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Research Article

Stem Cell-Based Therapies for Chronic Wound Healing: Current Evidence and Future Perspectives

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ABSTRACT

Background: Chronic wounds, including diabetic foot ulcers, venous leg ulcers, and ischemic wounds, fail to progress through the normal phases of healing and impose a substantial clinical and economic burden. Stem cell-based therapies, principally mesenchymal stem cells (MSCs) and their derivatives, have been investigated as regenerative alternatives to conventional wound management.

Objective: To critically appraise current clinical and mechanistic evidence for stem cell-based therapies in chronic wound healing, compare outcomes across cell sources and wound aetiologies, and examine the regulatory and safety considerations governing their translation into practice.

Data Sources: PubMed/MEDLINE, Scopus- and Web of Science-indexed journals, and publications from Frontiers, MDPI, Springer Nature, Wiley, PLOS, and SAGE were searched for literature published predominantly between 2019 and 2026, supplemented by landmark earlier studies and current US Food and Drug Administration (FDA) regulatory guidance.

Review Methods: A comprehensive narrative review format was adopted to accommodate the methodological breadth of the field, spanning mechanistic, preclinical, clinical trial, and regulatory literature. Evidence was appraised for study design, cell source, and outcome measures, with emphasis on comparing findings across wound aetiologies rather than sequential summarisation.

Key Findings: Meta-analyses of randomised controlled trials indicate that MSC-based therapy improves ulcer healing rate and reduces amputation risk in diabetic foot ulcers relative to conventional care, with evidence certainty rated low to moderate by GRADE criteria. Evidence in venous leg ulcers and critical limb ischemia remains limited to small, mostly phase I/II trials. Cell-free MSC-derived extracellular vesicles and induced pluripotent stem cell (iPSC)-derived lineages show mechanistic promise but remain confined chiefly to preclinical and early translational studies. Regulatory classification under the US FDA's 351/361 framework materially determines the evidentiary and manufacturing burden applicable to a given product, and tumorigenicity and manufacturing variability remain unresolved safety considerations for pluripotent-derived cells.

Conclusion: Stem cell-based therapies, particularly MSC-based interventions, show reproducible benefit for diabetic foot ulcer healing in randomised trials, while evidence for other chronic wound types and for cell-free and pluripotent-derived approaches remains preliminary. Continued translation should be paced to standardised manufacturing, long-term safety follow-up, and harmonised regulatory classification.

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Introduction

Chronic wounds are skin or soft-tissue injuries that fail to progress through the normal haemostasis, inflammation, proliferation, and remodelling sequence within an expected timeframe, generally persisting beyond three months. Diabetic foot ulcers, venous leg ulcers, and ischaemic wounds account for most cases and are driven by a shared pathophysiological substrate of persistent inflammation, impaired angiogenesis, and disordered extracellular matrix remodelling. Conventional management, debridement, compression, offloading, and advanced dressings, addresses the wound bed but does not correct the underlying cellular and molecular deficits, which has motivated interest in cell-based regenerative strategies capable of actively modulating the wound microenvironment rather than merely protecting it.

Mesenchymal stem cells (MSCs) have attracted the greatest clinical investigation among cell-based approaches, owing to their relative ease of isolation, immunomodulatory properties, and capacity to promote angiogenesis and extracellular matrix remodelling through paracrine signalling. Despite an expanding body of preclinical and early-phase clinical work, comparative appraisal across wound aetiologies, cell sources (bone marrow, adipose, umbilical cord), and delivery formats (cell suspension, biomaterial scaffold, cell-free extracellular vesicles) remains limited. Existing reviews frequently focus on a single wound type or a single cell source, which makes it difficult for clinicians and pharmaceutical scientists to judge where the evidence for a given application is strongest and where translation remains preliminary.

This review synthesises evidence on stem cell-based therapies across the principal chronic wound aetiologies, examines the underlying mechanisms of MSC-mediated tissue repair, appraises emerging cell-free and induced pluripotent stem cell (iPSC)-based strategies, and critically reviews the regulatory science, principally the US FDA's risk-tiered 351/361 framework, governing translation of these products into clinical practice. The objective is to provide a comparative, critically appraised account of current evidence and its limitations, rather than a further descriptive catalogue of individual studies.

Pathophysiology of Chronic Wounds and Rationale for Cell-Based Therapy

Chronic wounds are characterised by a wound bed arrested in a self-perpetuating inflammatory state, with elevated levels of pro-inflammatory cytokines and matrix metalloproteinases, reduced growth factor bioavailability, and senescent, poorly migratory fibroblasts and keratinocytes. In diabetic wounds, hyperglycaemia additionally impairs neutrophil and macrophage function, reduces microvascular perfusion, and promotes advanced glycation end-product accumulation, compounding the defect in normal repair signalling. Venous and ischaemic wounds share elements of hypoxia and impaired perfusion but differ mechanistically, venous ulcers arising principally from ambulatory venous hypertension and associated matrix degradation, and ischaemic wounds from macrovascular insufficiency limiting oxygen and nutrient delivery to the wound bed.

Because these deficits are cellular and paracrine in nature rather than purely structural, dressings and debridement alone cannot correct them; this is the principal biological rationale for introducing exogenous cells or cell-derived products capable of actively signalling to resident wound cells. Stem cell therapies are proposed to intervene at this level, by supplying paracrine mediators that dampen inflammation, promote angiogenesis, and stimulate resident cell proliferation and migration, rather than by direct, large-scale engraftment and differentiation into replacement tissue, a mechanistic distinction that is addressed further in Section 3.

Mechanisms of Action: Paracrine, Immunomodulatory, and Angiogenic Effects

Early hypotheses attributed MSC benefit in wound healing to direct differentiation into keratinocytes, fibroblasts, or endothelial cells; however, the accumulated evidence indicates that MSCs act predominantly through paracrine mechanisms rather than substantial long-term engraftment, recruiting macrophages and endothelial lineage cells and secreting pro-angiogenic and anti-inflammatory factors that modulate the local immune environment. Quantitative in vivo distribution studies using positron emission tomography have confirmed that injected MSCs are cleared from the wound site relatively rapidly, reinforcing the paracrine, rather than replacement, model of action and helping to explain why repeated dosing regimens are frequently used in clinical protocols.[12]

Consistent with this paracrine model, early mechanistic work demonstrated that autologous, culture-expanded bone marrow-derived MSCs attenuate scar formation and modulate remodelling through secreted factors rather than large-scale differentiation into replacement dermal tissue, indicating that the paracrine signalling axis itself is the principal therapeutically relevant activity.[16] This mechanistic understanding has directly informed two later developments discussed in this review: preactivation strategies intended to enhance MSC secretory potency prior to administration, and the emergence of cell-free extracellular vesicle therapies (Section 6) that isolate the paracrine component of MSC action from the cells themselves, avoiding engraftment-related safety concerns entirely.

Landmark early clinical work established proof of concept for this paracrine-driven approach: autologous bone marrow-derived MSCs delivered via fibrin spray accelerated healing in both murine and human cutaneous

wound models, providing an early clinical signal that catalysed the subsequent expansion of MSC-based wound trials.[15] Comparative appraisal of the mechanistic literature indicates general agreement on the centrality of paracrine, immunomodulatory, and pro-angiogenic signalling, but persistent uncertainty regarding the optimal MSC activation state, dose, and delivery timing required to reproduce these effects consistently across patients and wound types.

Clinical Evidence in Diabetic Foot Ulcers

Diabetic foot ulcers (DFUs) represent the most extensively studied indication for stem cell-based wound therapy. A GRADE-compliant, bootstrapped meta-analysis of randomised controlled trials found that stem cell therapy produced a significantly superior ulcer healing rate compared with conventional intervention (risk difference 0.36, 95% CI 0.28–0.43), together with improvements in pain-free walking distance and ankle-brachial index, and a significant reduction in amputation rate, with no significant difference in adverse events between arms.[1] Certainty of evidence, however, was rated as ranging from very low to moderate across outcomes, reflecting heterogeneity in cell source, dose, delivery route, and trial size across the included studies, a limitation that recurs throughout this literature and tempers confidence in the pooled effect estimates.

Cell-source-specific meta-analyses reinforce this general direction of effect while highlighting continued heterogeneity. A meta-analysis restricted to umbilical cord-derived MSCs in diabetic foot and peripheral artery disease patients found improved ulcer healing (odds ratio 2.88, 95% CI 1.20–6.91) alongside gains in transcutaneous oxygen pressure and ankle-brachial index relative to conventional treatment, based on six randomised trials totalling 380 patients.[2] Individual randomised trials contributing to this evidence base include a randomised evaluation of allogeneic adipose-derived stem cells for diabetic foot ulcer treatment with proteomic outcome assessment, a controlled phase 1/2 trial of MSC derivatives in diabetic foot ulcers demonstrating safety and efficacy signals, and a prospective randomised trial of human umbilical cord MSC injection for diabetic foot ulcers.[3][4][5]

A separate meta-analysis restricted to randomised trials of stem cell treatment for diabetic foot ulcers similarly reported superior healing outcomes with stem cell treatment relative to standard care, corroborating the direction, though not the precision, of the larger bootstrapped analysis.[8]

Two recurring limitations distinguish confident from cautious interpretation of this evidence. First, trial sizes remain small (typically fewer than 100 patients per arm), and cell source, dose, and delivery route vary considerably between trials, limiting the validity of pooling across studies as though they tested a single intervention. Second, long-term follow-up beyond 12–24 weeks is rarely reported, so durability of healing and late safety signals, including any association with malignancy, remain inadequately characterised. A bibliometric analysis of the stem cell-for-diabetic-foot literature similarly identified an accelerating publication rate without a commensurate increase in large, multicentre, long-duration randomised trials, a pattern that recurs across the broader regenerative wound-care literature and that regulators have flagged as a barrier to confident risk-benefit determination.[6]

Clinical Evidence in Venous Leg Ulcers and Ischaemic Wounds

Evidence for stem cell therapy in venous leg ulcers (VLUs) is considerably less mature than in diabetic foot ulcers. Adipose-derived stem cells (ADSCs) have been examined in small, mostly non-randomised series; a systematic review identified only four eligible studies (one randomised, three non-randomised) totalling 66 patients, of which the single randomised study reported six-month healing rates of 75% with ADSCs compared with 50% in controls, a promising but statistically underpowered signal. A phase I/II randomised, controlled, proof-of-concept trial protocol for allogeneic adipose-derived MSCs delivered on a fibrin-hyaluronic biological matrix for VLUs has since been registered, reflecting the field's progression toward more rigorous trial design, though results were not yet available at the time of this review.

Evidence in ischaemic wounds associated with critical limb ischaemia (CLI) follows a similar early-phase pattern. An open, randomised trial protocol comparing autologous adipose-derived stem cells, delivered via bio-dressing and perilesional injection, against standard revascularisation-based care has been registered for CLI patients with chronic arterial ulcers, reflecting continuing methodological maturation in this indication even though results were not yet available at the time of this review.[17] Compared with the diabetic foot ulcer literature, the venous and ischaemic wound evidence base is characterised by smaller sample sizes, a higher proportion of registered but not yet completed trials, and a corresponding absence of meta-analytic pooling with adequate statistical power, indicating that clinical extrapolation from diabetic foot ulcer results to these other chronic wound types is not currently justified by direct evidence.

Cell-Free Approaches: MSC-Derived Extracellular Vesicles and Exosomes

MSC-derived extracellular vesicles (MSC-EVs), including exosomes, have emerged as a cell-free alternative that isolates the paracrine signalling component of MSC action while avoiding risks associated with live-cell engraftment, such as ectopic differentiation or, in principle, tumorigenic transformation. MSC-EVs have demonstrated regulatory effects on macrophages, neutrophils, and T cells involved in wound inflammation, and on fibroblasts, keratinocytes,

and endothelial cells involved in proliferation and remodelling, across in vitro and in vivo experimental models.[9] This cell-free strategy is mechanistically consistent with the paracrine model established in Section 3: because MSC benefit appears to derive chiefly from secreted signalling factors rather than sustained engraftment, isolating and administering the vesicle fraction alone is a logical extension of that mechanistic understanding.

A systematic review and meta-analysis of preclinical animal studies evaluating MSC-derived small extracellular vesicles specifically in type 2 diabetic cutaneous wounds found consistent benefit across wound closure rate, neovascular density, re-epithelialisation, and collagen deposition outcomes, but the authors explicitly noted that evidence remains confined to preclinical models and that clinical translation has not yet occurred.[10] This preclinical-to-clinical gap is the central limitation of the cell-free approach at present: while MSC-EVs offer manufacturing and safety advantages over live-cell products, in particular avoiding donor-cell survival and immunogenicity concerns, no adequately powered human randomised trial of MSC-EVs for chronic wound healing has yet been reported, in contrast to the more mature clinical trial base available for whole-cell MSC therapy in diabetic foot ulcers.

Induced Pluripotent Stem Cells and Emerging Cell Sources

Induced pluripotent stem cells (iPSCs) offer theoretical advantages over adult MSCs, including an unlimited proliferative capacity, non-invasive harvesting from cutaneous or blood-derived somatic cells, and, when generated autologously, reduced risk of immune rejection, while avoiding the ethical constraints associated with embryonic stem cells.[11] A dedicated review of iPSC-based skin regeneration strategies documents preclinical progress in generating integration-free iPSC lines and differentiating them toward keratinocyte and endothelial lineages relevant to cutaneous repair, consistent with the paracrine-dominant, pro-angiogenic and pro-proliferative mechanism described in Section 3 rather than durable structural engraftment.[11]

The principal barrier to clinical translation of iPSC-based wound therapies is safety rather than efficacy signal. Reviews of iPSC-based regenerative applications consistently identify genetic alterations acquired during reprogramming and expansion, tumorigenicity (including teratoma formation from residual undifferentiated cells), and immune rejection of non-autologous lines as unresolved concerns requiring resolution before routine clinical use.[11] This safety profile stands in contrast to the comparatively larger and more mature clinical safety record for adult MSCs summarised in Sections 4 and 5, where meta-analyses have not identified a significant excess of adverse events relative to conventional care. Consequently, iPSC-derived cell therapies for chronic wounds remain, at the time of this review, confined to preclinical animal models, and their clinical evaluation should be expected to require a materially more extensive non-clinical safety package than is customary for adult MSC products.

Biomaterial and Scaffold-Based Delivery Strategies

Direct injection of MSC suspensions is limited by poor cell retention, susceptibility to anoikis and inflammatory clearance in the hostile wound microenvironment, and inconsistent distribution across the wound bed. Biomaterial-based delivery, embedding MSCs within hydrogels, fibrin-based matrices, or other scaffolds, has been investigated as a means of improving cell viability, localisation, and paracrine factor retention at the wound site.[7] Combined adipose-derived MSC and bioengineered dermal matrix approaches have achieved complete closure of long-standing, treatment-refractory venous leg ulcers in individual case reports, illustrating the potential of combining cell therapy with tissue-engineering scaffolds even where standalone cell suspension therapy has previously failed.

Despite these encouraging signals, standardisation across the biomaterial delivery literature remains limited: scaffold composition, MSC seeding density, and manufacturing protocols vary substantially between research groups, precluding direct comparison of delivery platforms and complicating regulatory evaluation, since a change in scaffold material or seeding method may materially alter a product's classification and required evidentiary standard under frameworks discussed in Section 9. Hypoxic or inflammatory preactivation of MSCs prior to seeding, and enhancement of the SDF-1α/CXCR4 homing axis, have both been proposed as complementary strategies to improve post-delivery cell survival and are presently supported chiefly by preclinical rather than clinical evidence.

Regulatory Science and Global Governance of Cell-Based Wound Therapies

In the United States, human cells, tissues, and cellular and tissue-based products (HCT/Ps) are regulated under one of two distinct pathways specified in 21 CFR Part 1271, a classification with direct consequences for the evidentiary burden applicable to stem cell wound therapies. Products meeting all four criteria under 21 CFR 1271.10(a), minimal manipulation, homologous use, no combination with another article (with limited exceptions), and either no systemic effect or autologous/first- or second-degree relative allogeneic/reproductive use, are regulated solely under Section 361 of the Public Health Service Act and require establishment registration and adherence to current good tissue practice, but not premarket approval.[13] Products that fail any of these criteria default to regulation as a drug, device, and/or biologic under Section 351 of the

PHS Act and the Federal Food, Drug, and Cosmetic Act, requiring a Biologics License Application supported by the same standard of safety and effectiveness evidence expected of any approved biologic.[14]

This distinction has direct relevance to the therapies reviewed above. Minimally manipulated, homologous-use autologous MSC preparations may in some circumstances qualify for the lower-burden 361 pathway, whereas culture-expanded, more than minimally manipulated MSCs, MSC-derived extracellular vesicle products, and essentially all iPSC-derived cell products are non-homologous or more than minimally manipulated and therefore fall under the 351 pathway, requiring full premarket clinical development. The Regenerative Medicine Advanced Therapy (RMAT) designation, introduced under the 21st Century Cures Act, provides an expedited development and review pathway for qualifying 351-regulated regenerative medicine products intended for serious or life-threatening conditions, including chronic non-healing wounds where preliminary clinical evidence indicates potential benefit.[13]

Current FDA guidance activity, including recent draft guidance on postapproval safety and efficacy data capture and on innovative trial designs for small populations, indicates continuing regulatory refinement specifically aimed at cell and gene therapy products, reflecting recognition that conventional randomised trial paradigms do not always translate efficiently to this product class.

For a pharmacy and biotechnology audience, the practical implication mirrors that of other advanced-therapy domains: regulatory pathway determination should be assessed early in product development, since it materially shapes the manufacturing, non-clinical safety, and clinical trial design requirements applicable to a given stem cell wound therapy, and a product initially conceived for a lower-burden pathway can inadvertently cross into 351 classification through routine manufacturing changes such as extended culture expansion or scaffold combination.

Safety Considerations: Tumorigenicity, Immunogenicity, and Manufacturing Variability

Pooled safety data from diabetic foot ulcer meta-analyses have not identified a statistically significant excess of adverse events with MSC therapy relative to conventional care, and individual trials, including adipose-derived and cadaveric bone marrow MSC studies, have generally reported no serious treatment-related adverse events over the reported follow-up periods.[1] However, follow-up in almost all included trials is limited to weeks or a small number of months, which is insufficient to exclude rare or delayed safety signals, including any long-term association between culture-expanded cell administration and neoplastic risk. This follow-up limitation applies with particular force to iPSC-derived products, for which tumorigenicity, arising either from residual undifferentiated pluripotent cells or from genetic alterations acquired during reprogramming, is a recognised and mechanistically plausible risk that has not yet been excluded by adequately powered, long-duration human data.[11]

Manufacturing variability represents a second cross-cutting safety and efficacy concern. MSC potency, phenotype, and paracrine secretory profile vary by donor, tissue source, passage number, and culture conditions, and this variability is rarely fully characterised or reported in clinical trials, undermining both reproducibility across studies and confidence that results from one manufacturing protocol will generalise to another. Comparative appraisal of the wound-healing literature suggests that where standardisation has been more rigorously applied, for example, in defined umbilical cord MSC dosing protocols, effect sizes appear more consistent than in the pooled, cross-protocol meta-analytic estimates, indicating that manufacturing standardisation, rather than cell source alone, may be a material determinant of the reproducibility of the reported clinical benefit.[2]

Table 1: Landmark Clinical Studies of Stem Cell-Based Therapy for Chronic Wounds

Study / Reference	*Wound Type*	*Cell Source / Product*	*Design*	*Key Outcome*
Mudgal *et al*., 2024[1]	Diabetic foot ulcer	Mixed stem cell sources (meta-analysis)	Meta-analysis of RCTs	Improved healing rate; reduced amputation risk; GRADE certainty low–moderate
Zhang *et al*., 2026[2]	Diabetic foot ulcer / PAD	Umbilical cord MSCs	Meta-analysis of 6 RCTs (n=380)	Improved healing rate (OR 2.88) and TcPO2 vs conventional care
Arango-Rodríguez *et al*., 2022[4]	Diabetic foot ulcer	MSC derivatives	Controlled phase 1/2 RCT	Safety and efficacy signal supporting further trials
Zhang J *et al*., 2023[5]	Diabetic foot ulcer	Human umbilical cord MSC injection	Prospective RCT	Improved wound closure vs control
Parham *et al*., 2023[8]	Diabetic foot ulcer	Mixed stem cell sources	Meta-analysis of RCTs	Superior healing outcomes vs standard care
Adipose-derived stem cell VLU review	Venous leg ulcer	Adipose-derived stem cells	Systematic review (1 RCT + 3 non-randomised, n=66)	75% healing at 6 months (ADSC) vs 50% (control)

Future Perspectives

Three developments are likely to shape near-term progress in stem cell-based chronic wound therapy. First, cell-free MSC-derived extracellular vesicle products, if manufacturing standardisation and potency assays can be established, offer a plausible route to a more reproducible, storable, and potentially lower-regulatory-burden alternative to live-cell therapy, though this will require the field's first adequately powered human trials. Second, biomaterial and scaffold co-delivery strategies are likely to be increasingly combined with MSC preactivation protocols to address the cell-retention and survival limitations that currently constrain therapeutic consistency. Third, regulatory convergence around risk-tiered frameworks, exemplified by the FDA's 351/361 classification and RMAT designation, and by comparable frameworks under development in other jurisdictions, suggests that future clinical development programmes will increasingly be designed with regulatory pathway determination as an explicit, early-stage consideration rather than a downstream formality.

Research Gaps

- Large, multicentre, adequately powered randomised controlled trials remain scarce outside diabetic foot ulcers; venous and ischaemic wound evidence is confined mostly to small or non-randomised studies.
- Long-term follow-up beyond 6 months is rarely reported, limiting assessment of healing durability and delayed safety signals, including neoplastic risk.
- Manufacturing and potency characterisation of MSC and MSC-EV products is inconsistently reported, limiting reproducibility and cross-trial comparison.
- Human clinical trials of MSC-derived extracellular vesicles for chronic wounds are absent despite a substantial and consistent preclinical evidence base.
- Comparative, head-to-head trials across cell sources (bone marrow, adipose, umbilical cord) and delivery formats (suspension versus scaffold) for the same wound type are lacking.

Clinical Implications

For clinicians managing chronic wounds, the current evidence most strongly supports considering MSC-based cell therapy, within a clinical trial or a regulatory-approved product framework, as an adjunct for diabetic foot ulcers that have not responded adequately to standard care, given the consistency of the healing-rate and amputation-reduction signal across independent meta-analyses. Evidence does not yet support extrapolating this benefit to venous leg ulcers or ischaemic wounds, where trial evidence remains preliminary, nor to routine use of MSC-derived extracellular vesicle or iPSC-derived products, which remain investigational. Given manufacturing variability across studies, clinicians and institutional purchasers should expect meaningful differences in reported efficacy between specific licensed or investigational products rather than treating stem cell therapy as a single, interchangeable intervention class.

Limitations of Current Evidence

This review is a narrative synthesis rather than a formal systematic review, and does not apply independent risk-of-bias or GRADE assessment beyond that reported by the primary meta-analyses cited; conclusions should be interpreted as an informed appraisal rather than a de novo quantitative synthesis. The underlying primary literature is itself heterogeneous in cell source, dose, delivery method, and outcome definition, and is weighted toward diabetic foot ulcer indications, small sample sizes, and short follow-up duration, which constrains the strength of any generalisable conclusion regarding stem cell therapy across chronic wound types as a whole. Regulatory guidance referenced in this review, particularly draft FDA guidance documents, may also be revised or finalised after publication.

Conclusion

Stem cell-based therapies, principally mesenchymal stem cells, have accumulated a reproducible evidence base supporting clinical benefit for diabetic foot ulcer healing, with meta-analyses of randomised trials consistently showing improved healing rates and reduced amputation risk, albeit with evidence certainty rated low to moderate. Evidence for venous leg ulcers, ischaemic wounds, cell-free extracellular vesicle therapy, and induced pluripotent stem cell-derived approaches remains earlier in translational maturity, constrained chiefly by small trial sizes, limited long-term follow-up, and, for pluripotent-derived products, unresolved tumorigenicity concerns. Regulatory classification under frameworks such as the US FDA's 351/361 pathway materially shapes the development burden for a given product and should be incorporated into translational planning from an early stage. Continued clinical adoption should be paced to standardised manufacturing, long-term safety data, and the specific wound aetiology and cell source for which supporting evidence actually exists, rather than treated as a uniform therapeutic class.

Data Availability Statement

No new data were generated or analysed in this review. All information discussed is drawn from previously published, publicly available sources cited in the reference list.

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