highlights the clinical complexity of managing vulvoperineal wounds in patients with hidradenitis suppurativa and concomitant systemic inflammatory diseases, such as Crohn's disease. In this setting, wound healing is influenced not only by the underlying inflammatory burden but also by several local and patient-related factors, including anatomical location, high exudate levels, risk of contamination, severe procedure-related pain, and significant psychosocial impact.^{1,6}

Vulvoperineal involvement represents a particularly challenging scenario due to the intimate anatomical site and the high likelihood of exposure to urine and fecal contamination. In addition, the presence of multiple comorbidities, including diabetes and chronic inflammatory conditions, may further impair tissue repair and increase the risk of infection and delayed healing. These factors underline the need for a comprehensive and individualized approach to care.¹

Although medical and surgical management of HS has been extensively discussed in the literature, evidence regarding local wound care remains limited. Recent publications emphasize the importance of individualized dressing selection based on exudate level, anatomical location, pain, and patient comfort. In particular, atraumatic dressings may improve adherence and reduce procedure-related pain, which is a major barrier to wound management in patients with severe HS.²⁻⁴

A key element in this case was the central role of nursing management. Pain control was not merely a supportive intervention but a prerequisite for effective wound care. At presentation, severe pain significantly limited the feasibility of local treatment. The introduction of a structured multimodal analgesic strategy, combined with atraumatic dressing techniques, allowed progressive improvement in treatment tolerance and enabled regular wound assessment and care. This finding supports the importance of integrating pain management into the core of wound care planning, particularly in anatomically sensitive areas.^{3,5}

Another relevant aspect was the implementation of strategies aimed at reducing local contamination. Temporary urinary catheterization facilitated safer dressing changes and contributed to limiting exposure of

the wound to urine, which may otherwise impair healing and increase infection risk. Although the use of urinary catheters must always be carefully balanced against the risk of catheter-associated complications, in this case it represented a pragmatic solution within a controlled and continuously reassessed clinical framework.

From a local treatment perspective, the use of an oxygen-enriched oleic matrix dressing appeared to support wound healing by contributing to bacterial burden control, maintenance of a favorable moist microenvironment, and reduction of dressing-related trauma. Its conformability and ease of application were particularly advantageous in a complex, irregular, and partially undermined wound. However, it is important to emphasize that the observed clinical improvement cannot be attributed to a single intervention alone. Rather, it likely reflects the combined effect of systemic therapy, optimized pain control, atraumatic local care, contamination management, and coordinated multidisciplinary follow-up.^{2,4,7}

Continuity of care also emerged as a relevant factor. The integration of hospital-based and home-based management, supported by patient education and regular follow-up, facilitated adherence to treatment and reduced the burden associated with repeated hospital visits. Over time, the patient demonstrated improved engagement in the care process, increased confidence in the care team, and better coping with her condition, suggesting a positive impact of both clinical and relational aspects of care.⁸

This case has several limitations. As a single-case observation, it does not allow generalization of findings. In addition, multiple interventions were implemented simultaneously, making it difficult to isolate the specific contribution of each component of the treatment strategy. Furthermore, the absence of standardized wound measurement tools, validated quality-of-life assessments, and objective biomarkers of inflammation limits the ability to quantify treatment effects over time.

Despite these limitations, this report provides a clinically relevant example of integrated management of a complex vulvoperineal wound in a high-risk patient. It highlights the importance of individualized, atraumatic, and multidisciplinary approaches, with particular emphasis on the role of nursing care in supporting treatment tolerance, preventing complications, and promoting wound healing.^{2,3}

In clinical practice, similar cases may benefit from structured care pathways that explicitly address pain control, contamination risk, tissue protection, and continuity of care across settings. Further case series and prospective studies are needed to better define effective management strategies for complex wounds in patients with hidradenitis suppurativa and associated systemic conditions.^{1,6}

Conclusion

The management of complex vulvoperineal wounds requires an integrated, multidisciplinary approach centered on pain control, atraumatic care, and contamination prevention. Nursing management plays a pivotal role in supporting treatment adherence and clinical outcomes. Further research is needed to define structured and reproducible care pathways.

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Reassessment-Driven Dressing Rotation in Chronic Wound Care: A Brief Report

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Abstract

Introduction. Chronic wounds are a major clinical challenge because of delayed healing, recurrence risk, and reduced quality of life

Methods. A 90-year-old frail patient presented with a chronic venous-related ulcer of the right lateral malleolus persisting for 10 years.

Wound management followed CARE guidelines with repeated assessment using the TIME framework, Triangle of Wound. Assessment, and NERDS/STONEES criteria. Treatment included PHMB cleansing, medical-grade honey, and hydrogel dressings adjusted according to wound progression.

Results. Baseline wound size was 5 × 4.5 × 0.8 cm with moderate exudate, partial fibrin coverage, and pain intensity of 6/10 on the VAS scale. Progressive reduction in exudate and inflammation was observed, followed by granulation and epithelialization. Complete wound closure occurred after 15 weeks, with pain reduction to 0/10 and no adverse events.

Discussion. Reassessment-guided dressing rotation within an advanced home-care pathway was associated with healing of a long-standing chronic ulcer.

Keyword: Chronic Wounds, Wound Care, Advanced Wound Care

Introduction

Dressing selection in wound care is a dynamic process that should evolve through ongoing clinical reassessment.¹⁻³ Changes in topical treatment are sometimes interpreted as uncertainty; however, dressing "rotation" may represent a structured, assessment-driven strategy aligned with evolving wound needs and therapeutic objectives.^{2,3} As wound characteristics change over time,

adapting the dressing regimen supports wound bed preparation, prevents complications, and maintains a patient-centred approach.²⁻⁴ This paper explores dressing rotation as a purposeful clinical choice, supported by a case vignette illustrating reassessment-guided decision making.

Current international guidance frames dressing selection as a goal-oriented process guided by structured clinical reassessment rather than a fixed, product-based approach.²⁻⁴ Across the

healing trajectory, topical management should be aligned with evolving wound needs and clearly defined objectives, including microbial/inflammation control, effective exudate management, maintenance of an optimal moist environment, protection of the wound edges and periwound skin, and support for atraumatic removal.²⁻⁴ Regular re-evaluation is therefore essential to recognise changes in wound trajectory (e.g., increasing exudate, maceration, odour, pain, inflammatory signs, or lack of progression) and to adapt the dressing strategy accordingly.

Within this framework, widely used clinical models support a systematic reassessment of tissue status, inflammation/infection indicators, moisture balance, and epithelial advancement (TIME/Wound Bed Preparation).^{5,6} The Triangle of Wound Assessment further reinforces the need to evaluate not only the wound bed, but also the wound edge and surrounding skin, where early deterioration may first become evident.⁴ In routine practice, structured clinical cues can be used to screen for superficial critical colonisation versus deeper infection (e.g., NERDS and STONEES), supporting timely escalation of topical antimicrobial strategies, diagnostics, or systemic therapy when indicated.^{7,8} These models help define phase-appropriate “dressing aims” over time (e.g., absorption, antimicrobial control, protection of the margins/periwound, support to debridement, or epithelial protection), reinforcing dressing rotation as a purposeful reassessment-driven strategy rather than an inconsistent change of plan.^{2,3,5,6}

The following case vignette illustrates how structured reassessment guided dressing rotation over time, aligning topical choices with evolving wound needs and patient-centred goals.

Dressing “rotation” should not be interpreted as an improvised gesture or a decision driven by therapeutic uncertainty or economic logic. Rather, it represents a conscious and structured care intervention, grounded in updated clinical assessment and in the principle of adapting topical treatment to wound evolution and to the needs of the person receiving care.

The decision to change a dressing should be based on systematic observation of the wound and periwound skin, including the quantity and quality of exudate, the presence of devitalised tissue, local signs suggestive of infection, periwound integrity, and overall tolerability of the dressing – both physically and emotionally.²⁻⁶ Structured documentation through serial photography,

together with validated frameworks such as TIME, the Triangle of Wound Assessment, and practical clinical indicators such as NERDS/STONEES, can support continuity and clinical consistency in decision making.^{2-7,9} However, technical evaluation alone is rarely sufficient to optimise outcomes. Each dressing change should be accompanied by clear and reassuring communication, enabling patients to understand the rationale for treatment adaptation and to perceive it as an integral component of a coherent care pathway, thereby promoting trust and adherence.^{2,3} Practice-based reports and audits on structured wound-care pathways suggest that dynamic reassessment combined with shared explanation of therapeutic choices may contribute to improved outcomes and patient satisfaction. Overall, structured dressing rotation integrated with effective communication may represent a key element in optimising wound care and strengthening the therapeutic alliance.^{1,10}

Methods

Clinical approach and reporting framework

This case was managed in an advanced home-care setting by a wound care nurse specialist, adopting a continuous reassessment approach with therapeutic adaptation across healing phases. This manuscript reports a descriptive single-patient case report developed in accordance with the CARE guidelines, with the aim of illustrating the clinical-care pathway of a frail older adult with a ten-year chronic ulcer and highlighting how clinical nursing reasoning and targeted dressing rotation can support wound progression.

The case was selected based on predefined clinical criteria, including a chronic wound duration of at least ten years without complete healing, geriatric frailty, and full adherence to the agreed care plan. Wound assessment and decision making were supported by validated tools, including the TIME framework, the Triangle of Wound Assessment, and the NERDS/STONEES criteria for screening clinically relevant signs suggestive of biofilm involvement and infection risk.³⁻⁶ Clinical monitoring focused on wound closure status and the time course of healing (weeks). Additional monitoring domains included exudate evolution, pain intensity assessed using the Visual Analogue Scale (VAS), adherence to the proposed regimen, and patient-reported satisfaction documented during follow-up.

Case vignette

A 90-year-old patient with geriatric frailty and reduced mobility was referred for advanced management of a chronic ulcer located at the right lateral malleolus. Relevant comorbidities included hypertension, osteoarthritis, and mild cognitive decline, which increased vulnerability in daily wound care. The wound had been present for over ten years and had never achieved complete closure, alternating periods of stability with recurrent episodes of worsening.

According to family members, previous management relied on traditional dressings and non-structured topical interventions, without systematic reassessment or a dynamic therapeutic plan guided by wound evolution. Dressing choices frequently alternated between dry dressings and topical products without clearly defined phase-oriented aims, contributing to prolonged tissue stagnation and recurrent deterioration.

At first assessment, key issues included the absence of an advanced phase-oriented approach, lack of targeted dressing rotation, limited structured evaluation of bacterial burden, and suboptimal adherence to treatment, partly influenced by long-standing distrust associated with repeated unsuccessful care. A personalised care plan was therefore established to support wound bed preparation, control suspected biofilm, and promote epithelial progression through reassessment-guided dressing rotation and consistent therapeutic communication aimed at strengthening patient involvement and trust.

Devices and therapeutic rationale

Advanced topical interventions were selected and rotated according to wound phase and reassessment findings, with the aim of controlling

microbial burden, supporting removal of non-viable tissue, and promoting progression toward granulation and epithelialization.^{9,11} In the initial phase, a polyhexanide plus poloxamer solution (PHMB) was used for wound cleansing, supporting disruption of biofilm and reduction of bacterial load while preserving viable tissue.¹¹

Medical honey was subsequently introduced either as a direct topical application or via impregnated dressings. Its use was guided by its reported antimicrobial and anti-inflammatory activity and its osmotic mechanism, which may assist exudate management, support wound bed cleansing, and promote granulation and epithelial progression.¹²

During the phase requiring further hydration and facilitation of tissue cleansing, a sterile hydrogel was incorporated to maintain an optimal moist environment and support autolytic debridement of devitalised tissue. In addition, hydrogel-based management was used to support comfort and local pain reduction while promoting a wound microenvironment favourable to cellular migration¹³, as summarised in Table 1.

Product selection and rotation were guided by structured reassessment and phase-specific dressing aims, with treatment adjustments aligned to wound trajectory and patient-centred needs.

Ethical considerations

Written informed consent for publication of clinical information and images was obtained from the patient and/or legal representative. All images were de-identified.

Results

Following implementation of the advanced

Table 1. Key nursing interventions in the management of complex vulvoperineal wounds.

Device	Mechanism of action	Clinical rationale	Main objectives
PHMB (Polyhexanide + Poloxamer)	Broad-spectrum antiseptic with anti-biofilm activity; surfactant facilitating microbial detachment	Supports reduction of bacterial load while preserving viable tissue; useful in early phases when biofilm or increased bioburden is suspected	Bioburden control; infection prevention; wound bed preparation
Medical honey	Osmotic antimicrobial activity; acidic pH; modulation of local inflammation	Supports wound bed cleansing and exudate management; may promote granulation and epithelial progression through osmotic and antimicrobial effects	Exudate management; local infection control; wound bed cleansing
Sterile hydrogel	Maintains a moist environment; hydrates devitalised tissue; supports cell migration	Facilitates autolytic debridement and supports newly formed tissue; may improve comfort	Hydration; autolytic debridement; pain reduction; support to granulation/epithelialisation

care plan, progressive clinical improvement in the wound bed and periwound condition was documented through serial reassessment and photorecording (Figures 1-2). Early evolution was characterised by a reduction in visible inflammatory signs and exudate, with changes consistent with improved local control of the wound microenvironment during the sequential use of PHMB and medical honey (Figures 3-4).

Subsequently, the introduction of a hydrogel-based moist environment supported ongoing tissue cleansing, with progressive reduction of devitalised material and the development of viable granulation tissue, followed by gradual epithelial advancement (Figures 4-5). Over the weeks, a marked clinical improvement was observed in exudate level, pain, and malodour, alongside increased patient comfort and perceived quality of life.

Healing progressed steadily, culminating in complete wound closure within 15 weeks, representing a substantially shorter healing trajectory compared with the prolonged non-healing history reported in the patient's previous care pathway (Figure 6).

This case illustrates how structured reassessment and phase-oriented dressing aims can guide topical treatment adaptation over time within an advanced home-care pathway.

Advanced nursing intervention

The care pathway was delivered within an advanced home-care setting through structured reassessment guided by the TIME framework, regular photodocumentation, and continuous monitoring of wound bed and periwound evolution. Management was dynamic and phase-oriented, with dressing rotation guided by clinical findings and predefined therapeutic aims (e.g., exudate control, microbial burden management, wound bed preparation, and support to epithelial progression).^{4,5,10} Caregiver involvement was integrated through periwound protection measures and reinforcement of adherence to the agreed plan, with ongoing attention to local risk factors.¹⁴

Clinical decisions were reviewed on a weekly basis to ensure continuity of care and timely adaptation of topical management according to wound trajectory and patient-centred needs.

Treatment steps

Topical management was adapted over time through scheduled reassessment and dressing rotation aligned with the healing phase and evolving wound needs.

Initial phase: Exudate and suspected increased bacterial burden control

During the initial phase, characterised by high exudate and clinical features suggestive of increased local bacterial burden, the primary aims were to optimise the wound microenvironment and support wound bed preparation. Dressings were performed every 48 hours, including cleansing with a polyhexanide plus poloxamer solution (PHMB), application of medical honey, and periwound skin protection using a barrier product. A highly absorbent polyurethane foam dressing was used to manage exudate.

Intermediate phase: Wound bed hydration and granulation support

As the wound bed showed progressive improvement with emerging granulation tissue and reduced devitalised material, dressing frequency was extended to every 72 hours. A sterile hydrogel was introduced in combination with polyurethane foam to maintain a moist environment and support ongoing tissue cleansing, while continuing periwound protection and structured monitoring.

Final phase: Epithelial progression and consolidation

In the later phase, characterised by consolidation of granulation and epithelial advancement, dressings were maintained every 72 hours. PHMB was reintroduced as part of reassessment-guided topical management to support wound stability, in combination with a moderately absorbent foam and continued periwound protection.

Clinical evolution and dressing rotation steps are summarised in Table 2.

Complete wound closure was achieved within 15 weeks, a notable outcome considering the ten-year chronicity and the prolonged non-healing history reported during prior management.



1
Figure 1. Baseline appearance of the right lateral malleolar ulcer at initial assessment (day 0), with periwound erythema and clinical features suggestive of local inflammation and clinical features consistent with increased local bacterial burden.



2
Figure 2 (day 17). After wound bed cleansing wound appearance showing reduced fibrinous tissue and lower exudate level, with improved periwound condition and decreased lower-limb oedema.



3
Figure 3 (day 30). Wound appearance showing increased granulation tissue and reduced devitalised material following reassessment-guided adaptation of topical management, with subsequent introduction of a hydrogel-based approach.



4
Figure 4 (day 62). Wound appearance showing increased granulation tissue and reduced local inflammatory signs during ongoing reassessment-guided topical management.



5
Figure 5 (day 91). Stable wound appearance with ongoing re-epithelialisation after reassessment-guided transition to a medical honey-based dressing.



6
Figure 6. Wound closure at day 102 (week 15), showing a stable clinical appearance at follow-up.

Table 2. Timeline of reassessment-guided dressing rotation and clinical evolution over 15 weeks until wound closure.

Week	Clinical reassessment findings	Dressing aims	Topical intervention	Observed response
0	High exudate; periwound erythema; clinical features suggestive of increased local bacterial burden	Exudate control; wound bed preparation; microbial burden management	PHMB cleansing + medical honey + high-absorbency foam + periwound barrier	Reduced oedema; reduced exudate; improved periwound condition
3	Reduced exudate; reduced devitalised material; emerging granulation	Maintain moist environment; support tissue cleansing; protect periwound	Hydrogel + foam + periwound barrier	Increased granulation; ongoing reduction of non-viable tissue
8	Predominantly viable tissue; improving wound bed stability	Support epithelial progression; maintain protection	Reassessment-guided topical management (PHMB as indicated) + moderate-absorbency foam + periwound barrier	Continued epithelial advancement
15	Wound closed	Maintain skin integrity	No dressing required	Stable closure at follow-up

Discussion

Chronic wound management requires a multidimensional approach integrating structured clinical assessment, phase-oriented topical interventions, and an effective therapeutic relationship.^{1,10} In this case, reassessment-driven dressing rotation combined with consistent patient communication was associated with progressive wound improvement along the healing continuum.

Complete closure of a chronic ulcer with a ten-year history was achieved within 15 weeks, representing a notable outcome in the context of geriatric frailty and prolonged non-healing under previous management. The strategy adopted relied on systematic clinical reasoning supported by validated assessment frameworks, including TIMERS/Wound Bed Preparation^{5,9}, the Triangle of Wound Assessment⁴, and NERDS/STONEES criteria⁷, which guided reassessment and the definition of phase-specific dressing aims over time. The sequential use of PHMB, medical honey, and hydrogel was implemented to address evolving needs such as local microbial burden management, exudate control, wound bed hydration, and support to granulation and epithelial progression, within a dynamic and individualised care plan.

This approach aligns with contemporary wound care models that emphasise continual reassessment – namely, cyclical evaluation of wound status and treatment response with timely adaptation of the topical strategy.⁵ Frameworks

such as TIMERS and the Triangle of Wound Assessment reinforce the need to update clinical decisions based on wound trajectory, supporting dressing changes as a structured component of evidence-informed practice rather than a marker of therapeutic uncertainty.^{5,15} In this perspective, dressing rotation can be conceptualised as a planned reassessment-driven optimisation process, anchored to measurable clinical findings and predefined objectives.⁵

A further relevant element in this case was patient and caregiver engagement through clear, continuous communication. Explaining the rationale for dressing changes appeared to strengthen trust, improve adherence, and reduce uncertainty related to treatment variation. This is clinically relevant, as patients may interpret frequent changes as an indicator of failure, whereas reframing dressing adaptation as a planned component of care may support acceptance and continuity.¹⁶

Practice-based reports and clinical audits suggest that structured reassessment pathways and shared explanation of treatment decisions may contribute to improved care processes and patient experience in chronic wound management. Within this context, the relational dimension can be considered an integral component of advanced wound care delivery, complementing technical expertise and supporting sustained engagement with the treatment plan.^{15,17}

Overall, this case highlights the role of nurses with advanced competencies in the

management of complex wounds, where clinical reasoning, ongoing assessment, and therapeutic communication operate as interconnected elements of contemporary practice.¹⁸ While conclusions are inherently limited by the single-case design, this experience supports the clinical plausibility and feasibility of reassessment-driven dressing rotation as both a technical and relational strategy within advanced home care.

Although limited by the single-patient design, lack of microbiological biofilm quantification, and relatively short follow-up, this case highlights the potential value of reassessment-guided wound management in home care. The patient reported reduced pain during dressing procedures and expressed satisfaction and greater confidence in the care plan, particularly when the rationale for dressing changes was explained during follow-up visits.

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Clinical Standardization of Platelet-Rich Plasma (PRP) and Platelet-Rich Fibrin (PRF) Treatments in Complex Wounds: A Protocol for Biological Optimization and Evidence-Based Practice

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Abstract

Introduction. Complex wounds represent a critical public health challenge, requiring effective adjuvant therapies to reverse cellular senescence. Autologous platelet derivatives, namely Platelet-Rich Plasma (PRP) and Platelet-Rich Fibrin (PRF), concentrate essential growth factors to accelerate tissue regeneration. However, the lack of methodological standardization limits clinical reproducibility.

Objective. To develop and scientifically validate a structured nursing protocol for the preparation and clinical application of PRP and PRF in complex wounds.

Methods. Technical analysis and theoretical validation of institutional protocol EP431, cross-referencing operational parameters (relative centrifugal force, processing times, and handling techniques) with high-impact clinical trials.

Results. The protocol establishes a relative centrifugal force of 1500 x g for 9 minutes for PRP (separator gel tubes, inverted 5-8 times) and 700 x g for 15 minutes for PRF. Evidence confirms that these parameters maximize platelet integrity and sustained cytokine release. Intradermal/subcutaneous injection techniques (0.1 mL/cm), an optimal 4-5 day application interval, and advanced perilesional silicone barriers are detailed.

Conclusion. Clinical standardization via protocol EP431 mitigates biological variability, ensuring a safe, reproducible, and robust evidence-based intervention.

Keyword: Platelet-Rich Plasma, Platelet-Rich Fibrin, Chronic Wounds, Wound Healing, Clinical Protocols, Regenerative Medicine

Introduction

The management of complex wounds—including chronic ulcers, dehiscent surgical wounds, burns, and refractory traumatic lesions—imposes a severe socioeconomic and clinical burden on global healthcare systems.¹ These lesions are frequently arrested in a pathological, self-perpetuating inflammatory stage characterized by an imbalance in matrix metalloproteinases (MMPs), premature degradation of structural proteins, and cellular senescence. Autologous platelet concentrates provide a supraphysiological delivery of growth factors, triggering native cellular cascades indispensable for real tissue repair. Despite clear biological plausibility, clinical implementation faces substantial heterogeneity. Methodological

discrepancies in centrifugation speeds, tube selection, and activation handling result in unpredictable biological profiles. This paper presents a comprehensive validation of protocol EP431 (originally presented at EWMA 2024, London)² to establish reproducible clinical excellence.

Operational Parameters and Preparation Methodology

The preparation of autologous concentrates requires strict technical adherence to avoid premature platelet activation or unwanted cellular lysis. Whole blood processing relies on precisely calibrated centrifugation forces and times adjusted to optimize biological yield.

Table 1. Material Requirements and Supply Checklist for Protocol EP431.

Category	Detailed Item Description	Clinical Purpose
Cleansing Solutions	1st: Sterile Saline Solution 2nd: Super-Oxidized Water	Ensure biological decontamination and mechanical cleansing of the wound bed without causing cell cytotoxicity.
Collection Tubes	PRP-specific tubes (with separator gel) PRF-specific tubes (without chemical additives)	Guarantee accurate separation of whole blood fractions during the specified rotation cycle.
Perilesional Protection	Specific barrier protection cream	Prevent maceration of the wound edges induced by chronic biological exudate.
Interfaces & Dressings	Silicone contact layer or paraffin gauze Self-adherent soft silicone foam dressing	Protect the applied platelet concentrate, maintain optimal moisture balance, and prevent mechanical trauma during removal.

Differential Centrifugation Mechanics:

- Platelet-Rich Plasma (PRP): Spun at 2800 rpm for 9 minutes (RCF of 1500 x g). Requires mandatory 5-8 gentle inversions to thoroughly homogenize the highly concentrated growth factors located right above the gel barrier.
- Platelet-Rich Fibrina (PRF): Spun at 1300 rpm for 15 minutes (RCF of 700 x g). Processed without additives; require immediate extraction and application of the un-retracted three-dimensional fibrin matrix.

Clinical Application Protocol and Therapeutic Approach

Administration must follow strict anatomical and physiological guidelines. The protocol mandates a precise dosage of 0.1 mL per linear or square centimeter, delivered via intradermal and subcutaneous micro-injections directly into the viable margins and wound bed. This ensures uniform local bio-distribution. Indications include vascular ulcers (venous/arterial), diabetic foot ulcers, dehiscent wounds, complex burns, and ischemic surgical flaps. Absolute contraindications comprise uncontrolled

active localized infections, malignancy within the wound bed (due to angiogenic risks), severe thrombocytopenia, or active systemic autoimmune flare-ups.

Biomolecular Mechanisms and Discussion

The therapeutic efficacy of protocol EP431 relies on highly coordinated cellular events. Autologous platelet derivatives act as an immuno-modulator, downregulating pro-inflammatory cytokines (TNF-alpha, IL-1) and driving macrophage polarization toward the pro-healing M2 phenotype. Angiogenesis is significantly accelerated via the sustained release of Vascular Endothelial Growth Factor (VEGF) and Fibroblast Growth Factor (FGF) from the alpha granules, restoring capillary density and tissue perfusion. Proliferation of fibroblasts and keratinocytes is driven by PDGF and TGF-beta, which ensure organized collagen deposition and limit hypertrophic scarring. Furthermore, concentrated platelets release antimicrobial peptides (AMPs), disrupting bacterial membranes and preventing biofilm formation.³

Scientific Evidence and International Validation

The operational parameters established in Protocol EP431 are heavily validated by seminal peer-reviewed literature:

1. Clinical Efficacy: Meznerics FA, et al. *J Clin Med.* 2022;11(24).¹ A robust systematic review and meta-analysis confirming that autologous platelet concentrates significantly increase complete closure rates and reduce healing time in chronic wounds compared to standard care.
2. Centrifugation Optimization: Eppley BL, et al. *Plast Reconstr Surg.* 2004;114(6).⁴ Demonstrates that intermediate-to-high relative centrifugal forces (around 1500 x g, matching the PRP parameters of EP431) maximize platelet recovery while preserving alpha granule structural integrity.
3. Infection Control: Zhang W, et al.³ *Tissue Eng Part B Rev.* 2019;25(3). Validates the exact molecular pathways involved in leukocyte phagocytosis and platelet-

derived AMP release, confirming the local bio-protective capacity against critical colonization.

Conclusion

The institutional protocol EP431 successfully addresses the historical challenge of methodological inconsistency in regenerative medicine. By standardizing the relative centrifugal forces (1500 x g for PRP; 700 x g for PRF) and specifying precise localized tissue delivery, it establishes a reliable, clinically reproducible model that significantly optimizes wound care outcomes and advances evidence-based nursing practice.

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