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Current Algorithms for Non-Surgical Management of Hypertrophic Scars and Keloids: An Updated Narrative Review

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Abstract:

Pathological scarring, encompassing hypertrophic scars and keloids, results from dysregulated wound healing characterised by persistent fibroblast activation, excessive collagen deposition, and abnormal profibrotic signalling pathways, leading to high recurrence rates and significant functional, cosmetic, and psychosocial burden. This narrative review evaluates current evidence-based non-surgical management strategies and emerging regenerative approaches, with emphasis on stepwise escalation and multimodal treatment algorithms. Silicone-based therapies remain the preferred first-line intervention due to their favourable safety profile and preventive efficacy, while intralesional corticosteroids continue to represent the cornerstone of second-line management, with botulinum toxin type A emerging as a steroid-sparing alternative through antifibrotic and neuromodulatory effects. For refractory lesions, intralesional 5-fluorouracil provides effective second-line escalation by directly inhibiting fibroblast proliferation, particularly when combined with corticosteroids. Laser-based modalities further enhance non-surgical management, with pulsed dye laser targeting vascular components and fractional CO_2 laser promoting dermal remodelling and improved drug delivery, with superior outcomes consistently reported in combination protocols compared to monotherapy. Across network meta-analyses, combination regimens incorporating corticosteroids, antimetabolites, lasers, and adjunctive modalities demonstrate improved scar appearance, symptom control, and recurrence prevention, supporting a multifactorial disease model. Long-term outcomes are strongly influenced by adjuvant strategies such as pressure therapy, tension reduction techniques, and structured postoperative surveillance, alongside patient-specific factors including age, ethnicity, anatomical location, and psychosocial burden, reinforcing the need for individualised treatment planning. Emerging regenerative therapies, including platelet-rich plasma, mesenchymal stem cells, and extracellular vesicle-based approaches, demonstrate promising antifibrotic and immunomodulatory effects in preclinical and early clinical studies, but remain limited by heterogeneity, small sample sizes, and lack of standardised protocols. Overall, current evidence supports a paradigm shift toward risk-stratified, combination-based, and biologically targeted management strategies aimed not only at scar reduction but also at durable long-term control and recurrence minimisation.

Keywords: Hypertrophic Scar, Keloid, Scar Management

Abbreviations:

5-FU - 5-Fluorouracil

BoNT-A - Botulinum Toxin Type A

ECM - Extracellular Matrix

EV - Extracellular Vesicle

MSC - Mesenchymal Stem Cell

PDL - Pulsed Dye Laser

PRP - Platelet-Rich Plasma

SGS - Silicone Gel Sheeting

SUCRA - Surface Under the Cumulative Ranking

SVF - Stromal Vascular Fraction

TAC - Triamcinolone Acetonide

TGF-β - Transforming Growth Factor-beta

Introduction and Background:

Keloids and hypertrophic scars are fibroproliferative disorders that arise from dysregulated wound healing characterized by excessive collagen deposition and extracellular matrix accumulation [1,3]. Although closely related, they remain clinically distinct entities. Keloids extend beyond the boundaries of the original wound, persist without spontaneous regression, and often demonstrate continued growth over time. In contrast, hypertrophic scars remain confined within the original wound margins, typically develop within weeks of injury, and may gradually regress over months to years [1,3]. This distinction is clinically important as it affects treatment selection, recurrence risk, and long-term outcomes.

The burden of keloids and hypertrophic scars extends beyond their visible appearance and encompasses functional, cosmetic, and psychosocial consequences. Functionally, scar contracture and reduced tissue elasticity may impair mobility, particularly when scars involve joints or areas subjected to repetitive movement, as commonly observed following burns. Symptoms such as pain, pruritus, stiffness, and recurrent inflammation may further affect daily activities and quality of life. Recurrent disease often necessitates repeated interventions, increasing both treatment burden and healthcare utilization. The cosmetic and psychosocial impact is equally significant. Keloids frequently present as raised, discolored lesions often in highly visible anatomical sites such as the face, neck, and earlobes, whereas hypertrophic scars commonly produce abnormal texture, pigmentation changes, and contour irregularities following burns or deep tissue injury. These visible alterations may negatively affect self-image, social interactions, and psychological wellbeing. Consequently, treatment success is increasingly evaluated not only through objective scar characteristics but also through patient-reported quality-of-life outcomes [1,2,3].

Management remains challenging because of the high recurrence rates associated with both conditions and the absence of a universally accepted gold-standard treatment. Historically, surgical excision, radiotherapy, laser therapy, and various topical approaches have been used with variable success, with monotherapy frequently producing suboptimal outcomes, particularly in keloids. This has driven increasing interest in multimodal treatment strategies combining surgical, intralesional, topical, and adjuvant therapies to improve long-term disease control [1,3].

This, along with the considerable heterogeneity within the current literature, highlights the need for algorithm-based management. Shen et al. evaluated 162 studies observing keloid and hypertrophic scar therapies, and reported substantial variation in treatment protocols, outcome measures, and study design, limiting direct comparison and preventing robust quantitative synthesis [3]. This was supported by an evidence-based review of 108 prospective studies, where marked heterogeneity across interventions and outcome reporting restricted pooled analysis despite the large volume of available evidence [1]. Collectively, these findings emphasize the need for structured treatment algorithms capable of guiding clinical decision-making while identifying priorities for future research [1,2,3].

Over the past decade, management strategies have progressively shifted away from surgery-centered approaches toward minimally invasive and non-surgical therapies. Although surgery remains important for selected resistant or extensive lesions, contemporary treatment increasingly relies on intralesional therapies, topical agents, and mechanical therapies [1,2]. Consequently, contemporary treatment paradigms for both keloids and hypertrophic scars increasingly emphasize individualized, multimodal, and predominantly non-surgical approaches tailored to scar characteristics, symptom burden, and recurrence risk. This transition reflects growing recognition that long-term control often depends on modulation of scar biology rather than excision alone.

I. Pathophysiology and Scar Biology

Forming a deep understanding of the pathophysiology involved in wound healing, and cellular biology of scar tissue is vital in deciding management, as minute factors influence the result. Physiological wound healing is a highly regulated process consisting of three overlapping phases: inflammation, proliferation, and remodeling. These phases are coordinated through dynamic interactions between immune cells, fibroblasts, keratinocytes, blood vessels, cytokines, and extracellular matrix (ECM) components. The inflammatory phase begins immediately after tissue injury and involves platelet activation, coagulation signaling, and recruitment of neutrophils and macrophages responsible for pathogen elimination and clearance of cellular debris. Under physiological conditions, this response is self-limited and transitions into the proliferative phase, during which fibroblast migration, angiogenesis, keratinocyte proliferation, and ECM deposition occur. The subsequent remodeling phase is characterized by collagen reorganization, progressive reductions in cellularity and vascularity, and replacement of immature type III collagen with structurally stronger type I collagen, ultimately resulting in scar maturation and restoration of tissue strength [2,3].

Pathological scarring, however, develops when the balance between ECM synthesis and degradation is disrupted, leading to prolonged inflammation, persistent fibroblast activity, and excessive collagen deposition. Hypertrophic scars and keloids are therefore regarded as fibroproliferative wound disorders characterized by dysregulation of multiple wound-healing pathways. Impaired ECM turnover results in excessive accumulation of matrix components and persistent deposition of immature type III collagen relative to type I collagen, contributing to tissue fibrosis, scar thickening, and prolonged persistence of an immature scar architecture. Fibroblast dysregulation appears central to this process. Pathological fibroblasts demonstrate increased proliferative activity, resistance to apoptosis, excessive ECM production, and enhanced differentiation into myofibroblasts, collectively driving progressive fibrosis and scar elevation [2,3].

Among the molecular mediators involved in scar fibrosis, transforming growth factor-beta (TGF-β) is considered one of the principal profibrotic cytokines. The TGF-β axis regulates multiple stages of wound healing, including inflammatory cell recruitment, angiogenesis, fibroblast proliferation, myofibroblast differentiation, keratinocyte migration, and ECM remodeling. However, the biological effects of TGF-β vary according to isoform. TGF-β1 and TGF-β2 are predominantly profibrotic, whereas TGF-β3 has been associated with antifibrotic effects and a more regenerative pattern of wound healing. Persistent activation of TGF-β-dependent signaling pathways promotes sustained fibroblast activation and excessive collagen production within pathological scars. Emerging evidence further suggests that transcription factors such as Foxn1 may influence scar formation through modulation of TGF-β isoform expression [2].

The pathogenesis of keloids is believed to result from an interaction between genetic predisposition and cutaneous injury, highlighting the combined influence of molecular susceptibility and local environmental factors such as chronic inflammation and mechanical tension. Despite partially overlapping histopathological features, hypertrophic scars and keloids differ substantially in their biological behavior. Hypertrophic scars remain confined to the original wound boundaries and may undergo partial spontaneous regression over time. In contrast, keloids extend beyond the margins of the initial injury, rarely regress spontaneously, and typically follow a more persistent clinical course. These differences suggest a greater degree of dysregulation within the fibroproliferative response in keloid formation [3].

Recurrence remains the major challenge in the management of hypertrophic scars and keloids. Persistent fibroblast activation, ongoing collagen synthesis, chronic inflammation, repeated trauma, mechanical tension, and incomplete suppression of profibrotic signaling pathways have all been implicated in recurrent scar formation [2]. Recurrence is therefore believed to reflect continued cytokine signaling and collagen production by residual biologically active fibroblasts within scar tissue. This likely explains the poor outcomes associated with monotherapy, particularly surgical excision alone, where recurrence rates have been reported to reach 70-100% [3]. In contrast, multimodal approaches combining surgical excision with adjuvant therapies such as radiotherapy or corticosteroid injections consistently demonstrate lower recurrence rates and improved outcomes across multiple

studies. Collectively, these findings highlight the importance of targeting both inflammatory and fibroproliferative pathways when managing pathological scars [2,3].

II. First-line Non-surgical Management: Silicone Therapy

Silicone-based therapies, including silicone gel sheeting (SGS) and topical silicone gel, are widely regarded as first-line non-surgical interventions for hypertrophic scars and keloids. Their favourable safety profile and ease of application make them consistently recommended ahead of other conservative modalities such as pressure therapy, intralesional corticosteroids, laser therapy, and cryotherapy, across evidence-based guidelines [5]. These two formulations differ primarily in delivery method, while sharing a similar underlying mechanism of action.

Silicone gel sheeting consists of a soft, medical-grade occlusive dressing applied directly over the scar surface. It conforms to the skin, maintains hydration, and is generally well tolerated in patients experiencing pain, pruritus, restricted mobility, or psychosocial distress related to visible scarring. The proposed mechanism of silicone therapy is primarily based on hydration and occlusion. Hypertrophic and keloid scars demonstrate impaired barrier function, leading to transepidermal water loss and a microenvironment that promotes fibroblast activation and excessive collagen deposition [4]. Silicone modulates this pathway by maintaining local hydration, thereby reducing fibroblast stimulation and attenuating collagen synthesis. In addition, occlusion alters the local biochemical environment, facilitating cytokine diffusion that may further suppress fibrotic signalling. Thermal effects generated beneath the occlusive layer may also contribute to gradual collagen remodelling and scar softening. Collectively, these mechanisms suggest a combined physical and biochemical effect, although the relative contribution of each pathway remains incompletely defined [4,5].

Despite widespread clinical use, high-certainty evidence remains limited. A 2023 Cochrane review by Tian et al, identified only two eligible randomized controlled trials involving 36 patients following screening of 484 records [4]. Within these studies, only one demonstrated statistically significant improvement in scar characteristics such as thickness, colour, and pliability, while the second showed no meaningful difference compared with control. Hence, the overall certainty of evidence was low due to small sample size, short follow-up duration, and risk of performance bias, with both trials lacking robust patient-reported outcome assessment and adverse effect reporting [4]. Nevertheless, this reflects limited high-quality evidence, rather than the absence of therapeutic effect.

Comparative evidence suggests limited clinical difference between silicone gel and silicone sheeting. An intraindividual randomized controlled trial by Pruksapong et al. demonstrated that both formulations produced significant improvement in scar thickness, stiffness, and texture compared with pressure therapy alone, with no statistically significant difference between the two modalities throughout follow-up [5]. A systematic review within the same analysis, incorporating seven randomized trials, confirmed similar outcomes across both forms. Consequently, selection is largely determined by practical considerations including anatomical location, patient compliance, environmental conditions, and cost [5].

Silicone therapy demonstrates stronger evidence in scar prevention than in established disease treatment. A meta-analysis of ten trials by Zhu et al. reported a relative risk of 0.70 (95% CI 0.49-0.99) for hypertrophic scar formation with prophylactic SGS use compared with control [7]. This supports its role in early postoperative or post-injury phases, particularly following burns, surgical incisions, or traumatic wounds. In contrast, evidence for established keloids remains less consistent, with the Cochrane review (Tian et al) failing to demonstrate superiority over placebo, alternative dressings, or intralesional corticosteroids [4]. However, this inconsistency is largely attributable to underpowered and methodologically limited studies rather than confirmed inefficacy, and silicone therapy continues to be used due to its safety and biological plausibility.

Timing of initiation, is a key determinant of effectiveness. Silicone therapy is typically commenced once complete re-epithelialisation has occurred, coinciding with peak fibroblast activity during early scar maturation. Recommended regimens vary by indication, with keloid-prone patients advised to use silicone for at least 12 hours daily over three to six months, while burn protocols frequently recommend near-continuous application up to 23 hours per day. Daily hygiene and prolonged adherence remain practical limitations, particularly in humid climates, where compliance is frequently reduced. In this context, topical silicone gel offers a functional advantage by providing a non-occlusive alternative suitable for mobile, curved, or exposed anatomical sites where sheeting is poorly tolerated or impractical [4,5].

III. Intralesional Therapy

Intralesional therapy represents the next escalation in the management of hypertrophic scars and keloids when conservative modalities such as silicone-based therapy, pressure therapy, and topical agents fail to achieve adequate response. This approach involves direct delivery of pharmacological agents into scar tissue to modulate fibroproliferative activity and extracellular matrix deposition. Among these, intralesional corticosteroids, particularly triamcinolone acetonide (TAC), remain the most widely used first-line injectable therapy due to their established anti-inflammatory, antiproliferative, and collagen-suppressive effects [1]. However, variability in response and a well-recognized adverse effect profile have driven increasing interest in steroid-sparing alternatives such as botulinum toxin type A (BoNT-A) [2].

Intralesional Corticosteroids: Triamcinolone Acetonide

Triamcinolone acetonide is considered the standard intralesional agent for both hypertrophic scars and keloids. Its mechanism of action is multifactorial, involving suppression of fibroblast proliferation, inhibition of collagen types I and III synthesis, and downregulation of transforming growth factor-β (TGF-β), a key profibrotic mediator. Additional effects include reduced glycosaminoglycan production, inhibition of angiogenesis, and local vasoconstriction, collectively leading to decreased cellular metabolism within the scar and progressive reduction in scar height, erythema, induration, pain, and pruritus [1].

Despite these well-characterized biological effects, clinical response remains heterogeneous. While some hypertrophic scars demonstrate marked regression following serial TAC injections, keloids frequently exhibit only partial response and recurrence after initial improvement. This variability likely reflects differences in fibroblast phenotype, collagen turnover, inflammatory signalling, lesion chronicity, and mechanical tension across anatomical sites [1]. Lesions in high-tension areas and established keloids generally demonstrate reduced responsiveness and higher recurrence rates, highlighting the importance of multimodal and individualized treatment strategies rather than corticosteroid monotherapy alone.

Adverse effects further limit long-term tolerability. Common complications include dermal atrophy, hypopigmentation, telangiectasia, localized pain, delayed healing, and, in cases of extralesional spread, subcutaneous fat atrophy and ulceration [1]. These effects are dose- and frequency-dependent, increasing with repeated administration. Consequently, balancing efficacy with safety remains a major limitation of corticosteroid-based intralesional therapy and has contributed to the development of adjunctive and alternative injectable modalities.

Botulinum Toxin Type A versus Corticosteroids

Botulinum toxin type A (BoNT-A) has emerged as a potential alternative or adjunctive intralesional therapy for hypertrophic scars and keloids. Unlike corticosteroids, BoNT-A does not directly suppress fibroblast activity through anti-inflammatory pathways but instead modulates scar biology through neuromuscular blockade. By inhibiting acetylcholine release at the neuromuscular junction, BoNT-A reduces local muscle tension and mechanical stress, both of which contribute to scar progression, particularly in keloids where mechanotransduction pathways play an important role in persistent fibroproliferation [2].

Beyond its biomechanical effects, BoNT-A has been associated with modulation of inflammatory signalling and reduction of pain and pruritus, likely through effects on peripheral nerve activity within scar tissue [2]. Compared with corticosteroids, it is also associated with a more favourable local safety profile, with minimal risk of dermal atrophy, hypopigmentation, or telangiectasia. However, its adoption remains limited by smaller studies, heterogeneous treatment protocols, and a comparatively shorter evidence base.

Current evidence suggests that BoNT-A may achieve comparable, and in some parameters superior, outcomes to intralesional corticosteroids, including improvements in scar flattening, pliability, and symptom relief. Several studies have also reported greater reductions in pain and pruritus, supporting a potential neuromodulatory advantage [2]. Nevertheless, corticosteroids remain the reference standard because of extensive clinical experience and a more robust evidence base. At present, BoNT-A is best positioned as a steroid-sparing or adjunctive option in selected patients, particularly those with steroid intolerance or refractory disease [2].

IV. Antimetabolite Therapy – Second-line Escalation

Among non-surgical options for keloids and hypertrophic scars, intralesional 5-fluorouracil (5-FU) is one of the most extensively studied second-line therapies, particularly in steroid-refractory lesions. 5-FU is a pyrimidine antimetabolite that inhibits thymidylate synthase, disrupting DNA synthesis and reducing the proliferation of rapidly dividing fibroblasts. This results in decreased collagen synthesis, reduced extracellular matrix deposition, and suppression of the fibroproliferative activity central to keloid progression [7].

The therapeutic rationale for 5-FU is based on the central role of hyperactive fibroblasts in pathological scar formation. Experimental and clinical evidence demonstrates that 5-FU reduces fibroblast proliferation and promotes apoptosis within scar tissue, directly targeting the cellular drivers of abnormal wound healing. Unlike corticosteroids, which primarily exert anti-inflammatory and antifibrotic effects, 5-FU acts directly at the level of cellular replication and matrix production [7].

In clinical practice, intralesional 5-FU is most commonly used for corticosteroid-resistant or recurrent keloids. Studies have demonstrated improvements in scar height, pliability, erythema, pain, and pruritus. However, monotherapy is limited by local adverse effects including injection-site pain, ulceration, and post-inflammatory pigmentary changes, restricting its use as a first-line intervention [7].

Current evidence increasingly supports combination regimens, particularly 5-FU with triamcinolone acetonide. This approach combines corticosteroid-mediated suppression of inflammatory and TGF-β-driven fibrotic pathways with direct fibroblast inhibition by 5-FU, resulting in improved outcomes compared with either treatment alone. Combination therapy has also demonstrated improved tolerability, as corticosteroids may mitigate some of the local adverse effects associated with 5-FU while maintaining efficacy [7].

Overall, intralesional 5-FU, particularly when combined with corticosteroids, represents an effective second-line escalation strategy for resistant keloids and recurrent disease. Its complementary mechanism of action and favourable efficacy profile make it a valuable extension of standard intralesional therapy.

V. Laser-Based Non-Surgical Management

Laser-based therapies represent an important component of modern multimodal management of hypertrophic scars and keloids, particularly when used in combination regimens rather than as isolated interventions. Among vascular-targeted modalities, pulsed dye laser (PDL) remains one of the most widely studied techniques. Operating at a wavelength of 585 nm, PDL primarily targets microvascular components within scar tissue, reducing erythema and vascular congestion. It is frequently combined with non-ablative or ablative fractional CO_2 lasers to address both vascular and structural components of pathological scars; however, reported efficacy and durability remain variable, necessitating patient-specific selection and cautious interpretation of outcomes [8].

PDL demonstrates particular benefit in erythematous and actively inflamed scars, where vascular proliferation and redness are predominant features. In these cases, it contributes to reduction in erythema and improvement in overall scar appearance, especially when integrated into combination protocols [8]. However, its isolated effect on scar texture and thickness remains limited, reinforcing its role as an adjunct rather than standalone therapy.

In contrast, fractional CO_2 laser functions primarily as a tissue remodelling modality. It creates controlled microthermal zones of partial ablation within scar tissue, inducing collagen remodelling and reorganisation of dermal architecture. This leads to reduction in scar thickness, stiffness, and irregularity, while also improving penetration of topical or intralesional agents when used in combination regimens [10]. Consequently, fractional CO_2 is increasingly utilised not only for structural remodelling but also as a drug-delivery adjunct within multimodal protocols.

Combination therapy using PDL and fractional CO_2 laser has demonstrated superior outcomes compared with monotherapy approaches. A systematic review and meta-analysis including 247 patients reported significant improvements in Vancouver Scar Scale, Observer Scar Assessment Scale, and Patient and Observer Scar Assessment Scale scores, with mean differences of -3.80, -19.44, and -18.09 respectively, indicating consistent superiority of combined modalities over control groups [9]. Importantly, adverse effects remained minimal, supporting the safety and synergistic efficacy of this approach.

Laser-assisted delivery combined with intralesional corticosteroids represents another widely studied strategy, particularly fractional CO_2 combined with triamcinolone acetonide. Fractional ablation enhances dermal permeability, allowing improved corticosteroid penetration while simultaneously contributing to structural remodelling of scar tissue. A pooled analysis of 19 randomised clinical trials involving 1,775 patients demonstrated significant reductions in Vancouver Scar Scale, pain, pruritus, and scar thickness, with mean differences of 2.52, -1.04, -0.86, and SMD of -2.36 respectively compared with steroid monotherapy [10]. Additionally, reductions in fibrotic and angiogenic mediators including TNF-α, VEGF, EGF, and TGF-β1 were observed, suggesting modulation of key pathogenic pathways involved in scar formation.

From a safety perspective, fractional CO_2 combined with triamcinolone did not demonstrate increased rates of erythema, infection, ulceration, or pigmentation changes compared with corticosteroid monotherapy, indicating a favorable safety profile alongside improved efficacy [10]. However, methodological limitations across included trials highlight the need for more standardised, high-quality comparative studies.

Scar maturity remains an important determinant of laser response. Evidence suggests that both early and mature scars may respond to fractional CO_2 and PDL-based therapies, although outcomes remain heterogeneous across studies [9]. Some data support early intervention within the first six months of scar formation, while other studies demonstrate benefit in established mature scars, reflecting a lack of

consensus regarding optimal timing. This variability highlights the need for clearer stratification of patients based on scar age and biological activity, rather than uniform treatment protocols [9].

Overall, laser-based therapy functions most effectively as part of a staged, combination-based approach rather than a standalone modality. Its role is best understood within a broader multimodal framework that targets vascular activity, dermal remodelling, and enhanced drug delivery, with increasing emphasis on patient-specific and scar-stage-guided treatment planning.

VI. Combination and Advanced Intralesional Strategies

Why Monotherapy Fails:

For a long time, injecting TAC into keloid was used as a standard approach, and is still used widely. The problem is that TAC on its own simply does not deliver reliable results. Recurrence rates with TAC monotherapy range from 33% to 100%, which is a really wide and discouraging range[11]. To understand why, we have to look at what is actually happening inside a keloid.

Keloid formation is driven by several overlapping processes at once, fibroblasts keep multiplying when they should not, collagen is produced far in excess of what is needed, inflammation persists long after a wound should have healed, and new blood vessels grow in as to sustain all of this activity [12, 14]. A single drug can only target a few of these at a time. So while TAC reduces inflammation, it leaves fibroblast proliferation and collagen synthesis largely unchecked. 5-fluorouracil (5-FU) disrupts fibroblast DNA and triggers cell death, but its results when used alone are modest. Verapamil lowers collagen production yet consistently underperforms steroids. Bleomycin kills fibroblasts effectively but lacks strong standalone evidence. Even cryotherapy, which physically breaks down the fibrous tissue, carries high recurrence when used without support [13, 14]. The consistent message across the literature is clear that one drug is not enough, and the field has moved firmly toward combinations.

Intralesional Combination Therapies:

The logic behind combining treatments is straightforward, let's say if each agent targets a different part of the problem, together they cover more ground. TAC and 5-FU work through entirely different mechanisms. TAC suppresses inflammation while 5-FU shuts down fibroblast activity and collagen synthesis, so combining them attacks the scar from two sides simultaneously [11, 12]. A network meta-analysis by Chandra et al. (2025), which combined 22 randomised controlled trials and 1,398 patients, confirmed that TAC with 5-FU significantly outperformed TAC alone, with a relative risk of 1.43 (95% CI: 1.05 to 1.93) [11]. When pulsed dye laser (PDL) was added to this combination, results improved even further, reaching an RR of 2.98 (95% CI: 1.26 to 7.02). PDL works by targeting the blood vessels that feed the scar, cutting off the supply that keeps fibroblasts active.

TAC combined with bleomycin has become one of the most impressive options for keeping keloids from coming back. Bleomycin is cytotoxic to fibroblasts in a durable way, and it works alongside the anti-inflammatory action of steroids rather than overlapping with it [11, 12]. Sanchez Cruz et al. (2026), whose analysis covered 51 studies and 3,234 participants, found this combination ranked highest for recurrence prevention among all intralesional regimens, with a SUCRA score of 0.73 [12].

Botulinum toxin A has emerged as a genuinely exciting option. It relaxes myofibroblast contraction, reduces wound tension, disrupts fibroblast signalling pathways, and suppresses the TGF-beta activity that drives collagen overproduction [13]. Wu et al. (2023), covering 23 RCTs and 1,539 patients, found TAC plus Botulinum toxin A to be the most effective injectable combination tested, outperforming every monotherapy. Botulinum toxin A also happens to be the safest option as Sanchez Cruz et al. found Botulinum toxin A-based combinations were associated with significantly fewer adverse events than corticosteroids alone, with an RR of just 0.29 (95% CI: 0.09 to 0.95) [12]. High efficacy and low side effects is a rare combination in this field.

Cryotherapy paired with intralesional steroids is well supported, particularly for smaller, firm keloids. Freezing the tissue breaks apart the dense fibrous matrix, which allows the corticosteroid to penetrate more deeply than it could, while both treatments independently suppress the blood vessel activity that sustains fibroblast proliferation [14]. Feng et al. (2026), pooling 13 studies and 1,012 cases, showed a significantly higher excellent response rate for this combination compared to control interventions, with an RR of 1.19 (95% CI: 1.03 to 1.36, p = 0.01) [14]. The strongest benefit was seen against steroid alone.

Network Meta-Analysis Comparisons:

Network meta-analysis is the most useful tool we have for comparing multiple treatments at once. Unlike a standard trial that compares two options, network meta - analysis draws on both direct and indirect evidence across many studies, allowing researchers to rank treatments that have never been tested and compared. Three major network meta - analyses published between 2023 and 2026 now give us the clearest picture available.

Chandra et al. (2025) found that TAC with bleomycin reduced recurrence by 96% compared to TAC alone (RR = 0.04; 95% CI: 0.00 to 0.84), and TAC with 5-FU plus brachytherapy reduced it by 77% (RR = 0.23; 95% CI: 0.07 to 0.73), both reaching statistical significance [11].

Sanchez Cruz et al. (2026) expanded the scope to 51 studies across 23 different interventions and found that 5-FU combined with corticosteroids and YAG laser was the most effective regimen overall, with an RR of 2.73 (95% CI: 1.36 to 5.48) [12]. Adding a laser to attack the scar's blood vessels while simultaneously targeting fibroblast activity from two directions is a logical step, and the data backs it up. Interestingly, this larger dataset found no statistically significant differences in recurrence between

treatments, to which the authors attributed to short and inconsistent follow-up durations across the included trials rather than true equivalence [12].

Wu et al. (2023) focused on five injectable agents and found Botulinum toxin A alone already outperformed TAC and 5-FU in monotherapy settings, and that both TAC plus Botulinum toxin A and TAC plus 5-FU outperformed every agent used alone. Importantly, no statistically significant difference was found between these two top combinations in direct comparison [13].

Ranking of Treatments:

SUCRA (Surface Under the Cumulative Ranking) analysis takes network meta - analysis findings and converts them into probability based rankings, making it easier to build a treatment algorithm that is rooted in evidence rather than habit. Across all four meta-analyses reviewed, the same hierarchy keeps appearing.

For efficacy, Chandra et al. placed excision plus brachytherapy at the top (SUCRA = 95.11%), followed by excision plus TAC (94.99%), then TAC plus 5-FU plus PDL (75.48%), and TAC plus 5-FU (58.43%). TAC alone did not even cross the 50% probability threshold [11]. Wu et al. ranked TAC plus Botulinum toxin A first for injectable treatments (SUCRA = 96.7%), with TAC plus 5-FU a strong second (83.5%), and TAC alone near the bottom at 23.1% [13].

For recurrence prevention, which arguably matters more in the long run than short term improvement, TAC plus bleomycin ranked first in Chandra's analysis (SUCRA = 95.6%), which is then followed by excision plus brachytherapy (93.31%), cryotherapy plus TAC (73.99%), and TAC plus 5-FU plus brachytherapy (65.50%) [11]. Sanchez Cruz et al. similarly placed corticosteroids plus bleomycin (SUCRA = 0.73) and Botulinum toxin A (SUCRA = 0.69) at the top for recurrence reduction [12].

For safety, Botulinum toxin A and verapamil came out best across analyses. Sanchez Cruz et al. found Botulinum toxin A had the highest probability of fewest adverse events (SUCRA = 0.78), with corticosteroids plus Botulinum toxin A ranking first overall for safety (SUCRA = 0.92) [12]. Taken together, the rankings point toward a practical framework. For non surgical candidates who need strong results with low recurrence risk, TAC plus 5-FU plus PDL or TAC plus bleomycin are the evidence based first choices. For refractory or recurrent keloids where definitive control is the goal, excision plus brachytherapy leads consistently, though surgical risk must be factored in. For patients where tolerability is a priority, Botulinum toxin A based combinations offer a well supported, and a gentle route. Across all four analyses, one principle holds constant that no single combination fits every patient, and treatment must be tailored to the individual keloid, the patient's profile, and what is actually available [11, 12, 13, 14].

VII. Adjuvant Therapies and Special Populations: Complications, Recurrence Prevention, and Patient-Specific Considerations

Although first-line conservative therapies and intralesional interventions remain the cornerstone of non-surgical management for hypertrophic scars and keloids, long-term outcomes are largely determined by adjuvant strategies aimed at recurrence prevention and optimisation of scar remodelling. Increasingly, keloids are no longer conceptualised as isolated cutaneous lesions but rather as chronic fibroproliferative disorders with persistent dysregulation of wound-healing pathways [1]. The limitations of a purely lesion-centred approach have become evident through high recurrence rates and inconsistent long-term outcomes, reinforcing a shift toward patient-centred, mechanism-based management that targets the underlying biological drive of abnormal scarring [1,2].

Pressure Therapy and Compression Garments

Pressure therapy represents one of the most established adjuvant modalities in scar management. Rather than acting as a purely mechanical dressing, it functions as a biologically active intervention that modulates scar metabolism [3,4]. Sustained compression within the therapeutic range of approximately 15-25 mmHg has been shown to reduce scar thickness and vascularity by inducing a controlled hypoxic environment, thereby limiting oxygen and nutrient availability to metabolically active fibroblasts [4]. This downregulation of fibroblast activity results in reduced collagen synthesis and promotes gradual scar maturation and flattening [3].

Clinical efficacy is highly dependent on adherence, with optimal outcomes requiring prolonged daily use—often exceeding 20 hours per day over several months [3]. However, compliance remains a major limiting factor, particularly in long-term regimens, significantly influencing real-world effectiveness. Tahir et al. demonstrated in a systematic review and meta-analysis that compression therapy contributes to reductions in scar elevation and recurrence, particularly when integrated into multimodal protocols, with the greatest benefit observed following surgical excision where it functions primarily as a recurrence-prevention strategy rather than standalone therapy [3].

Recurrence Prevention Strategies

Recurrence remains the defining challenge in keloid management due to the persistent fibroproliferative activity that distinguishes these lesions from normal wound healing [1]. Modern strategies therefore prioritise minimising mechanical tension across wounds, as tension is a key driver of fibroblast activation and scar propagation [1]. This includes the use of tension-reducing closure techniques, careful wound planning, and prolonged postoperative immobilisation in high-risk anatomical regions.

Surveillance plays a central role in early recurrence detection, with clinical indicators such as induration, erythema, and progressive thickening serving as early warning signs of reactivation [2]. Early identification allows timely intervention before full re-establishment of keloid activity. Current evidence consistently demonstrates that monotherapy is associated with higher recurrence rates, whereas multimodal approaches provide superior long-term control [1,2].

Surgical Excision and Adjuvant Therapy

Surgical excision is no longer considered a curative intervention but rather a debulking procedure reserved for large, symptomatic, or refractory lesions [1]. Excision alone is associated with unacceptably high recurrence rates because it fails to address the underlying dysregulated wound-healing environment [1]. The immediate postoperative period represents a critical therapeutic window in which adjuvant therapies such as corticosteroid injections, radiotherapy, and silicone-based dressings are essential to suppress post-surgical fibroblast activation and reduce recurrence risk.

A systematic review and meta-analysis by Cardenas et al. similarly demonstrated improved outcomes when surgical excision was combined with structured adjuvant protocols, reinforcing the concept that surgery must be embedded within a broader multimodal strategy rather than used in isolation [2]. Consequently, contemporary treatment algorithms increasingly reserve excision for selected cases and emphasise mandatory adjunctive therapy to achieve durable long-term control.

Pediatric Considerations

Paediatric keloid management requires special consideration due to ongoing growth, psychosocial development, and differences in treatment tolerance. Beyond physical symptoms, keloids in children are associated with significant psychological burden, including reduced self-esteem, cosmetic distress, and social anxiety [5]. These factors expand treatment goals beyond scar reduction to include preservation of function, psychological wellbeing, and minimisation of treatment burden.

Minimally invasive approaches such as silicone-based therapy are often preferred due to better tolerability and safety profiles. In contrast, compression therapy may be limited by discomfort, heat intolerance, and poor long-term adherence in paediatric populations. Additionally, most treatment recommendations remain extrapolated from adult studies, reflecting a significant evidence gap in paediatric-specific scar management literature [5].

Early intervention is particularly important in children with known risk factors or family history of pathological scarring, as prompt management during early scar evolution may reduce progression to more aggressive disease phenotypes requiring complex interventions [5].

Ethnic Susceptibility and Racial Considerations

Ethnic background is a significant risk factor in keloid development, with individuals of African, Asian, and Hispanic descent demonstrating increased susceptibility and recurrence risk [6]. This necessitates more proactive preventive strategies following skin injury, surgery, or trauma, particularly in high-risk anatomical regions.

Treatment selection must also account for pigmentary safety, as dyschromia associated with certain therapies may significantly impact patient satisfaction, particularly in darker skin types. High-risk

populations may benefit from earlier intervention, closer surveillance, and more aggressive multimodal preventive strategies following cutaneous injury or surgical procedures [6].

Key Clinical Perspective

The evolving paradigm in keloid management is moving away from uniform treatment approaches toward personalised, risk-stratified care models. Individual patient history, including personal or familial predisposition to pathological scarring, may in the future guide automatic initiation of preventive multimodal protocols following skin injury or surgery [5,6].

The integration of pressure therapy, silicone-based modalities, intralesional pharmacotherapy, and surgical adjuncts reflects a synergistic treatment philosophy targeting mechanical, biochemical, and cellular drivers of scar formation. Ultimately, the objective is no longer limited to lesion reduction but extends to long-term modulation of the underlying fibroproliferative process, ensuring durable and patient-specific outcomes across diverse clinical populations [6].

VIII. Future Directions and Regenerative Therapies

Intralesional pharmacologic injections and laser-based interventions have long formed the backbone of non-surgical management for hypertrophic scars and keloids [25]. However, regenerative medicine represents an emerging paradigm shift, aiming not merely to suppress scar activity but to actively modulate and restore normal wound healing pathways through enhancement of endogenous repair mechanisms [23]. This approach reframes pathological scarring as a dysregulated regenerative process rather than a static fibrotic endpoint, opening new avenues for biological intervention.

Current regenerative strategies primarily include platelet-rich plasma (PRP), stromal vascular fraction (SVF), and mesenchymal stem cell (MSC)-based therapies, including conditioned media and extracellular vesicle (EV) platforms [23,24]. Across early clinical studies, a systematic review reported overall improvement in scar-related outcomes in approximately 72% of cases, with no significant adverse effects reported [25]. Among these modalities, PRP remains the most extensively studied, while SVF and stem cell-conditioned media are comparatively less represented. These therapies are primarily thought to act through the release of growth factors and paracrine signalling molecules that modulate inflammation, reduce fibroblast activity, and downregulate excessive collagen deposition [23,24].

Mesenchymal stem cell-based therapy has emerged as one of the most promising regenerative approaches due to its immunomodulatory, antifibrotic, and tissue-remodelling properties. Preclinical evidence from systematic reviews of in vitro and animal studies demonstrates favourable macroscopic and histological improvement following MSC administration or conditioned media application, including reduced fibrosis and improved extracellular matrix organisation [23]. However, significant translational limitations remain, particularly regarding variability in animal models, lack of standardised delivery protocols, and absence of defined dose-response relationships across different cellular sources.

Extracellular vesicles, particularly MSC-derived exosomes, represent a cell-free alternative designed to retain the therapeutic benefits of stem cell signalling while reducing concerns related to cell transplantation safety. A systematic review and meta-analysis of animal studies demonstrated significant reductions in scar size compared with controls, with a standardised mean difference of -2.78 (95% CI -3.88 to -1.69) [24]. Additionally, reductions in type I and III collagen deposition, fibroblast proliferation, and profibrotic mediators such as TGF-β1 and α-smooth muscle actin were observed, supporting a clear antifibrotic effect at the molecular level [24].

Despite these promising findings, multiple translational barriers remain. EV production at clinical scale is technically challenging, storage stability is limited, and there is currently no consensus regarding dosing, delivery routes, or treatment standardisation [24]. Furthermore, the majority of available evidence is derived from animal models in which scar formation occurs over short timeframes and does not replicate the chronic, relapsing nature of human keloids, which evolve over months to years [23].

Importantly, methodological limitations further constrain interpretation of existing data. A 2026 meta-analysis highlighted the absence of clearly reported randomisation procedures and allocation concealment across included studies, increasing risk of bias [24]. Additionally, despite inclusion of human trials, the total clinical sample remains limited to approximately 377 patients across eight studies, restricting the strength of current conclusions [25].

Overall, regenerative medicine represents a promising but still preliminary frontier in scar management. While early biological and preclinical outcomes are encouraging, clinical translation remains limited by heterogeneity, small sample sizes, and lack of standardised protocols. Future progress will depend on well-designed controlled trials, reproducible manufacturing systems, and validated outcome measures capable of bridging the gap between experimental efficacy and clinical applicability.

Conclusion:

Pathological scar formation results from persistent fibroblast activation, excessive collagen deposition, and dysregulated profibrotic signalling, which collectively contribute to recurrence and justify a multimodal therapeutic approach. Current evidence supports a stepwise non-surgical strategy, with silicone-based therapies forming the foundation of early management, particularly during initial scar maturation. In cases of persistent or recurrent disease, intralesional corticosteroids remain the cornerstone of treatment, while emerging agents such as botulinum toxin type A provide additional benefit through complementary antifibrotic and neuromodulatory mechanisms. This escalation from topical and barrier-based interventions toward targeted intralesional therapy reflects the structured nature of contemporary scar management algorithms.

As disease severity progresses or response to monotherapy becomes inadequate, second-line and combination strategies play a central role in improving outcomes. Intralesional 5-fluorouracil represents a key escalation option, particularly when combined with triamcinolone acetonide, through

synergistic inhibition of fibroblast proliferation and inflammatory signalling. Laser-based modalities further expand the therapeutic armamentarium, with pulsed dye laser targeting vascular components and fractional CO_2 laser contributing to dermal remodelling and enhanced drug delivery. Across multiple network meta-analyses, combination regimens consistently demonstrate superior outcomes in scar appearance, symptom control, and recurrence prevention compared with single-modality therapy, reinforcing the concept that keloids and hypertrophic scars arise from interconnected biological pathways requiring integrated management.

Long-term success is increasingly dependent on recurrence prevention strategies and patient-specific planning rather than isolated procedural choice. Adjuvant measures such as pressure therapy, tension reduction techniques, and structured postoperative surveillance remain essential components of comprehensive care, particularly in high-risk individuals. Additionally, factors such as age, ethnicity, anatomical location, and psychosocial burden significantly influence therapeutic selection and outcomes, highlighting the importance of individualised treatment algorithms. Emerging regenerative therapies, including mesenchymal stem cells and extracellular vesicle-based approaches, offer promising biological modulation of wound healing but remain limited by early-stage evidence and lack of standardisation. Overall, current literature supports a clear paradigm shift toward combination-based, risk-adapted, and biologically targeted management aimed at durable control and minimisation of recurrence.

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