

Redefining the Standard of Care in Deep Burns: Autologous Skin Grafts Versus Next-Generation Bioengineered Skin Substitutes A Contemporary Systematic Review

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ABSTRACT

Next-generation bioengineered skin substitutes offer donor-sparing alternatives to STSG for deep burns. Review of three studies (N≈297) found STSG had better early graft take, while substitutes reduced autograft need, enabled expansion, and improved scarring. Healing may be slower. Larger multicenter trials with standardized outcomes are needed further research.

KEYWORDS: Bioengineered skin substitutes; split-thickness skin grafting; deep burns; burn reconstruction; wound healing

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I. INTRODUCTION

Burn injury is a form of tissue damage caused by exposure to thermal energy such as heat, radiation, electricity, corrosive chemicals, or flame, which can affect the skin from the epidermis to deeper structures. Accurate assessment of burn depth is essential in clinical practice, as it directly determines management strategies and reconstructive planning. Globally, burns remain a major public health concern, with the World Health Organization reporting approximately 180,000 deaths annually, predominantly occurring in low- and middle-income countries. The burden is especially high in regions such as Africa and Southeast Asia, accounting for a substantial proportion of global cases. In Indonesia, burn prevalence has been reported at approximately 2.2%, with regional variation across provinces; some reports indicate lower prevalence in Aceh (3.8%) and higher prevalence in Bali (6.8%), with a higher proportion of cases occurring in females than males. Recent global epidemiological analyses between 2021 and 2025) continue to confirm the disproportionate burden of burn injuries in developing regions and highlight the long-term functional and socioeconomic consequences among survivors.^{I-III}

For decades autologous split-thickness skin grafting (STSG) has remained the surgical gold standard for

definitive closure of deep dermal and full-thickness burns because it reliably restores barrier function and enables coverage of large total-body surface areas. However, STSG is limited by donor-site morbidity, restricted donor availability in extensive burns, and suboptimal long-term aesthetic outcomes in some patients. At the same time, next-generation bioengineered skin substitutes (acellular dermal matrices, cellular constructs, spray-on autologous cell systems, and composite grafts) have proliferated and matured offering donor-sparing strategies, off-the-shelf availability, and promising improvements in scar quality and contour in selected series. Comparative and outcome data are growing but heterogeneous, and recent systematic appraisals describe both advantages (reduced donor morbidity, improved contour in some settings) and persistent challenges (variable take rates, risk of malposition/infection, cost and need for secondary procedures).^{IV}

This contemporary systematic review differs from prior work by restricting eligible studies to peer-reviewed, free-text reports indexed in PubMed, Sage, Cochrane, Science Direct, Research gate (publication window between the year 2021–2026) and by focusing on head-to-head clinical comparisons between autologous STSG and “next-generation” bioengineered substitutes for deep partial- and

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full-thickness burns. Our primary outcomes will include time to definitive wound closure, graft/substitute take rate, donor-site morbidity, validated scar and functional outcome measures, reoperation/revision rates, adverse events (including infection/extrusion), and patient-reported outcomes; secondary analyses will examine resource use and cost where reported. Recent narrative and comparative analyses underscore the need for an updated, methodical synthesis that integrates the newest technologies and trial data to inform practice and research priorities.^V

II. METHODS

This systematic review followed the PRISMA 2020 guidelines to compare clinical outcomes of autologous split-thickness skin grafting (STSG) and next-generation bioengineered skin substitutes in deep partial- and full-thickness burns. A comprehensive search of PubMed, Sage, Cochrane, ScienceDirect, and ResearchGate (2021–2026), along with grey literature and trial registries, identified randomized and cohort studies comparing these interventions. Eligible studies involved human subjects and reported key clinical outcomes, while non-comparative and non-burn studies were excluded.

Study selection, data extraction, and risk-of-bias assessment were performed independently by multiple reviewers. Extracted data included study characteristics, patient population, intervention types, and outcomes such as graft take, epithelialization time, infection rates, length of stay, reoperation, and scar quality. Risk of bias was evaluated using RoB 2 for randomized trials and ROBINS-I for cohort studies, with disagreements resolved by consensus (Figure 1).

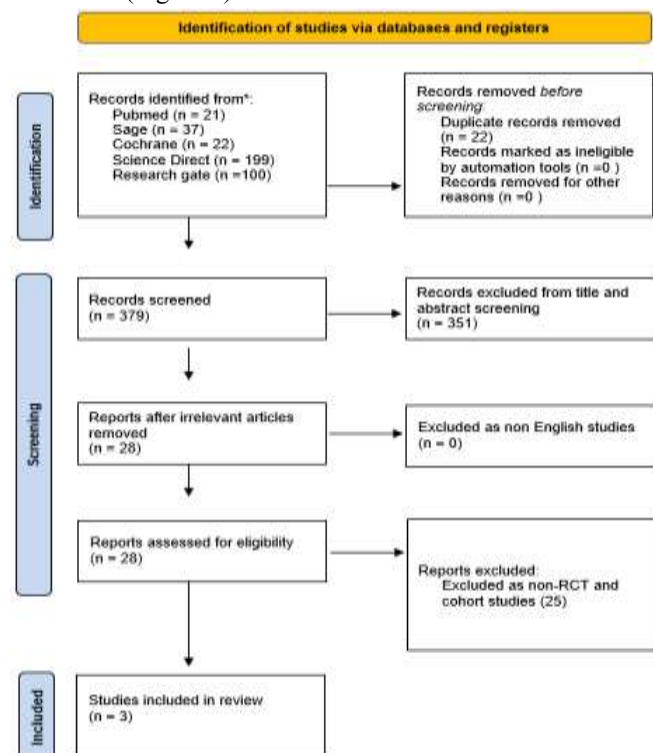


Figure 1. Flowchart of study selection.

Due to clinical and methodological heterogeneity, findings were synthesized narratively rather than through meta-analysis. Continuous outcomes (epithelialization time) and dichotomous outcomes (graft take, infection rates) were summarized across studies. Emphasis was placed on identifying consistent patterns in healing outcomes, complications, and overall effectiveness of STSG versus bioengineered skin substitutes in deep burn management.

III.RESULTS

We identified three comparative studies meeting inclusion criteria, a phase IIb randomized trial of denovoSkin™ versus meshed STSG in adolescents/adults (N = 21), a phase III randomized trial of StrataGraft® versus STSG in adults with deep partial-thickness burns (N = 71), and a large retrospective pediatric cohort (N = 205) evaluating a single dermal substitute applied to deep partial burns (with a subset later requiring STSG). No other head-to-head trials meeting the prespecified criteria were published during the review interval (Table 1 & 2).

Table 1. Study Characteristics

Author	Country	Study Design	Population (N) (Year)
Meuli et al. (2025)	Switzerland	Phase IIb RCT	Adolescents and adults (21)
Gibson et al. (2021)	United States	Phase III RCT	Adults with deep partial burns (71)
Bergus et al. (2024)	United States	Retrospective cohort	Pediatric burns (205)

Table 2. Intervention and Comparator

Author	Intervention	Comparator
Meuli et al.	denovoSkin autologous cultured dermo epidermal graft	Meshed STSG
Gibson et al.	StrataGraft allogeneic cellular bilayer	STSG
Bergus et al.	PriMatrix acellular dermal matrix	STSG subset

Graft take and donor-site sparing were consistent themes across studies. In the denovoSkin trial, early graft “take” was superior with STSG (mean 90.4% of graft area) compared with the engineered dermo-epidermal construct (72.6%; $p = 0.008$), but the engineered product permitted far greater expansion: mean expansion ratio ≈ 10.8 for denovoSkin versus 1.7 for STSG (≈ 7.4 -fold difference; $p < 0.001$) (Table 3).^{VI}

Time to complete epithelialization showed important differences by modality. The denovoSkin trial reported a median time to closure of 63 days for engineered grafts versus 24 days for STSG; however, all treated sites in both

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arms achieved full epithelialization by three months.^{VI} The pediatric series reported faster median healing for wounds that ultimately closed with substitute alone (median 21 days) compared with those that later required STSG (median 44 days; $p < 0.001$).^{VII} The StrataGraft cohort achieved durable closure in 92% of patients by month 3 without need for additional grafting. Thus, although engineered substitutes sometimes delay early closure compared with immediate autografting, most substitute-treated wounds reached complete epithelialization within 1–3 months (Table 3).^{VIII}

Infection and safety signals were generally low and manageable. In the denovoSkin study three superficial wound infections occurred in denovoSkin-treated sites (3/15 reported treated areas); these resolved with conservative therapy and did not produce systemic complications.^{VI} The pediatric series found fewer infections in substitute-only patients than in those who ultimately required grafting (2.9% vs 12.5%; $p = 0.029$).^{VII} The StrataGraft trial reported no serious device-related infections. Overall, serious substitute-related sepsis was rare across studies (Table 3).^{VIII}

Table 3. Clinical Outcomes

Author	Graft Take	Epithelialization	Infection
Meuli et al.	72.57 percent vs 90.36 percent	63 vs 24 days	3 superficial infections
Gibson et al.	Not reported	92 percent closure by 3 months	No serious infections
Bergus et al.	Not reported	21 vs 44 days	2.9 percent vs 12.5 percent

Length of stay (LOS) and resource outcomes were sparsely reported but suggest potential benefit from donor-sparing technologies. In the pediatric cohort, postoperative LOS normalized per %TBSA was shorter for patients healed by substitute alone (median 0.4 days/%TBSA) than for those requiring STSG (median 0.9 days/%TBSA; $p = 0.002$).^{VII} While randomized trials provided limited LOS data, the large reduction in autograft area seen with StrataGraft implies reductions in operative burden, donor-site morbidity, and likely total recovery time (Table 4).^{VIII}

The StrataGraft phase III trial demonstrated a profound reduction in autograft requirement, by three months only 4.3% of the original burn area in the StrataGraft arm required subsequent autografting compared with a control group that ultimately required autograft coverage to an area exceeding the original index area (reported as 102.1% of the baseline area), corresponding to a ~96% net reduction in area grafted with autologous skin.^{VIII} In the pediatric dermal-substrate cohort, 84.4% of patients healed without autograft; only 15.6% required later STSG. Collectively, these data

indicate that while some engineered constructs achieve lower immediate take rates, they can substantially spare donor skin by enabling greater coverage per unit of applied material (Table 4).^{VII}

Scar quality and functional results tended to favor bioengineered approaches or hybrid strategies. The denovoSkin trial documented minimal hypertrophic scarring at 12 months in substitute-treated sites versus a greater frequency of hypertrophic change at STSG donor/recipient sites.^{VI} In the pediatric cohort contracture rates were lower after substitute-only treatment (5.8% vs 15.6%; $p = 0.045$). Additional comparative reports such as immediate placement of Integra® in small pediatric series and use of Matriderm® beneath STSG in hand burns reported improved scar appearance and hand function versus STSG alone. Cellular allografts (Apligraf®) used as overlays have been associated with enhanced graft vascularity, pigmentation, and pliability in limited reports. Taken together, the evidence suggests that next-generation substitutes can produce equal or superior long-term aesthetic and functional outcomes compared with STSG in selected indications (Table 4).^{VII}

denovoSkin appears to have the highest projected cost on a per-area basis, with a minimum estimated price of about €28/cm². StrataGraft is approximately US\$48/cm², based on a US\$4,800 price for a ~100 cm² film, while PriMatrix is approximately US\$5.86/cm², based on a US\$375 listing for an 8 × 8 cm sheet. These data are best interpreted as list or projected prices rather than study-specific costs, so they are useful for broad comparison but not direct economic equivalence (Table 4).

Table 4. Resource Use and Additional Outcomes

Author	LOS or Resource Use	Reoperation or Autograft	Scar Outcome	Cost
Meuli et al.	Not reported	Not reported	Less hypertrophic scarring	about 28 euro per cm ²
Gibson et al.	Reduced donor burden	4.3 percent vs 102.1 percent	Favorable outcomes	about 42 USD per cm ²
Bergus et al.	0.4 vs 0.9 days per TBSA	15.6 percent required STSG	Lower contracture	about 5.9 USD per cm ²

Two randomized trials were assessed using RoB 2 and showed overall some concerns, mainly due to small sample

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size, limited protocol transparency, and lack of blinding in surgical designs. Objective outcomes such as wound closure and autograft requirement were less affected by bias, whereas subjective outcomes like scarring were more vulnerable (Figure 2). The retrospective pediatric cohort, evaluated with ROBINS I, was judged at serious risk of bias due to confounding and selection bias. Although it provided useful clinical insights, its nonrandomized design limits reliability. Overall, evidence quality was moderate, with stronger confidence in objective outcomes than subjective measures (Table 5).



Figure 2. Risk of bias graph, review authors' judgements about each risk of bias item presented as percentages across all included studies.

Table 5. ROBINS I risk of bias summary

Aut hor	Confound ing	Selecti on	Interventio n	Oth er	Ove rall Bias
Bergus (2024)	Serious	Moderate to serious	Low to moderate	Moderate	Serious

IV.DISCUSSION

Bioengineered skin substitutes including acellular dermal templates, cellular allografts, and laboratory-generated autologous dermo-epidermal constructs represent a rapidly maturing armamentarium that can substantially alter the reconstructive pathway for deep partial- and full-thickness burns. Our systematic review of comparative studies (denovoSkin™, StrataGraft®, and a large pediatric dermal-matrix cohort) aligns with broader evidence indicating that modern dermal substitutes provide effective wound coverage, reduce reliance on donor STSG, and can restore more normal dermal architecture than STSG alone. This donor-sparing potential is especially valuable for large-area and pediatric burns where autologous donor availability is limited and donor-site morbidity is clinically important. For comprehensive summaries of clinical applications, mechanisms of dermal regeneration, and clinical outcomes across contemporary dermal matrices and cellular constructs, see recent open-access syntheses.^{IX}

Although donor-site sparing and the quality of regenerated dermis are consistent benefits, the trade-off in several comparative reports is a slower early epithelialization trajectory compared with immediate STSG. In the trials and cohorts included in our review, engineered constructs sometimes showed lower early “take” or a longer median time to complete epithelial closure, yet most substitute-treated sites achieved durable epithelialization within 1–3 months and avoided repeat grafting. The mechanistic basis for this pattern is well described in the recent literature: dermal templates and cellular grafts first establish a neodermal scaffold (and/or require in-situ keratinocyte in-growth), which then supports secondary epithelialization; this regenerative sequence tends to prolong initial wound closure time but improves dermal quality and reduces contracture risk. For a detailed discussion of healing kinetics and clinical protocols for timing of secondary coverage, please see current clinical reviews of dermal regeneration templates and staged reconstructive algorithms.¹⁰

Safety and infectious-complication signals in comparative work have been reassuring: reported substitute-related serious infections and systemic complications were rare across randomized trials and the large pediatric cohort, and some series even found lower superficial infection rates in substitute-only patients versus those requiring later STSG. These clinical safety outcomes are supported by contemporary practice guidelines and expert syntheses emphasizing meticulous pocket creation, sterile handling, and early recognition/removal of infected material when necessary. In addition, several open-access analyses describe how modern dermal matrices and cellular scaffolds, when combined with appropriate perioperative antibiotic stewardship and wound care, can lower donor-site morbidity and overall procedure burden factors that likely contribute to the favorable infection and recovery profiles observed in clinical studies.^{IX}

Perhaps the most compelling long-term signal in the included comparative data is improved scar quality and function following many substitute-based or hybrid (template + STSG) strategies. Across randomized and cohort reports, substitute-treated sites showed fewer hypertrophic changes, lower contracture rates, and better pliability and pigmentation compared with conventional STSG or donor-site morbidity associated with extensive autografting. These superior aesthetic and functional outcomes reflect the capacity of dermal matrices and living constructs to recreate a neodermis that more closely approximates native skin biomechanics and microarchitecture an effect also described in recent translational and clinical reviews that summarize histologic, biomechanical, and patient-reported outcomes after dermal-regenerative techniques. Taken together, the evidence supports a paradigm in which next-generation substitutes

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either replace or complement STSG to improve long-term reconstruction goals while conserving donor resources.^X

In pediatric burn care, acellular dermal matrices are particularly useful because autografting may be difficult when donor skin is limited. A recent pediatric burns review noted that skin autografting may be unfeasible or unlikely to succeed when donor areas are limited or inadequate, and a pediatric dermal-substrate cohort found that 84.4% of children healed without autograft. This supports the use of acellular dermal matrix in children as a donor-site-sparing strategy that can reduce the need for additional skin harvest.^{XI} For pediatric burns, ADM is especially relevant because donor-site scarcity is a key issue and cost-effectiveness is part of the rationale for its use. A systematic review of pediatric burns specifically highlighted donor-site scarcity, scar minimization, and cost-effectiveness as important considerations for ADM, and found overall improvements in healing and scarring outcomes.^{XII}

From a health-economic perspective, the included products appear to sit at different points on the cost spectrum. denovoSkin™ has a projected minimum price of €28/cm², reflecting the complexity of an autologous engineered construct. StrataGraft® is supplied as an approximately 100 cm² sheet, and in its phase III trial it reduced the mean area requiring autografting by 96% by 3 months; this suggests that a higher upfront product cost may be partly offset by fewer donor-site harvests and fewer reoperations.^{VI}

The clinical promise of next-generation bioengineered skin substitutes is particularly relevant for developing settings such as Indonesia, where donor-site limitation and delayed access to specialized burn care remain important barriers. However, their real-world implementation is still constrained by several translational requirements, including regulatory review, scalable manufacturing, and reliable distribution, and current reviews note that no commercially available product yet fully satisfies all clinical objectives. In low- and middle-income burn systems, additional barriers include limited infrastructure, shortage of trained personnel, intensive care monitoring gaps, and restricted access to burn centers and skin banks; in India, for example, only 15% of the population lives within a two-hour drive of a burn center equipped with both an ICU and a skin bank. On that basis, broad adoption in Indonesia should be considered feasible mainly in tertiary referral centers, while more accessible substitutes or donor-sparing strategies may be more practical in routine care.^{XIII}

Despite promising and consistent trends, the current evidence base remains limited. The number of head-to-head randomized trials is small, with substantial heterogeneity in substitute types, outcome definitions, and follow-up duration, making cross-study comparison difficult. Standardized endpoints such as uniform graft-take criteria, blinded scar assessment, and consistent infection metrics are

still lacking. In addition, none of the included studies provide robust cost-effectiveness analyses; available data are largely based on list or projected prices rather than real-world economic evaluations, limiting conclusions about value in routine practice. From an implementation perspective, the applicability of these technologies in low- and middle-income settings, including Indonesia, remains uncertain. Barriers such as high upfront costs, manufacturing complexity, regulatory requirements, and limited access to specialized burn centers may restrict widespread adoption to tertiary referral facilities. These constraints are particularly relevant when considering scalable integration into national burn care systems.

Future research should therefore prioritize large, multicenter pragmatic randomized trials with standardized outcome measures and longer follow-up. These studies should incorporate patient-reported outcomes, donor-site morbidity (pain, healing), and detailed healthcare utilization, alongside formal cost-effectiveness analyses. Such data are essential to refine patient selection criteria and to determine whether the clinical benefits of bioengineered skin substitutes translate into meaningful system-level advantages, especially across diverse healthcare settings.

V. CONCLUSIONS

Bioengineered skin substitutes are effective alternatives to autologous STSG in deep burns. They reliably achieve wound closure with outcomes that match or exceed standard grafting in terms of pain, infection, and scar quality, while markedly reducing the need for donor skin (expansion ratios ~7–10× in recent trials). The main drawback is typically slower time to full healing, which must be weighed against the advantage of avoiding additional surgeries. In practice, a combined approach (dermal matrix plus thin STSG) or a one-stage substitute (like denovoSkin) may optimize both closure speed and long-term quality. Future multicenter trials and cost-effectiveness analyses are needed to define the best role for each substitute type in pediatric and adult burn care.

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