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Up-to-date approach to manage keloids and hypertrophic scars: A useful guide

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Abstract

Keloids and hypertrophic scars occur anywhere from 30 to 90% of patients, and are characterized by pathologically excessive dermal fibrosis and aberrant wound healing. Both entities have different clinical and histochemical characteristics, and unfortunately still represent a great challenge for clinicians due to lack of efficacious treatments. Current advances in molecular biology and genetics reveal new preventive and therapeutical options which represent a hope to manage this highly prevalent, chronic and disabling problem, with long-term beneficial outcomes and improvement of quality of life. While we wait for these translational clinical products to be marketed, however, it is imperative to know the basics of the currently existing wide array of strategies to deal with excessive scars: from the classical corticotherapy, to the most recent botulinum toxin and lasers. The main aim of this review paper is to offer a useful up-to-date guideline to prevent and treat keloids and hypertrophic scars.

Keywords

Scar; Keloid; Corticoids; Criotherapy; Laser; Review

1. Introduction

Cutaneous scar management has relied mainly on the experience of practitioners rather than on the results of large-scale randomized, controlled trials and evidence-based studies [1].

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Patients with keloids or hypertrophic scars suffer a severe impairment of quality of life, by causing physical, psychological and social sequelae [2]. Even normal visible scars may represent an important stigma [3]. The prevalence of hypertrophic scarring following burns is about 67%, but further epidemiological research is still necessary. Excessive scarring represents the first morbidity cause in burn survivors [4].

The formation of a scar is the normal physiologic response to wounding in adults. However, an alteration of extracellular matrix (ECM) metabolism – an imbalance between its destruction and deposition – may lead to excessive scarring [5]. Wound healing, and therefore scar formation, involves three distinct phases: inflammation (the first 48–72 h after trauma, supposed to be started by the release of IL-1 by keratinocytes) [6], proliferation (which may last for up to 6 weeks) and remodeling or maturation (scars mature during a period of at least 1 year [5]).

A prolonged or excessive inflammatory phase is believed to be the onset of excessive scarring, with hypertrophic scars and keloids as minor and major clinical signs (Table 1).

Still to date, it remains much more efficient to prevent excessive scars than to treat them. The most successful treatment of a hypertrophic scar or keloid is achieved when the scar is immature but the overlying epithelium is intact. In the past, the most recommended treatment strategy has been prophylaxis using silicone gel sheeting or paper tape starting on the second week after wounding, combined with other treatments, including massage, pressure therapy and intralesional corticotherapy, depending on each patient and scar's origin and type [1].

Generally, most of the therapeutic approaches may be used for both hypertrophic scars and keloids. Nevertheless, it is important to differentiate them before performing any surgery or laser treatment [5]. Briefly, keloids (Fig. 1) extend beyond the original wound borders, in contrast to hypertrophic scars (Fig. 2). Blood type A, hyper-Immunoglobulin (Ig) E syndrome (high allergy risk), hormone peaks (puberty, pregnancy), age 10–30 years old, and Hispanic, Afro-American or Asian (but not albino) background have all been associated with high risk of developing keloid scars [5,7]. Keloid pathophysiology is still complex, with both genetic and environmental factors involved. Abnormal fibroblasts have been shown to play a key role, but new lines of research have driven attention to keratinocytes and altered signaling crosstalks [8,9]. Furthermore, increased number of mast cells have been associated with enhanced HIF-1α (hypoxia inducible factor-1α), VEGF (vascular endothelial growth factor) and PAI-1 (plasminogen activator inhibitor-1) expression, all well known fibrosis promoters. TGF-β signaling with preponderance of TGF-β1 or 2 expression due to alteration of POMC (proopiomelanocortin) gene expression among other mechanisms and epithelial-to-mesenchymal transition have also been shown to play a major role in keloid formation [10,11]. Increased interleukin-6 (IL-6), PDGF (platelet derived growth factor), $\alpha_1\beta_1$-integrin and Ig A, G and M expression have all also been linked to keloid pathogenesis [3]. Besides that, keloid formation has been associated with immune alteration of sebaceous glands and enhanced androgen receptors expression with enhanced sebum secretion and lipid metabolism alteration, neurogenic inflammation, infection and mechanotransduction [12]. Regarding hypertrophic scars pathophysiology, activation of

myofibroblasts has been classically reported to play a key role. This has been shown to be driven by an orchestrated interplay of platelets, macrophages, T-lymphocytes, mast cells, Langerhans cells, keratinocytes and fibroblasts. The net reported result mainly consists of an alteration of ECM (extracellular matrix) metabolism: excessive production and altered remodeling of ECM, with enhanced expression of types I and III collagen and cutaneous profibrotic pathological crosslink of collagen, in the form of pyridinoline type with increased LH2b (telopeptide lysyl hydroxylase-2b). Furthermore, hemostasis alteration (due to enhanced expression of PAI-1 and chronic fibronectin deposition), increased neovascularization and time of re-epithelialization have also been involved in hypertrophic scar pathogenesis. Decreased apoptosis and increased inflammation have also been described to play a major role. Regarding this latter, increased expression of T helper 2 cells, IL-4, IL-5, IL-6, IL-13 and IL-21, but decreased levels of IL-12 and interferon-γ (IFN-γ), have also been shown to be related in the literature [13,14]. More detailed description about both types of excessive scarring scapes from the scope of this review, which will focus on offering an evidence based description of the currently used strategies to manage keloids and hypertrophic scars, from the classical corticotherapy to the most recent botulinum toxin and lasers.

2. Classical treatment and preventive options for keloids and hypertrophic scars

2.1. Massage therapy

Massage therapy, manual or mechanical (i.e., compressed air, threadlike showers, vacuotherapy, etc.), is standard therapy in rehabilitation centers specializing in the treatment of scars and burns [15].

Although there is no scientific evidence, it has been shown that massage therapy not only reduces scar-related pain and itching [16], but also increases range of motion, reveals patients' anxiety and improves their mood and mental status [17].

A recent meta-analysis including 144 patients from 10 different publications who received scar massage concluded that although scar massage is anecdotically effective, its evidence is weak, regimens used are heterogeneous, and outcomes measurements are subjective and not standardized [18]. There is currently an ongoing interventional randomized clinical trial (clinical trials.gov identifier: NCT00175344) by University of British Columbia studying postoperative scar massage in women with breast cancer [19]. Further well-designed and large-sample clinical trials are warranted.

2.2. Pressure garments

Another treatment strategy that also alleviates itching and pain associated with abnormal scars but also with no scientific evidence is the use of pressure garments [20]. However, pressure garments still represent the current standard first-line prophylactic therapy for hypertrophic burn scars [21].

Mechanical compression is shown to reduce collagen synthesis by several mechanisms. These include decreased blood, oxygen and nutrients delivery to the scar, MMP-28 (matrix metalloprotease-28) downregulation and increase of PGE2 (prostaglandin-E2), which activates collagenase [22].

It has been reported that pressure garments should be worn at least 23 h a day, at 20–40 mm Hg (better around the low range), starting as soon as possible after wound re-epithelialization, for 6–24 months [21]. Pressures below 10 mm Hg have been shown to produce no beneficial effects, whereas pressures exceeding 40 mm Hg may lead to maceration and paresthesias [23]. Pressure and radius are inversely correlated. Indeed, effectiveness of pressure therapy depends mainly on the anatomic area where it is applied [24]. Concave and flexion areas are the least effective ones, whereas trunk and limbs are the most suitable anatomic locations to apply pressure therapy. A meta-analysis concluded that the potential morbidity and costs of pressure therapy currently appear to outweigh its still unproved efficacy [25]. The main disadvantage of pressure therapy is the low patient-adherence to the treatment (less than 40%) mostly due to the significant discomfort associated with this therapy [21]. Other risks include skin rash and erosion (specially in humid and hot climates, or if too much pressure is applied), pruritus, swelling and even skeletal and dental deformities [26–28].

Given current lack of evidence, well-designed clinical trials are required to examine the effectiveness, risks and costs of pressure garment therapy [25].

2.3. Adhesive tape support/silicone gel sheeting

Hydration and occlusion have been suggested in the literature to be the main mechanisms of action of topical adhesive tape (plastic or paper) and silicone materials (sheets, strips, gels, creams, sprays and foams; available over the counter or custom-made). Accordingly, it seems that silicone in particular is not always required. In fact, silicone and non-silicone gel dressings may be equally effective in the treatment of hypertrophic scars [29]; however, studies have shown that silicone gel and silicone gel sheeting (SGS) appear to provide an appropriate occlusion level to treat abnormal scars, in contrast to other materials, such as vaseline [30]. Among the different available silicone formats, although silicone gel and SGS have equivalent efficacy in the management of excessive scarring after an operation, silicone gel currently appears to be the preferred silicone therapy, due mainly to ease of use, as Mustoe and colleagues advocate [30].

On the other hand, application of microporous hypoallergenic paper tape with an appropriate adhesive to fresh surgical incisions, beginning at 2 weeks and used for a minimum of 3 months after surgery, has been reported to be effective in controlling scar tension, eliminating stretching forces, and preventing hypertrophic scarring [31]. It may become more cost effective and theoretically can be worn for 4–7 days continuously, even during bathing.

Silicone sheets are recommended to be worn for 12–24 h a day for at least 2 months, beginning 2 weeks after wound healing. Silicone gel should be applied twice daily and has

the advantage of additionally be used in areas where the sheets will not conform [32]. Folliculitis is a possible adverse effect, specially for silicone sheets [33].

Although topical silicone materials (silastic or elastomers and gel sheets) may not have any effects on mature hypertrophic scars [34], they appear to flatten, soften and increase pliability of fresh scars [35]. However, a randomized controlled trial with intraindividual comparison showed no added beneficial effect when applying silicone underneath the pressure garment in burn hypertrophic scars [36]. Silicone gel sheeting in pathological scars has been reported to have at best a class 3 scientific evidence [37]. Indeed, a recent Cochrane meta-analysis including 20 clinical trials found that although silicone gel sheeting decreased scar thickness and improved scar color with statistical significance, the analyzed studies had poor quality and were highly susceptible to bias, with weak evidence of the efficacy of silicone gel sheeting to prevent abnormal scarring in high risk patients [38]. Once again, one of the most popular anti-scarring strategies in the clinics lacks enough scientific evidence and well designed research studies are warranted prior to set appropriate high-quality professional recommendations or protocols.

2.4. Intralesional corticosteroid injections

Intralesional corticosteroid injections improve scar pliability, diminish its volume and height and reduce scar-related itching and pain [20]. The most used current protocol involves insoluble triamcinolone acetonide (TAC) (10–40 mg/ml), alone or better in combination with lidocaine, weekly, biweekly or monthly.

Despite relatively few randomized, prospective studies, there is a broad consensus that injected triamcinolone is efficacious. It is first-line therapy for the treatment of keloids, and second-line therapy for the treatment of hypertrophic scars, if other less invasive treatments have not been efficacious [1,39–41]. The main milestone of this treatment is the high frequency of side effects, up to 63% [1], such as hypopigmentation, skin atrophy, telangiectasias, rebound effects, ineffectiveness and injection pain. These side effects seem to be diminished when using corticosteroids concomitantly with 5-FU [5].

It has been reported that corticosteroids suppress healing and pathological scarring by three mechanisms: anti-inflammatory and immunosuppressive effect, vasoconstriction, and inhibition of fibroblast and keratinocyte proliferation due to an antimitotic effect [20].

The rates of response to intralesional corticosteroid injections vary from 50% to 100%, with a recurrence rate of 9% to 50% [29]. Results may be improved when corticosteroids are combined with other therapies such as surgery, pulsed-dye laser (PDL), irradiation, 5-fluorouracil and cryotherapy [1,5,42,43]. Surgical excision with intraoperative local injection of triamcinolone acetonide followed by repeated injection at weekly intervals for 2–5 weeks, and then monthly injections for 4–6 months, may yield a good result [20].

2.5. Laser and light-based therapy

Many different lasers have been studied and utilized in the treatment of hypertrophic scars and keloids including CO_2, Er:YAG and PDL, among others [44].

The vascular PDL (pulsed dye laser) 585–595 nm is a nonablative non-fractional laser that has been recognized as an excellent first-line treatment, and specially preventive strategy for hypertrophic scars [45]. Indeed, the primary indication for PDL is to reduce erythema [46]. The conventional short-pulsed dye laser (585 nm PDL) has been described as the most appropriate and effective system for the treatment of scars, with improvement in scar texture, color, and pliability, as well as minimal side effects [47,48]. Indeed, this type of laser improves the appearance of hypertrophic scars, keloids, erythematous scars and striae, and diminishes pruritus [47,49,50]. Thick keloids or thick (>1 cm) hypertrophic burn scars do show minimal improvement with 585-nm PDL treatments though, but it seems that enhanced clinical results are achieved when PDL is combined with intralesional corticosteroids or 5-fluorouracil injections [44,51], or when other lasers are used, like the fractional CO_2 laser. Fractional laser therapy may indeed aid to deliver TAC into the scar and maximize its anti-scarring effects when injected immediately after the laser treatment [52]. The main side effect of PDL 585 nm is prolonged purpura [20,44,51], so a newer laser, the first known LPDL (long-pulsed dye laser) or PDL 595 nm, with a cryogen-spray cooling device, was developed and it currently appears to be a good alternative [49] and it has gained much popularity. Similarly, another less-invasive method, IPL (intense pulsed light), seems to be as effective as LPDL in improving the appearance of hypertrophic surgical scars, minimizing even more the risk of purpura [49]. With similar results to PDL, it has been reported that the Q-switched, 532 nm, frequency-doubled Nd:YAG laser appears also to be promising to manage hypertrophic scars and keloids [48].

One of the most recent developments introduced into laser technology in clinics is the nonablative fractional laser (NAFL). Nonablative fractional lasers have shown significant improvement in the pigmentation and the thickness of surgical scars and have shown early promise in the treatment of atrophic scars, hypertrophic and hypopigmented scars [53]. NAFL offers a new option for the treatment of surgical scars and may outperform the PDL [54]. Recently, nonablative fractional lasers (1540/1550 nm) with a 15 mm handpiece have also been successfully used for the treatment of keloids [44]. However, data regarding recurrence rates in a long-term follow-up is still lacking. The traditional non-fractional continuous wave-CO_2 laser and Nd:YAG 1064 nm had high scar recurrence rates and therefore were abandoned [51].

One of the recommended laser protocol regimens for both keloids and hypertrophic scars described in the literature involves 585–595 nm PDL with non-overlapping laser pulses ranging from 6.0 to 7.5 J/cm^2 (7 mm spot) or 4.5 to 5.5 J/cm^2 (10 mm spot), 1.5–3 ms, applied over the entire surface of the scar, with up to 7 days purpura as the most common side effect after the 585-nm PDL, 2–6 sessions every 6–8 weeks [5,44]. Generally, first results are seen after the second treatment. Darker pigmented patients or patients with scars in sensitive areas (i.e. chest) should have the energy densities decreased by 10% [55], and may require longer treatment intervals, to avoid post-inflammatory hyperpigmentation.

Regarding burn scar management protocols with lasers and lights, Hultman et al. have suggested the use of PDL, fractional resurfacing CO_2 laser and IPL in a timely manner: 6–36 months after burn, one year after burn or several years after burn, respectively. The primary aims are to minimize hyperemia and prevent hypertrophic scarring with the PDL, to

soften, release and flatten the scar with the CO_2 laser, and to correct residual color cosmetic sequelae and chronic folliculitis with the IPL [56]. The aforementioned group reported the successful use during the almost 5 months of mean follow-up of a prospective before-after cohort study of one or more of the following therapeutic strategies in a total population of almost 150 burn patients: PDL 595 nm (the Candela V-beam; Wayland, MA, USA) at 5–11 J/cm^2 – selection depending on the Fitzpatrick skin type – with none or less than 30% overlap and 1–2 passes, with a 7 mm spot size and pulses of 1.5 ms; “ablative” fractional CO_2 laser resurfacing (the Lumenis UltraPulse; Santa Clara, CA, USA; the deep dermal DeepFX™ better combined with the microablative ActiveFX™, constituting the TotalFX™, at 15 mJ or 70–90 mJ per micropulse and frequency of 600 Hz or 150 Hz, respectively), and the IPL [57]. Of all 3 types of laser/light modalities, PDL was the most used. As laser therapy may easily counteract abnormal scarring associated dysfunctions or contractures in burn patients and therefore avoid reconstructive surgeries of burn sequelae, an earlier use of PDL to prevent hypertrophic scars and alleviate pruritus may be postulated. Furthermore, it has been suggested that the PDL should be offered as standard management of patients with facial hypertrophic burn scars, where it has been shown to be able to completely resolve persistent scar erythema even as long as 17 years post-burn [51].

Despite the increasing popularity and optimism regarding laser in scar management after burn or other injuries, laser therapy remains an emerging technology with limited follow-up study and lack of multicentric controlled studies [1,20]. More research is needed to evaluate the efficiency, safety, dosage regimens, appropriate type and timing, and scar recurrence rates of all the otherwise promising wide array of laser and light-based therapeutic techniques [44].

2.6. Cryotherapy

Cryotherapy is a very effective method to treat small scars, such as severe acne scars [58]. Cryotherapy combined with intralesional triamcinolone has been described as the most common traditional therapy for hypertrophic scars and keloids [20]. Its main handicap is permanent hypopigmentation as a common side effect [1]. Monthly-sessions are recommended (not more often, to favor postoperative healing), and success rates after 2 sessions using contact or spray cryosurgery with liquid nitrogen vary between 30 and 75%, being higher in hypertrophic scars than keloids [1,59]. From the three most used methods to apply cryotherapy, the new intralesional cryoneedle has shown increased efficacy compared with that obtained using either contact or spray probes [7].

2.7. Radiotherapy

There is a consensus that ionizing irradiation is an effective way to treat keloids [60]. Superficial X-rays, electron-beam therapy and brachytherapy have been used with good results in scar reduction protocols, primarily as adjuncts to surgical removal of keloids [61].

Best results can be achieved with 1500–2000 rads (15–20 Gy) over five or six sessions in the early postoperative period (24– 48 h after keloid surgical excision) [1,20], although recent keloid reports advocate for higher doses, 25–30 Gy [62]. Radiotherapy (brachytherapy as first line followed by electron-beam therapy [62]) is the most efficacious

treatment available in severe cases of keloids, combined with surgical excision [6,35]. Its main disadvantage is the malignancy risk as possible but rare side effect [1,20,46,60,63].

2.8. Fluorouracil (5-FU)

5-FU is a chemotherapy drug, a pyrimidine analog with antimetabolite activity [64], effective in the treatment of keloid scars [65], especially during the first 5 years of appearance. Wound ulceration, hyperpigmentation and pain are potential complications of the treatment [5,20]. Weekly intralesional 5-FU injections (50 mg/ml) for 12 weeks resulted in reduction in scar size of at least 50% with no recurrence in 24 months [66].

The triple combination of 5-FU, corticosteroids and PDL is a successful multifaceted approach for the treatment of hypertrophic scars and keloids [67] and it currently appears to be the most promising therapy for keloids [42].

2.9. Interferon

Interferon (IFN) subdermal injections are reported to be more efficient than triamcinolone acetonide injections in preventing postsurgical recurrence of keloids. However, these painful injections may require regional anesthesia [1,20,68] and flu-like adverse effects are also common [2].

Interferon-α, β, and γ have been shown to increase collagen breakdown [1]. Furthermore, IFN-α2b has been suggested to have antiproliferative properties [5]. IFN-γ inhibits TGF-β and therefore fibrosis, via initial activation of Jak1, which in turn stimulates the negative regulator of collagen YB-1 (Y-box protein-1), which activates Smad7, eventually leading to TGF-β1 suppression [69]. However, there is a study where IFN-γ failed to antagonize TGF-β-mediated fibrotic response in keloid-derived dermal fibroblasts [70].

In vivo, intralesional IFN-γ has been shown to be effective in improving the appearance of keloids and hypertrophic scars, and in reducing keloid recurrence after excision [71], with variable treatment regimens. For instance, 0.01–0.1 mg, 3 times a week for 3 weeks [72], or a unique weekly maximal dose of 0.05 mg for 10 weeks [73]. IFN-α2b intralesional injection is usually used at 1.5 million IU twice daily over 4 days in keloids or three times weekly for hypertrophic scars [1,74].

Although IFN is an expensive form of therapy, it remains a promising therapeutic approach for excessive scarring [5].

2.10. Bleomycin

Bleomycin induces apoptosis, inhibits collagen synthesis via decreased stimulation by TGF-β1 [75], and is frequently used as an antitumor agent. It has also antibacterial and antiviral activity [76]. Intralesional multiple jet injections of bleomycin 0.1 ml (1.5 IU/ml) at a maximum dose of 6 ml to avoid toxicity (cutaneous and less frequent pulmonary), 2–6 sessions within a month, may currently be indicated as a therapy for keloids and hypertrophic scars unresponsive to intralesional steroid injection [77,78], such as patients with old scars [1]; however, its use is still uncommon.

2.11. Imiquimod 5% cream

Imiquimod is a immune-response modifier and Toll-like receptor (TLR) agonist [79], approved for the treatment of genital warts, basal cell carcinoma and actinic keratoses [5].

Imiquimod stimulates interferon and TNF-α, which increases collagen breakdown and reduces fibroblast-mediated collagen production, respectively [80]. The cream is applied on alternate nights for 8 weeks after surgery. Adverse effects include irritation and hyperpigmentation [81]. Although many clinical studies suggest the beneficial effect of imiquimod in the prevention of postsurgical keloid recurrence [82–84], it still remains questionable [79].

2.12. Tranilast

Tranilast (N-(3,4-dimethoxycinnamoyl) anthranilic acid) is an anti-allergic drug that inhibits the release of histamine and prostaglandins from mast cells, a H1 receptor antagonist [85]. It also suppresses collagen synthesis of keloids and hypertrophic scar-derived-fibroblasts by downregulating TGF-β1 [86]. This drug is approved in Japan and Korea for the treatment of hypertrophic scarring [87].

2.13. Botulinum toxin A

Botulinum toxin A (Botox®, Allergan, Irvine, CA, USA) is a potent neurotoxin that produces a temporary flaccid paralysis (chemoimmobilization) of striated muscle for a period of 2–6 months [88]. For more than 30 years, its application has proven safe and efficient in the treatment of a variety of disorders, including hyperfunctional facial lines [89]. Using a primate model, local botulinum toxin A-induced paralysis of the musculature subjacent to a cutaneous defect minimizes the repetitive tensile forces on the wound edges, improving scar cosmesis [88].

Botulinum toxin A has been used for the treatment of keloids by intralesional injection in a prospective, uncontrolled study [90]. Intralesional botulinum toxin was given at a concentration of 35 U/ml, with the total dose varying from 70 to 140 U per session, at 3-month intervals for a maximum of 9 months. At 1 year follow-up, the therapeutic outcomes were good ($n = 5$), fair ($n = 4$) and excellent ($n = 3$), with no patients failing therapy or showing signs of recurrence [90].

Xiao and colleagues studied 19 patients suffering from hypertrophic scars who received intralesional injections of botulinum toxin (2.5 U/cm^3 per lesion at 1-month intervals) for 3 months. At 6-month follow-up, all of the patients showed acceptable improvement of the scars and therapeutic satisfaction was very high [91].

Some reports suggest that using intramuscular BTA in conjunction with scar revision on the face helps to reduce the development of a widened scar [92]. However, controversy is served [93,94], and larger, randomized, controlled studies need to be conducted to test the effect of chemoimmobilization in scarring [95].

2.14. Surgery

Surgical treatment of keloids has been usually recommended to be used in mature scars with complementary conservative strategies, such as radiotherapy, interferon, bleomycin, cryotherapy or corticoids, to avoid recurrence [1] (decreasing the risk from 50% to 8% as a combined treatment [96]). It is important to note that laser and light-based therapies may eliminate the need of classical scar excision and reconstructive surgery in some cases [57]. Surgical treatment of excessive scars requires a careful personalized indication and patient selection on a case-by-case basis. For instance, surgery may be indicated to release a disabling immature or early-stage scar in a stable patient that suffers a hypertrophic scar that causes a severe contracture that impedes proper rehabilitation in the early period after burn. In this case, closure by local flaps like Z-plasties or others, dermal substitutes and skin grafts, or the use of tissue expanders or free flaps may be indicated. Indeed, most clinicians recommend surgical treatment of hypertrophic scars in general as first-line treatment if disabling scar contractures are present [97]. In the case of operative treatment of mature keloid scars, it is recommended to perform an intramarginal fusiform excision, so an incomplete resection, with a 308 angle with the cutaneous tension lines [98]. As a general rule, closure of the wound should be done with minimal tension and sutures, leaving everted wound borders. Z-plasties, W-plasties and advancement local flaps may indeed be indicated [99,100]. Stitches are recommended to be applied on few planes to eliminate tension and therefore prevent keloid recurrence, reabsorbable into the fascia or subcutaneous tissue (in the form of tensile reduction sutures applied on the deep and superficial fascia with few or no dermal sutures to prevent a high strange body reaction and a worse scar) [97], and usually simple non-reabsorbable mono-filament stitches for the skin. Undermining should not be encouraged [33]. Tangential shaving has also been described for raised scars, with optimal outcomes [99].

3. Special cases

As it has been aforementioned, scar clinical research is still far of providing sufficient accurate and unbiased studies, although a growing concern is detected and this may prompt to design new, high-quality clinical trials. Having said that, and taking into account the few controversial scientific evidence often encountered surrounding this topic, some recommendations could be suggested in special cases. Regarding keloids, patients suffering of generalized multiple keloids or very large keloids may be offered multimodal symptomatic treatments and long-term follow-up [97], including radiotherapy or antimetabolite therapy. Indeed, it has been reported in the literature that radiotherapy is the most efficacious treatment available in severe cases of keloids, combined with surgical excision [6,35], and flap reconstruction. Other more non-invasive approaches may consist of combining PDL, fractional CO_2 laser and TAC [101].

Other challenging scars are represented by presternal keloids, which are very frequent after heart open surgeries and easily tend to recur. In the case of small presternal keloids, surgery with additional adjuvant therapy (radiation or TAC), or non-surgical treatment, such as TAC, laser and 5-FU, may be suggested [102]. Indeed, in presternal keloids, surgery followed by brachytherapy may specially give good results. For breast keloids, SGS,

pressure therapy and tamoxifen may be useful, although the combination of PDL, TAC and 5-FU may also be used as first-line therapy. In both presternal and breast keloids, local or free flaps may be indicated for reconstruction.

If we consider excessive scar management in the context of extreme ages, radiotherapy, antimetabolites and corticoids would not be recommended to be used in children, in order to avoid harmful side effects, like growth abnormalities. At this young age, silicone materials and pressure garments at the accurate pressure (not more, to avoid growth restrictions) are the most used anti-scar strategies, although laser under anesthesia may become a promising new armamentarium. Indeed, the response of silicone materials in children is usually poor, due to low patient-adherence to treatment (depending on age, it is difficult to be successful in teaching a children to apply topical silicone with discipline, or even to be able to maintain the silicone in place enough time before the child removes it or makes the area dirty while playing, just to name a few examples). Surgery may also be indicated when significant physical or psychical excessive scar-related sequelae are detected in children. In the elderly, corticoids are also not very advisable to be used, although some chronic illnesses require even its systemic use due to chronic age-related diseases. Pressure garments should be carefully used in the elderly, because there is increased fragility of skin with aging, and their use would augment the risk of skin erosions and ulcerations. The good thing of aging is that it is accompanied with less risk of excessive scarring.

Independently of age, lasers emerge as a non-invasive scar treatment in all ages when appropriately applied, although young children and some elderly people with dementia may require prior sedation, and side effects should also be carefully monitored, balancing the relationship between risk and benefits.

In the context of excessive scar management in general, the International Guidelines of the ‘‘International advisory panel on scar management’’ from 2002 appear in the literature (Tables 2 and 3) [1] as general recommendations of scar management independently of age (new updated guidelines are planned to be published in 2014). The authors have designed updated scar management recommendations based on previous reports and clinical experience (Table 4). To conclude, a general summary of miscellaneous scar treatment modalities is also reported in Table 5.

4. Conclusions

Hypertrophic scars and keloids represent old but still unresolved challenges. From the classical scar management strategies, corticosteroids keep playing a predominant role, especially if combined with 5-FU and PDL in a triple therapy, to enhance results and diminish their side effects. Lasers and light-based therapies are becoming more and more used nowadays and appear promising in the management of scars for many reasons: depending on the laser technology chosen, they can be used to enhance the delivery of other adjuvant treatments such as TAC and therefore increase their efficacy, they may serve to relieve scar-associated symptoms such as pain and pruritus, and they may revolutionize for instance the classical and current surgical-focused burn sequelae field and turn it into a less-invasive or non-surgical management. However, finding the appropriate “holy grail” for

these clinical milestones warrants further well-designed research of current approaches, as well as innovation and development of new molecular-based or regenerative medicine therapies.

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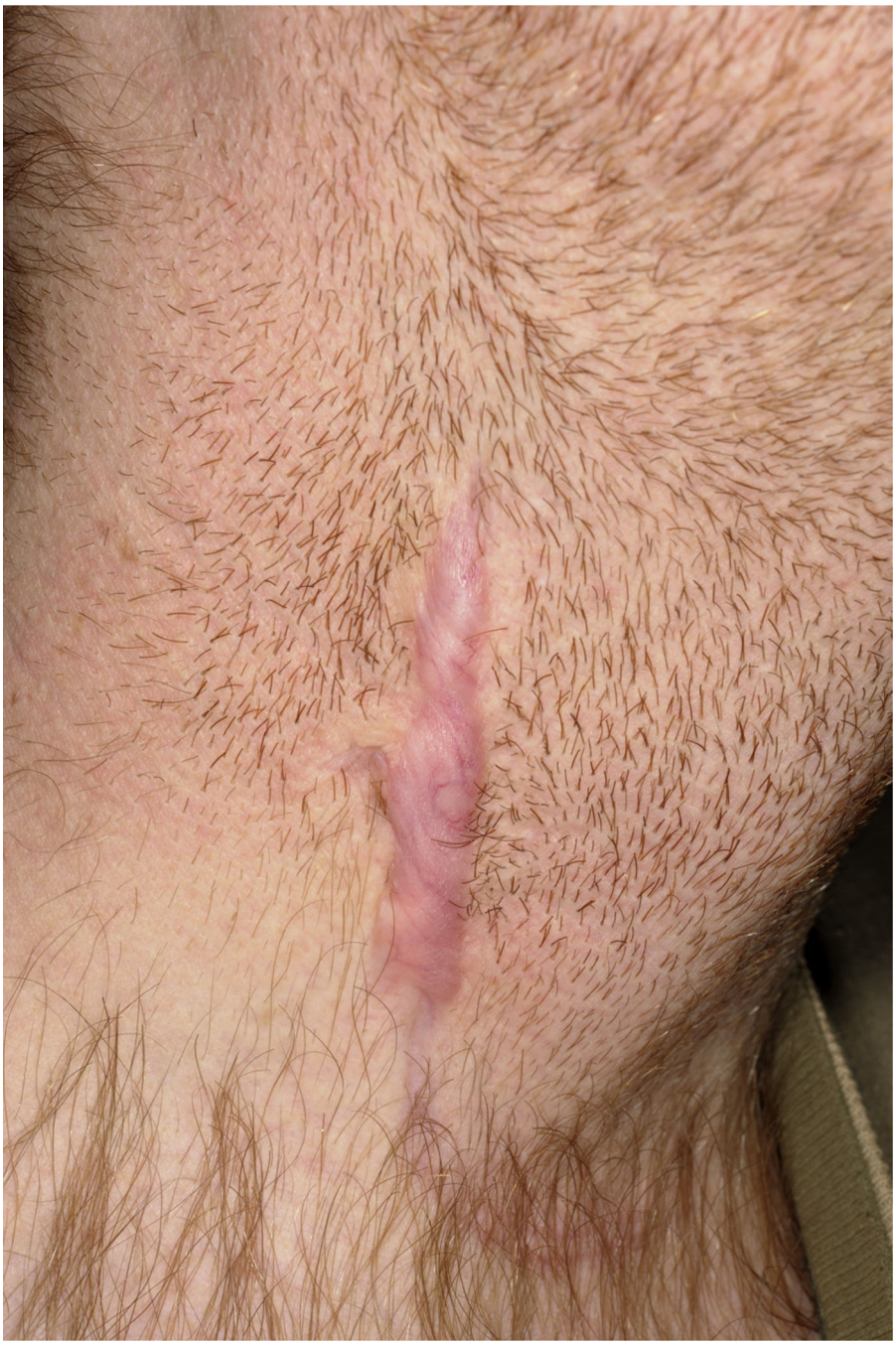

Figure 1.
Hypertrophic scar on the right side of the neck after removal of a benign cutaneous lesion.

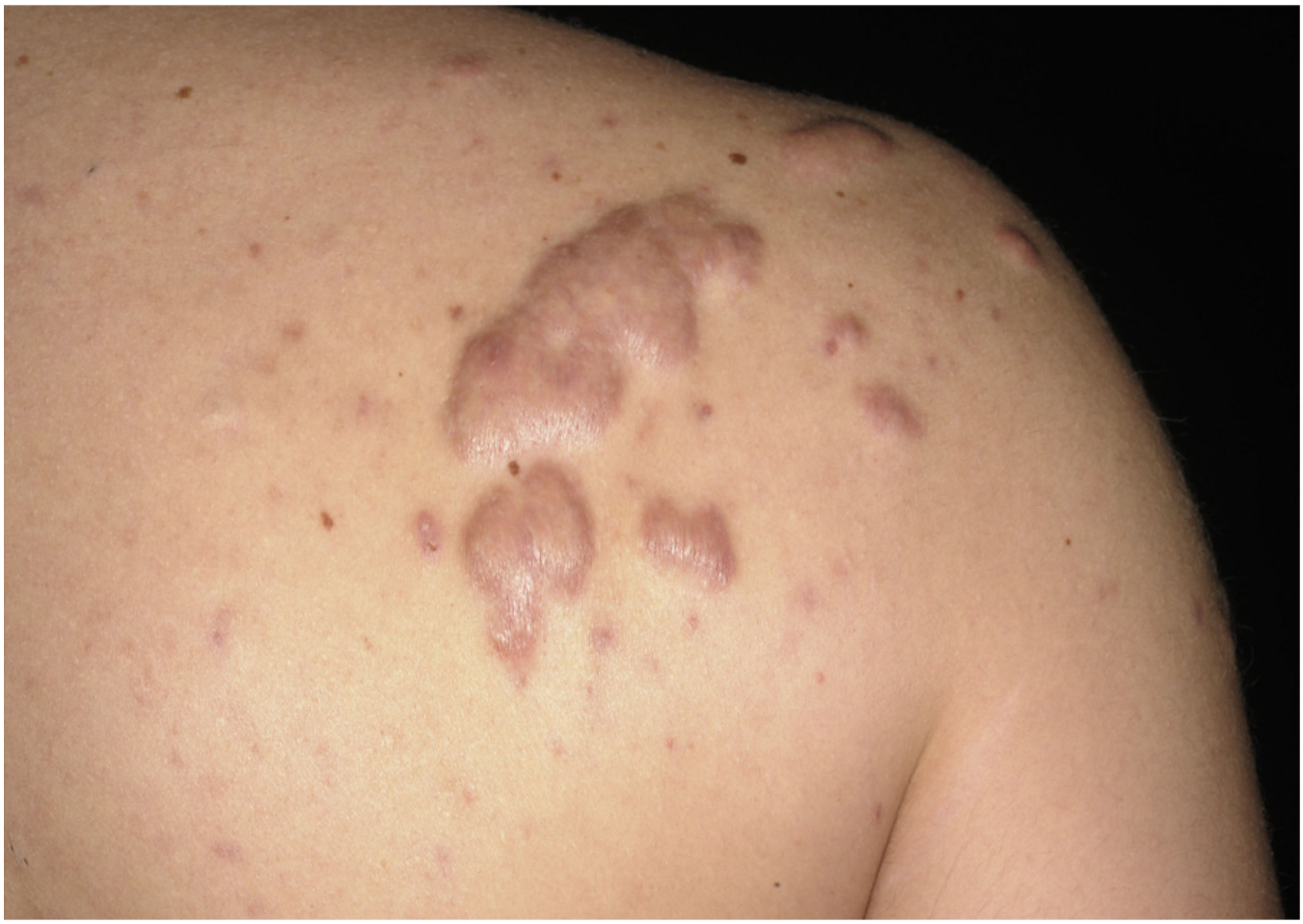

Figure 2.
Keloid on the right scapular back region as a consequence of severe acne scarring.

Table 1

Differential diagnosis between keloids and hypertrophic scars.

Keloids	Hypertrophic scars
Grow beyond the borders of the original wound	Remain confined to borders of the original wound
Pruritic and extremely painful	Less pruritic and rarely painful
Predominant anatomical sites (earlobes, chest, shoulders, upper back, posterior neck, cheeks, knees)	No predominant anatomical sites (but commonly occur on extensor surfaces of joints or when skin creases at a right angle)
Posttraumatic or spontaneous	Only posttraumatic
Not associated with contractures	Associated with contractures
Do not regress spontaneously	Regress spontaneously
Do not improve with time; there is continuous growth.	Improve with time (regress or stabilize)
Develop later:	Develop sooner:
Appear at 3 months or later after initial scar, then gradually proliferate indefinitely	Generally appear within 1 month, grow for 6 months, then regress often within 1 year
More common in darker skin types	Less association with skin pigmentation
Genetic predisposition (autosomal dominance inheritance susceptibility loci on chromosomes 2q23 and 7p11; may also be recessive)	Less genetic predisposition
Thick collagen fibers*	Fine collagen fibers*
Absence of myofibroblasts and α-SMA	Presence of myofibroblasts and α-SMA
Collagen type I > III	Collagen type III > I
COX-2 overexpression	COX-1 overexpression
High recurrence rates following excision (although often recur late, 6 months up to 2 years afer surgery).	Low recurrence rates following excision
If excised, combined treatment needed (corticosteroids better than radiation)	
Rare incidence	Frequent incidence

Abbreviations: α-SMA, α-smooth muscle actin; COX, cyclooxygenase.

*Classical studies show that keloid are characterized by large, thick, wavy, randomly-oriented and closely or loosely packed collagen fibers and no collagen bundles, whereas hypertrophic scars present fine, wavy, well-organized and parallel-oriented collagen fibers and bundles. However, recent research proposes that both types of excessive scarring show parallel and separated collagen fibers, in opposed to normal skin (with higher distance between collagen bundles in keloids) [93]. Actually, histomorphology of each scar not only differs from patient to patient, but also among scars from the same patient and among areas of the same scar [94], complicating even more the differential diagnosis.

Table 2

Classical excessive scar prevention recommendations [1].

1	Use hypoallergenic microporous tape for a few weeks after surgery.
2	Begin silicone gel sheeting as a first-line prophylaxis, at 2 weeks after surgery or soon after surgical closure. Continue it at least for 1 month.
3	Consider concurrent intralesional corticosteroid injections as second-line prophylaxis for more severe cases.
4	If silicone gel sheeting, pressure garments and intralesional corticosteroid injections are not successful after 12 months of conservative therapy, surgical excision with postoperative application of silicone gel sheeting should be considered.

Table 3

Classical post-burn excessive scar prevention recommendations [1].

First-line therapy: Massage, silicone gel sheeting, pressure garments. PDL if available. Antihistamines/gabapentin might be used to alleviate pruritus.
Second-line therapy: corticoids, surgery (Z-plasty, excision + grafting, flap)

Table 4

New updated recommendations for excessive scar management.

PREVENTION	HTS	Basic scar care	Hydration/topical moisturizer	
	KELOID		Massage	
			UV protection (sunscreen)	
		Non-concerned patient/low-cost measures	Hypoallergenic microporous paper tape	
		Concerned patient	SGS	
TREATMENT	HTS	With contractures	Surgery to release scar	
		Without contractures	First line	SGS 6 w and optional laser[a]
			Second line	TAC + optional cryotherapy combined[b]
			Third line	Laser[b] (PDL or fractional laser therapy)
	KELOID	First line	TAC + 5-FU + laser therapy + SGS	
		Second line	Surgery + aforementioned conservative measures + optional additional brachytherapy	

Note: These are just general recommendations. Each scar has to be studied in a case-by-case basis.

Abbreviations: HTS, hypertrophic scar; SGS, silicone gel sheeting; TAC, triamcinolone acetonide.

[a] And/or pressure garments for 6–12 months, mainly in burn scars and other special cases; regarding laser, it was initially reserved as third-line therapy, but due to promising clinical results despite few scientific evidence, some consider to start with laser as well, which may help to enhance the efficacy of further treatments (such as TAC delivery). Cost-effectiveness studies should be performed first to confirm.

[b] In the case of major burns and large scars, laser would be second line strategy, as TAC is usually scarcely used.

Table 5

Other miscellaneous current practices against scarring.

Verapamil	Usually intralesional 2.5 mg/ml [81], but also topical 7% cream [103].
	It is a calcium antagonist that decreases collagen production in the ECM and stimulates collagenase synthesis, reducing fibrotic tissue production [81].
Topical retinoic acid (0.05% isotretinoin)	Clinical studies suggest that it lightly diminishes the size and symptoms of keloids, but it should not be considered first-line therapy [79]
Hyaluronic acid	Controversial results: While some argue it may prevent excessive scarring [104], others [105] defend the opposite
Radiofrequency	Although collagen fibril changes have been reported, significant clinical improvement is still lacking [106]
Dermatography	Microsurgical needle tattooing provides camouflage pigmentation and induces scar atrophy via the cutting action of the needles.
	Dyspigmentation and textural abnormalities of large scars can be reduced with dermatography [107].
Pentoxifylline	This anti-fibrinolytic drug, popularly used to manage peripheral vascular disease, inhibits burn scar fibroblasts in vitro [108]
Fibrostat	Putrescine 50 mmol/l
Colchicine	Alters cytoskeleton and the mitotic phase of the cell cycle. Inhibits inflammation and may prevent keloid recurrence [109]
Mitomycin C	Appears to prevent scar tissue formation, but not keloid recurrence [110]
Ultraviolet light	UVA1 increases collagenase activity [109]
Epicatechin gallate	Catechins are a type of polyphenolic compound with in vitro antioxidant and anti-inflammatory activity [111]
Anogeissus latifolia	It is a deciduous tree native to India whose bark is used in tanning and contains leucocyanin and ellagic acids. It has antimicrobial and healing properties [112]
Butea monosperma	It is the bark of a tropical evergreen, with antioxidant and wound healing properties [112]
Curcumin	It blocks fibroblast proliferation [112]
MEBO	=Moist Exposed Burn Ointment. Contains multiple herbs with beta-sitosterol [112].
Mederma skin gel	Onion extract gel with scarce scientific evidence yet, although onion extracts are gaining popularity in the literature [81,94]
Contractubex gel	Contains onion extract with heparin and allantoin [81]
Vitamin E	May actually worsen scars or cause contact dermatitis [112]
Adipose-derived mesenchymal stem cells	Promising preclinical studies [113], but more research warranted