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REVIEW ARTICLE

Postinflammatory Hyperpigmentation: Epidemiology, Clinical Presentation, Pathogenesis and Treatment

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Abstract Postinflammatory hyperpigmentation (PIH) is a reactive hypermelanosis that develops following cutaneous inflammation. Common causes of PIH include intrinsic skin conditions (e.g., acne and eczema) as well as external insults to the skin, such as burn injuries and dermatologic procedures. PIH more commonly occurs in individuals with darker skin, for whom it is often a source of significant psychological distress. Several therapeutic modalities are available for the treatment of PIH, including topical agents, chemical peels, and energy-based devices. We review the epidemiology, clinical presentation, pathogenesis, and treatment of PIH.

Key Points

Postinflammatory hyperpigmentation (PIH) is an acquired hypermelanosis of the skin that commonly affects skin of color.

PIH develops after inflammation of the skin and may result from an intrinsic skin condition (e.g., acne, eczema) or an external injury to the skin.

Treatment options for PIH include topical products, chemical peels, and energy-based devices.

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1 Introduction

Postinflammatory hyperpigmentation (PIH) is an acquired hypermelanosis of the epidermis or dermis that occurs following cutaneous inflammation or injury. Although this pigmentary change can be observed in all skin types, it more frequently affects individuals with Fitzpatrick skin types (FST) IV–VI due to increased reactivity of melanocytes within the skin [1, 2]. PIH often presents with dark macules or patches, which typically occur in the same distribution as the initial skin insult.

PIH can have a profound psychological impact on patients and has been associated with decreased quality of life in several studies [3–6]. This is particularly problematic given that the hyperpigmentation can take several months to years to resolve, even with appropriate treatment [7]. Topical products are currently the gold standard for treatment of PIH, but chemical peels and laser treatments are being used increasingly with positive results. This article reviews the pathogenesis, clinical presentation, and treatment of PIH, including topical therapies, chemical peels, and laser and light devices.

2 Epidemiology

PIH occurs at all ages with equal incidence in males and females. In a number of worldwide studies, higher rates of pigmentary disorders have been reported among individuals of African, Asian, and South American ancestry, with PIH being the most common diagnosis [8–10]. In the USA, a single-center study of 1412 patient visits found that dyschromias (excluding vitiligo) were the second most common diagnoses among Black and Hispanic patients yet were not within the top ten diagnoses in Caucasian patients

[11]. Analyses of the National Ambulatory Care Survey (NAMCS) similarly found dyschromias to be one of the top ten diagnoses in African Americans and Hispanics but not Whites or Asians/Pacific Islanders [12, 13]. Among Arab Americans, concerns regarding PIH are more frequently reported by individuals with darker skin tones (originating from Yemen) than by those with lighter skin tones (from Lebanon and Syria) [8]. A similar phenomenon is seen in Asia, where Malays and Indians living in Singapore have a higher incidence of PIH than do lighter-skinned Chinese [14]. Thus, it appears to be the degree of skin pigmentation, rather than ethnicity, that influences the frequency, intensity, and duration of PIH [3].

3 Clinical Presentation

PIH presents with hyperpigmented, asymptomatic macules or patches in the distribution of the inciting inflammatory skin condition or cutaneous injury (Fig. 1). While pigment deposition in the epidermis causes tan to dark brown lesions, dermal PIH is often characterized by darker brown or blue/gray discoloration of the skin [3, 15]. Regardless of the pigment location, these lesions may darken or spread if the underlying condition is not adequately controlled. Exposure to ultraviolet (UV) radiation may also worsen PIH [16, 17]. Typically, epidermal lesions will fade within a few months with appropriate treatment. Dermal PIH takes longer to resolve and, in some cases, may be permanent [18].

The severity of PIH can be quantified using various hyperpigmentation scoring systems. For acne-induced PIH, the postacne hyperpigmentation index (PAHPI) is a reliable and validated system for quantifying the severity of hyperpigmentation [19]. PAHPI evaluates the size, intensity, and number of PIH lesions in order to create a global severity ranking, which has been shown to have excellent intra- and inter-rater reliability. Various non-standardized, non-validated scoring systems [i.e., Hyperpigmentation Area and Severity (HASI) score] have been used to evaluate PIH in the past, limiting the comparison and reproducibility of hyperpigmentation assessments within and between studies [19–22]. Skin spectrophotometers may also be used to objectively quantify the degree of skin pigmentation and track improvement in discoloration [22–25]. Narrowband reflectance spectrophotometers, which are commonly used in the evaluation of disorders of hyperpigmentation, measure the amount of light absorbed and reflected by the skin in order to calculate the melanin content (melanin index or "M") of the skin. Use of scoring systems and spectrophotometry devices are typically isolated to research studies, although they may be used in clinical practice.

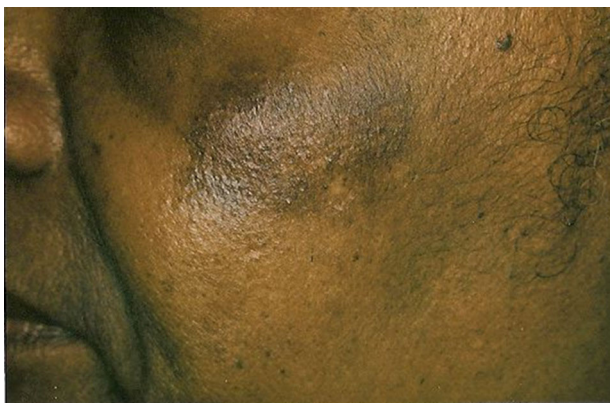

Fig. 1 Postinflammatory hyperpigmentation of the cheek following acute contact dermatitis

The histopathology of PIH is classically described as having increased epidermal melanin content, melanophages in the superficial dermis, and some degree of lymphohistiocytes surrounding blood vessels in the dermal papilla. However, a recent study identified two distinct histopathological patterns of PIH – epidermal and dermal pigment types; the epidermal pigment type involved an increased amount of melanogenesis and melanin deposition within the epidermis without any change in melanocyte number [26], and the dermal pigment type involved increased pigment deposition in the dermis and decreased pigmentation in the epidermis, despite increased epidermal melanogenic activity. Dermal PIH also demonstrated significant dermal perivascular lymphocytic infiltration and higher expression of several markers (cluster of differentiation [CD]-68, c-kit, matrix metalloproteinase [MMP]-2), suggesting the key role of skin inflammatory injury, and particularly macrophage and mast cell infiltration, in this subset [26].

4 Pathogenesis

PIH results from overproduction or abnormal release of melanin in response to either endogenous or exogenous inflammatory conditions [27]. This begins with the oxidation of arachidonic acid to produce eicosanoids involved in cell signaling [28]. Prostaglandins and leukotrienes, along with cytokines and reactive oxygen and nitrogen species released during the inflammatory response, stimulate the proliferation of melanocytes and increase the amount of melanogenesis [2, 29]. In particular, leukotriene C_4, leukotriene D_4, prostaglandin E_2, histamine, and thromboxane B_2 have all been shown to have melanocyte stimulating properties in vitro [29]. Upregulation of these metabolites is associated with higher levels of immunoreactive tyrosinase, resulting in increased melanin synthesis and transfer of melanosomes to keratinocytes [3, 29].

4.1 Common Causes of Postinflammatory Hyperpigmentation (PIH)

Some endogenous causes of cutaneous inflammation that result in PIH include acne vulgaris, atopic dermatitis (AD), psoriasis, and lichen planus (Fig. 2) [30]. Irritant contact dermatitis, burns, chemical peels, non-ionizing radiation therapy, and laser resurfacing are all examples of exogenous causes of PIH (Table 1) [18, 31].

Acne vulgaris is one of the leading causes of PIH in skin of color (Fig. 3). A study of 239 patients found that 65.3% of African Americans, 52.7% of Hispanics, and 47.4% of Asians with acne develop PIH as a result of the condition [32]. Subclinical inflammation—neutrophils and T-lymphocytes infiltrating clinically non-inflamed lesions—may contribute to PIH [24, 33]. Early and aggressive treatment of acne in patients with skin of color is essential for mitigating the risk of PIH, although care should be taken to minimize or prevent irritation [34, 35].

PIH also occurs in up to 90.1% of African American and Hispanic patients with pseudofolliculitis barbae [36]. Atopic hyperpigmentation of the neck, which results from a combination of PIH and frictional melanosis, has been found to occur in 14.3% of Asians with AD [37]. PIH commonly occurs following the resolution of eczematous and inflammatory skin conditions (e.g., AD, contact dermatitis, psoriasis), although the true prevalence of PIH in these conditions has not been reported [18, 30, 31, 38].

4.2 Procedural Therapies and Risk of PIH

Procedural treatments of the skin, including energy-based devices and chemical peels, may also be associated with a risk of iatrogenic PIH in darker-skinned patients (Fig. 4).

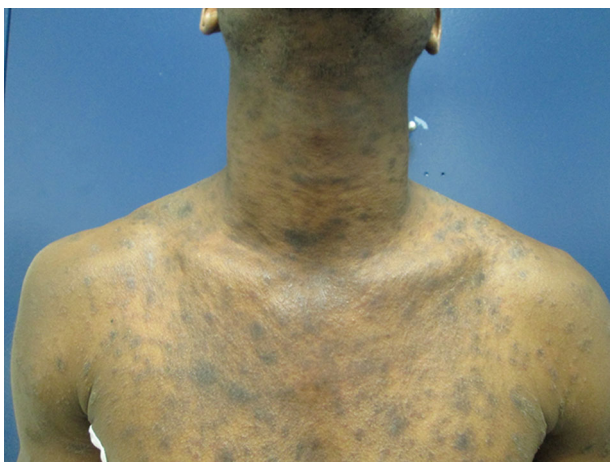

Fig. 2 Atopic dermatitis with severe postinflammatory hyperpigmentation in an African American male

Table 1 Important etiologies of postinflammatory hyperpigmentation

Inflammatory skin conditions
Acne
Atopic dermatitis
Psoriasis
Lichen planus
Pityriasis rosea
Lichen simplex chronicus
Immunologic skin conditions
Lupus erythematosus
Sarcoidosis
Scleroderma and morphea
Dermatomyositis
Immunobullous disorders
Allergic/hypersensitivity
Arthropod bite
Papular urticaria
Contact dermatitis
Polymorphous light eruption
Viral infection
Herpes simplex
Herpes zoster
Viral exanthems
Bacterial or fungal infection
Impetigo
Pityriasis versicolor
Dermatophytosis
Drug-induced
Phototoxic drug eruption
Fixed drug eruption
Erythema multiforme and Stevens–Johnson Syndrome
Physical injury
Minor abrasions and cuts
Burns
Friction
Radiation
Dermatologic procedures
Dermabrasion
Cryotherapy
Lasers
Intense pulsed light
Chemical peels
Microneedling
Neoplastic
Mycosis fungoides

Laser hair removal, laser resurfacing, intense pulsed light treatments, and other commonly used laser and light modalities can result in PIH as an adverse effect of treatment [39–43]. Risk of PIH can be reduced by careful

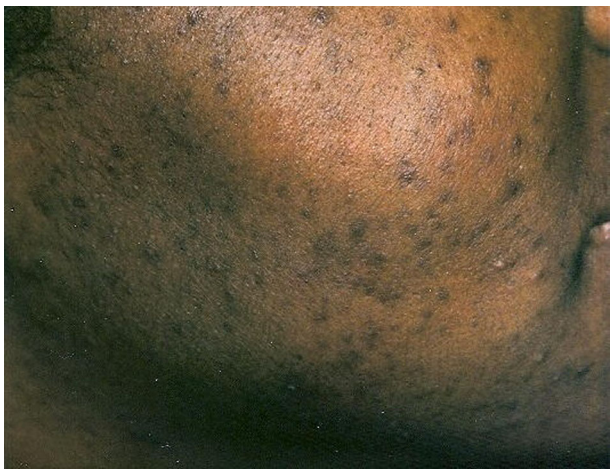

Fig. 3 Acne vulgaris with postinflammatory hyperpigmentation

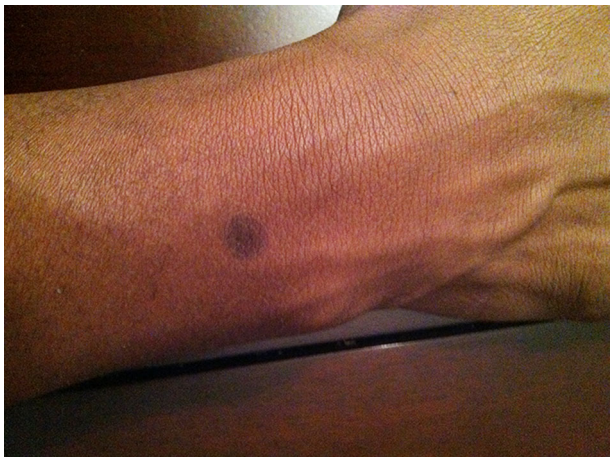

Fig. 4 Postinflammatory hyperpigmentation of the arm resulting from use of 1064-nm neodymium-doped yttrium aluminum garnet laser

selection of treatment parameters—such as lower fluences and longer pulse durations in laser hair removal and lower treatment densities in fractional laser resurfacing [39, 42, 43]. Vigilant pre- and post-procedure sun protection is also an important factor in reducing the risk of procedure-associated PIH. Some research suggests that use of topical skin-lightening agents, topical steroids, epidermal growth factor-containing creams, and oral tranexamic acid may reduce the risk of PIH after laser therapy; however, overall results have been mixed [39, 44–47].

4.2.1 Fractional Resurfacing

Although non-ablative fractional resurfacing is considered to be safe and effective in all skin types, it carries a higher risk of PIH in darker skin [39, 43, 48–50]. A study of 18 patients with FST IV–VI treated with 1550-nm fractional erbium-doped glass (Er: glass) laser reported PIH in 43% of patients treated with lower-density and 71% of patients treated with higher-density settings, even despite pre-treatment with hydroquinone 4% [39]. Another prospective study of 1550-nm fractional Er: glass laser in Asian women with FST III–IV found PIH in 6.7% of patients, with a higher risk seen in those treated with higher treatment densities, even when lower fluences were used [43]. Similarly, a retrospective review of 1540-nm fractional Er: glass laser for the treatment of acne scarring and skin rejuvenation in Asian skin demonstrated PIH in 7.1% of Chinese individuals treated with low-density/high-energy settings (for acne scarring) versus 12.4% treated with high-density/low-energy settings (for rhytides and pigmentation) [42]. Although both high-energy and high-density settings may increase the risk of PIH, treatment density appears to play a greater role in the development of PIH [49]. To minimize the incidence of PIH following non-ablative fractional resurfacing, several treatment parameters may be changed. In addition to decreasing the treatment density and energy, the risk of PIH may be decreased by reducing the number of passes per session, extending the interval between treatments, and providing additional cooling between passes [49].

4.2.2 Q-Switched Lasers

Similar to fractional resurfacing devices, Q-switched lasers are safe for use in diverse patient populations when treatment settings are tailored to the patient's skin type [41, 51, 52]. Nonetheless, inflammation of the skin induced by these lasers may result in PIH in darker skin types [41, 53]. A multi-center study of 532-nm Q-switched neodymium-doped yttrium aluminum garnet (QS-Nd: YAG) for treatment of solar lentigines resulted in PIH in 20.3% of patients, with equal risk seen in patients with FST III and IV. Interestingly, patients with invisible pores (smooth skin) were more likely to experience PIH than those with rougher skin texture [54]. A study of 532-nm frequency-doubled QS-Nd: YAG and 694-nm Q-switched ruby laser (QSRL) in the treatment of solar lentigines in 193 patients with FST III–V demonstrated PIH in 23.18–33.33% of patients treated until there was obvious immediate whitening of the skin versus 7.47–8.47% of those who were treated until slight immediate whitening was seen [53]. The risk of PIH did not differ between skin types.

4.2.3 Ablative Lasers

Ablative lasers should be used with caution in patients with darker skin types because of the high risk of PIH. A study

of dual-mode Er: YAG in the treatment of moderate to severe acne scars in patients with FST I–V demonstrated PIH in 44% of patients, most of whom had darker skin phototypes [40]. A similar risk of PIH was seen with multiple-pass, variable-pulsed Er: YAG laser for treatment of facial photodamage, rhytides, and atrophic scarring. PIH occurred in 40% of patients and took an average of 10.4 weeks to resolve with use of topical de-pigmenting agents and superficial chemical peels [41]. A retrospective chart review of 500 consecutive patients (FST I–V) treated with CO_2 laser resurfacing demonstrated PIH in 37% of patients overall and 100% of patients with FST IV and V [55].

4.2.4 Chemical Peels

Superficial chemical peels (e.g., 20–30% salicylic acid [SA], 20–70% glycolic acid [GA], 10–30% trichloroacetic acid [TCA], Jessner's solution) are typically associated with a low risk of PIH when titrated to an optimal concentration and duration of peel. Medium (e.g., 35–50% TCA, Jessner's solution plus 35% TCA) and deep (e.g., phenol) chemical peels are more likely to induce PIH in patients with skin of color and, therefore, should be used with caution in these groups [56, 57]. Small studies of 20–30% SA in patients with FST III–V, including Asian, Hispanic, and African American individuals, have demonstrated no cases of PIH [58–60]. A study of SA 35% peel in patients with FST IV–VI reported PIH in 12% of cases, although hyperpigmentation resolved within 7–10 days and occurred less frequently in those concurrently treated with hydroquinone [61]. GA 35–50% appears to be associated with a slightly higher risk of PIH in skin of color, with studies demonstrating a prevalence of 7.5–20% [62–65]. As with SA peels, use of hydroquinone priming may reduce the rate of PIH [63]. Tretinoin is somewhat less effective than hydroquinone but is also associated with a decreased risk of PIH when used before and after GA peels [63].

4.2.5 Microneedling

Data on the risk of PIH with microneedling is mixed. Several studies have demonstrated no PIH with use of microneedling for acne scars, but others have reported PIH in up to 14% of patients [66–69]. As with other procedures, the highest rate of PIH due to microneedling has been observed in patients with darker skin types [70]. Combination of microneedling and chemical peels, including GA 30% and TCA 20%, is associated with a lower risk of PIH than microneedling alone [69–71].

5 Treatment

The treatment of PIH involves a multi-faceted approach that includes topical and procedural therapy (e.g., chemical peels and laser and light treatments). Regardless of the therapeutic modality chosen, the first step in management of PIH is prevention and treatment of the predisposing inflammatory condition [27, 72].

For acne-induced PIH, prompt and aggressive management of the underlying acne is paramount and may be accomplished with a number of topical and systemic medications [34]. Medications should be chosen based on severity of acne. Topical antibiotics and/or retinoids alone would be an appropriate first-line therapy for mild to moderate comedonal or papulopustular acne, whereas severe nodulocystic or refractory papulopustular acne generally requires oral therapies (e.g., oral antibiotics, isotretinoin, or spironolactone) [34, 35]. Several studies in skin of color populations have demonstrated the safety of topical retinoids, benzoyl peroxide, dapsone, and azelaic acid in the treatment of acne in darker skin types [20, 22, 34, 35, 75–86]. Many of these topical medications have also been associated with improvement in PIH [20, 75, 85, 86].

Avoidance of UV exposure through the use of sun-protective clothing (i.e., long-sleeved shirts, pants, wide-brimmed hats) and sunscreen with sun protection factor (SPF) 30+ is also essential for preventing worsening of PIH. A recent study found that use of SPF 30 or 60 sunscreen in African American and Hispanic individuals resulted in lightening of pre-existing pigmentary abnormalities [73]. Unfortunately, data suggests that only 50% of patients with PIH use sunscreen [16, 17, 74]. Healthcare providers must emphasize the importance of sunscreen and other sun-protective behaviors in patients with PIH, particularly those with darker skin types, who are less likely to use photoprotection [74].

5.1 Topical Treatments for PIH

5.1.1 Hydroquinone

Hydroquinone is a commonly used de-pigmenting agent that inhibits melanogenesis by acting as an alternative substrate for the enzyme tyrosinase [87]. Hydroquinone may also result in inhibition of DNA/RNA synthesis, destruction of melanocytes, and degradation of melanosomes [72, 88]. This topical medication is considered to be the gold standard of treatment for disorders of hyperpigmentation and is often used as first-line therapy for PIH (Table 2).

Table 2 Published data on topical products for the treatment of postinflammatory hyperpigmentation

Topical product and strength/ vehicle	N (FST/ race)	Study design	Etiology of PIH	Results	Adverse effects	References
Tretinoin 0.1% cream	54 (Black)	Ran, DB, PC	Inflammation	40% lightening of lesions, 23% decrease in epidermal melanin content with tretinoin (vs. 18 and 3% with PL, respectively)	Minimal lightening of normal skin, retinoid dermatitis (50%)	[22]
Clindamycin/ tretinoin 1.2%/0.025% gel	33	Ran, DB, PC	Acne	On scale of 0–4, − 1.2 improvement in PIH score in active group (vs. − 0.9 in PL), but no significant difference in number of patients achieving ≥ 2-point improvement	Low incidence of scaling, erythema, burning, stinging, and itching	[75]
Tazarotene 0.1% cream	74 (III–IV)	Ran, DB, PC	Acne	Significantly greater decrease in overall disease severity, pigmentary intensity of lesions, and area of hyperpigmentation vs. vehicle	Trace erythema, burning, and peeling; mild dryness	[20]
Adapalene 0.1% gel	65 (Black)	OL	Acne	Two-thirds of patients experienced reduction in number of hyperpigmented macules and density of hyperpigmentation	80% of patients agreed or strongly agreed with the statement: "product did not irritate the skin"	[86]
Dapsone 5% gel	68	OL	Acne	Anecdotal improvement in hyperpigmentation noted by some investigators after 12 weeks	Slight increase in peeling from baseline, but decreased erythema, dryness, oiliness, and burning	[85]
AA 20% cream	52 (IV–VI)	Ran, DB, PG	NR	Significantly greater decrease in pigmentary intensity with AA vs. vehicle as measured by investigator subjective scale (17.2 vs. 3.9% mean decrease) and chromometer analysis (20 vs. 3.9% decrease)	Greater burning and stinging than vehicle	[23]
AA 15% gel	20 (IV–VI)	OL pilot	Acne	All subjects (100%) demonstrated at least a 2-point improvement in investigator global assessment (scale 0–5) at 16 weeks	Erythema, dryness, peeling	[76]
AA/GA vs. HQ 20% cream/ 15–20% lotion vs. 4%	65 (II–V)	Ran, DB, PG	NR	AA/GA was as effective as 4% HQ in treatment of hyperpigmentation. Physician-rated mean intensity (scale 0–5) decreased from 3 to 2.4 (AA/GA) and 2.3 (HQ). ~ 25% mean improvement in hyperpigmentation in both AA/GA and HQ groups	Slightly greater peeling, burning, stinging, or dryness with AA/GA than HQ	[100]
HQ/retinol 4%/ 0.15% micro-sponge	12 (II–VI)	OL	NR	Based on physician global assessment, mean improvement in PIH of 39%, 77%, and 77% from baseline to weeks 4, 8, and 12, respectively	Diffuse erythema and scaling in one patient. Otherwise, dryness, erythema, peeling, burning and pruritus were not significant	[21]
HQ/retinol/ antioxidants 4%/ 0.15% micro-encapsulated	17 (II–VI)	OL	NR	Based on investigator global improvement assessment, 63% of subjects had > 75% overall improvement in pigmentation at week 12	Contact dermatitis in one patient. Erythema and dryness improved from baseline. Itching, stinging, and burning were unchanged	[89]

Table 2 continued

Topical product and strength/ vehicle	N (FST/ race)	Study design	Etiology of PIH	Results	Adverse effects	References
HQ/GA 4%/ 10% cream	35 (IV–VI)	OL	Acne, irritation, trauma, or other	Based on physician assessment, 4% of subjects cleared completely, 76% demonstrated substantial improvement, and 20% cleared slightly. Degree of pigmentation decreased substantially from baseline to week 12 based on mexameter readings	89% with minimal or no symptoms. There was minimal burning, irritation, itching that peaked at week 4	[25]

AA azelaic acid, *DB* double-blind, *FST* Fitzpatrick skin type, *GA* glycolic acid, *HQ* hydroquinone, *N* number, *NR* not reported, *OL* open-label, *PC* placebo-controlled, *PG* parallel-group, *PIH* postinflammatory hyperpigmentation, *PL* placebo, *ran* randomized

While hydroquinone monotherapy is typically effective, combining hydroquinone with other skin-lightening or anti-inflammatory products, including alpha-hydroxy acid, ascorbic acid, retinoids, corticosteroids, and antioxidants, may result in further improvement in pigmentation with decreased risk of skin irritation (which itself may worsen hyperpigmentation) [16, 72]. An open-label study of 21 patients (17 with PIH) treated with combination microencapsulated 4% hydroquinone, 0.15% retinol, and antioxidants found a significant reduction in lesion size, degree of pigmentation, and severity of disease beginning after 4 weeks of treatment and continuing until the end of the study [89]. A fixed combination of hydroquinone 4%, tretinoin 0.05%, and fluocinolone 0.01% has also been shown to be effective in the management of PIH. A study of triple therapy cream versus dyad comparators (hydroquinone and fluocinolone, hydroquinone and tretinoin, and fluocinolone and tretinoin) was studied in 792 patients with PIH and demonstrated a higher rate of clear or almost clear skin after 8 weeks in those treated with triple therapy cream versus dyad comparators [90].

The long-term use of hydroquinone for the management of PIH is limited by the risk of developing exogenous ochronosis [91]. This difficult-to-treat condition occurs when homogentisic acid deposits in the dermis and presents as dark brown macular and papular hyperpigmentation at the site of hydroquinone application. It should be suspected in patients whose hyperpigmentation paradoxically worsens with use of hydroquinone [91].

5.1.2 Retinoids

Topical retinoids, including tretinoin (all-*trans*-retinoic acid), tazarotene, and adapalene, are commonly used for the treatment of disorders of hyperpigmentation, including PIH. Their efficacy in decreasing pigmentation appears to be due to inhibition of tyrosinase, induction of melanocyte apoptosis, and acceleration of epidermal cell turnover [92, 93]. One must be careful with the use of retinoids given the risk of skin irritation (erythema, dryness, scaling), which may result in worsening of PIH [22, 27]. Concentration and dose frequency should be titrated and vehicles carefully selected based on patient tolerance.

Several studies have established the efficacy of retinoids in the treatment of PIH. A 40-week randomized, double-blinded, vehicle-controlled trial of 0.1% tretinoin in the treatment of PIH in 54 Black patients found superior efficacy of tretinoin compared with vehicle as early as 4 weeks into treatment [22]. There was 40% lightening of the hyperpigmented skin in those treated with tretinoin versus 18% lightening in the vehicle group. In the tretinoin group, minimal lightening of the normal skin was noted. In addition, 50% of subjects developed retinoid dermatitis [22].

Adapalene 0.1% gel and tazarotene 0.1% cream have also shown promise in the treatment of PIH [20, 86]. A randomized, double-blind, vehicle-controlled study of tazarotene in 74 patients with FST III–IV with acne-induced PIH demonstrated significant reduction in overall disease severity score, intensity of hyperpigmentation, and area of hyperpigmentation compared with vehicle [20]. Overall, trace erythema, burning, and peeling were observed. An open-label study of 65 Black individuals with moderate facial acne treated with adapalene showed significant reduction in the number of hyperpigmented macules and the density of hyperpigmentation in two-thirds of patients. The majority of subjects reported no irritation of the skin with use of adapalene [86].

Retinoids are commonly combined with other skin-lightening agents to improve treatment response. An open-label, split-face study of 0.01% tretinoin/2% mequinol versus 4% hydroquinone cream in patients with facial PIH demonstrated treatment success in 81 and 85% of patients, respectively [94]. An open-label study of 0.1–0.4% tretinoin gel plus hydroquinone 5% and lactic acid 7% ointment in Asian individuals achieved treatment success in

85.7% of patients with long-standing PIH. Significant skin irritation and erythema were noted, due to the high concentration of tretinoin. Nonetheless, recurrence of PIH rarely occurred with this treatment regimen [95].

For acne-induced PIH, treatment with combination therapy including a retinoid has been shown to be efficacious. In a study of 33 patients with skin of color, those treated with combination clindamycin 1.2% and tretinoin 0.025% demonstrated superior improvement in both acne severity and PIH score than those treated with placebo [75].

5.1.3 Azelaic acid

Azelaic acid is a dicarboxylic acid that plays a role in the treatment of diverse conditions because of its anti-infective, anti-inflammatory, anti-keratinizing, and anti-melanogenic properties [96]. Its efficacy in treating disorders of hyperpigmentation results from its ability to inhibit tyrosinase, mitochondrial enzymes, and DNA and protein synthesis, resulting in decreased melanogenesis [97–99].

Studies of azelaic acid alone in the treatment of PIH are limited. However, a multi-center, randomized, double-blind study of azelaic acid 20% cream versus vehicle demonstrated a 17.2% mean decrease in investigator-rated pigmentary intensity and 20% mean decrease in chromometer-measured melanin [23]. An open-label study of azelaic acid 15% gel demonstrated a 2-point improvement in investigator global assessment of pigmentation (scale of 0–5) in 100% of patients after 16 weeks of treatment [76]. A study of combination azelaic acid 20% cream and GA 15–20% lotion versus hydroquinone 4% demonstrated a 25% mean improvement in pigmentation in both groups [100]. This suggests that azelaic acid, at least in combination with glycolic acid, is as effective as hydroquinone in the management of PIH. However, there appears to be a slightly higher rate of peeling, burning, stinging, and dryness with azelaic acid [100].

5.1.4 Cosmeceutical Products for PIH

Other medications known to be effective in the treatment of hyperpigmentation include kojic acid, deoxyarbutin, niacinamide, *n*-acetylglucosamine, ascorbic acid (vitamin C), licorice (*Glycyrrhiza glabra*) extract, and *Polypodium leucotomos* [18, 101, 102]. These products have been associated with positive results in the management of melasma, solar lentigines, and UV-induced pigmentation when combined with other skin-lightening agents, but studies in PIH are lacking [102–112]. Nonetheless, their antioxidant properties (*Polypodium leucotomos*, ascorbic acid), inhibition of tyrosinase (deoxyarbutin, kojic acid, *n*-acetylglucosamine, ascorbic acid, licorice extract), and melanosome transfer (niacinamide) suggest that these non-prescription ingredients also may be efficacious in the treatment of PIH when used in combination therapy [101, 102].

A recent study of full-face iontophoresis mask and a vitamin C preparation followed by a mandelic/malic acid skin care regimen demonstrated 78% improvement in hyperpigmentation due to PIH or melasma [113]. An in vitro study of *Lespedeza bicolor* extract suggested this product may have a role in the treatment of PIH because of its anti-inflammatory, antioxidant, and anti-tyrosinase effects [114].

5.2 Laser and Light-Based Treatment for PIH

A multitude of different lasers are currently available for the treatment of cutaneous hyperpigmentation. Given the wide absorption spectrum of melanin (250–1200 nm), both visible and near infrared lasers may be used with success to target excess melanin within the skin [115]. In general, lasers with shorter wavelengths, such as the 578-nm copper bromide, 511-nm light-emitting diode (LED), and intense pulsed light (IPL) lasers, lead to more preferential absorption by melanosomes, but only penetrate the skin superficially [116, 117]. Near infrared light lasers, such as 1064-nm QS Nd:YAG, are capable of dermal penetration but less effectively target epidermal melanosomes [52, 118, 119]. Since the absorption coefficient of melanin dramatically decreases with increasing wavelength, use of higher wavelengths will minimize the absorption by endogenous melanin within the skin, thus decreasing the risk of pigmentary sequelae following laser therapy [115, 120].

The majority of the studies evaluating the efficacy of lasers in the treatment of PIH have been small non-randomized clinical trials, case reports, and case studies (Table 3) [52, 118, 119, 121–124]. The greatest evidence exists for use of 1064-nm QS-Nd: YAG [52, 118, 119, 123, 125]. A non-randomized clinical trial of 20 Asian patients treated with weekly QS-Nd: YAG for acne vulgaris demonstrated good to excellent improvement in PIH in 95% of patients [52]. The non-laser group demonstrated no improvement in PIH. Another non-randomized study of 78 Indian patients receiving bi-weekly QS-Nd: YAG treatments demonstrated good to excellent improvement in 86% of patients, with minimal side effects [119]. Case reports, case series, and retrospective cohort studies have demonstrated similar results [118, 123, 124, 126]. Other Q-switched lasers appear to be ineffective in the treatment of PIH. Several case series of QSRL have failed to demonstrate improvement in PIH and suggest this laser may actually lead to exacerbation of PIH [127–129].

Fractional resurfacing has also shown promise in the treatment of PIH, although evidence for its use is limited to

Table 3 Clinical trials and case series evaluating the efficacy and safety of laser therapy in the treatment of postinflammatory hyperpigmentation

Tx	Type of study	*N*	No./ frequency of tx	Follow-up	Results	Adverse effects	References
694-nm QSRL	Case series	8	1 tx	4 weeks	Fairly good clearing in 4/8, no change in 3/8, and worsening in 1/8 patients	None reported	[127]
694-nm QSRL	Case series	4	1–4 tx. Every 2 weeks	12 months	No change in 1/4 patients and worsening of hyperpigmentation in 3/4 based on subjective evaluation and histological examination	Patchy hypo- and hyperpigmentation	[128]
578-/511-nm Copper Bromide/ LED	Case series	2	4–5 tx. Every 2 weeks	10-12 months	Significant clinical improvement	Mild, transient tingling and erythema	[116]
550-,570- and 590-nm IPL	Clinical trial, non-randomized	19	3–7 tx. Every 3–4 weeks	11–32 months	Based on physician grading scale, 79% of subjects demonstrated > 50% clearing, 32% showed > 75% clearing, and 11% had no change	Transient blisters (16%) and mild erythema (5%)	[117]
560- to 890-nm Pulse-in-Pulse mode IPL	Clinical trial, non-randomized	25	8 tx. Every 1–2 weeks	2 months	Based on investigator assessment, 92% of patients achieved > 50% improvement at follow-up	None reported	[7]
1064-nm QS-Nd:YAG	Case series	3	5 tx. Every 1 week	2 months	Significant clearance or improvement was noted in all patients at follow-up	None reported	[118]
1064-nm QS-Nd:YAG	Case series	5	5–10 tx. Every 1 week	3–6 months	Significant clinical improvement in all patients that was maintained at follow-up	None reported	[123]
1064-nm QS-Nd:YAG	Clinical trial, non-randomized	20	5 tx. Every 1 week	3 months	Based on scoring by blinded evaluator, 95% of patients in the laser group achieved > 75% improvement in PIH vs. no improvement in topical-only group	Mild, transient erythema	[52]
1064-nm QS-Nd:YAG	Clinical trial, non-randomized	78	6 tx. Every 2 weeks	3 months	Based on assessment by a blinded investigator, 86% of subjects had good to excellent improvement in PIH	Mild, self-resolving tingling, erythema and punctate bleeding (100%), confetti-like hypopigmentation (1.3%)	[119]
1550-nm Er:glass fractional	Clinical trial, randomized, observer-blinded	6	5 tx. Every 3 weeks	3 months	No significant improvement in the lesions was seen based on clinical assessment, reflectance spectroscopy and biopsy of lesions	PIH in 33%, present at 3-month follow-up	[133]
1927-nm thulium fractional	Clinical trial, non-randomized	10	1–2 tx	1 month	Based on blinded investigator photographic assessment, 40% of patients demonstrated > 75% improvement and 30% demonstrated 51–75% improvement	Mild erythema, edema, and desquamation	[132]

Er:glass erbium doped glass laser, *IPL* intense pulsed light, *LED* light-emitting diodes, *N* number of participants, *PIH* postinflammatory hyperpigmentation, *QS-Nd: YAG* Q-switched neodymium-doped yttrium aluminum garnet, *QSRL* Q-switched ruby laser, *tx* treatment(s)

Table 4 Glycolic acid and salicylic acid chemical peels in the treatment of postinflammatory hyperpigmentation

Peeling agent	% Peel	Depth	Adjuvant/comparator	*n*	FST	Results	Rate of PIH	References
GA	20–50	Superficial	MKF	35	III–V	Combination GA peel and MKF was associated with significantly better improvement in PIH than MKF alone	None	[136]
	50–68	Superficial	HQ 2%/GA 10% + tretinoin 0.05%	19	IV–VI	Greater and more rapid improvement in PIH in peel plus topical group than topical only group	None	[138]
SA	20–30	Superficial	HQ 4%, no comparator	25[a]	V–VI	Moderate to significant improvement in PIH in all subjects	12%. Resolved in 7–10 days	[61]
	20–30	Superficial	Tretinoin 0.1%	45	II–IV	Combination of SA peel and tretinoin was more effective than both peel and topical tretinoin used alone as monotherapy	None	[141]
	30	Superficial	None	24	NR	Non-statistically significant improvement in PIH as measured by increased lightness	None	[142]
	20–30	Superficial	None	11	IV–VI	Non-statistically significant improvement in PIH on peel-treated side of the face (vs. untreated side of face)	40%. Transient	[5]

Conc. concentration, *GA* glycolic acid, *HQ* hydroquinone, *MKF* Modified Kligman's formula, *n* number of subjects, *NR* not reported, *PIH* postinflammatory hyperpigmentation, *SA* salicylic acid

[a] 5 with PIH

case reports and small clinical trials (ten or fewer subjects). Case reports of fractional non-ablative 1550-nm Er: glass and 1927-nm fractional thulium fiber have shown marked improvement, with near complete clearing in one patient [121, 122, 130, 131]. A non-randomized study of the 1927-nm fractional thulium laser in ten patients demonstrated >50% improvement in seven patients and 75% improvement in four [132]. A randomized, observer-blinded study of 1550-nm fractional Er: glass in six patients with PIH failed to demonstrate any improvement in hyperpigmentation. Further, laser therapy caused PIH in 23% of patients [133]. Fractional ablative CO_2 laser has been associated with complete resolution of PIH in one patient with FST III, but larger studies to corroborate these findings are lacking [134].

An open-label study of IPL in the treatment of 19 Chinese patients (FST III–IV) with PIH demonstrated clinical improvement with use of 550-, 570-, and 590-nm devices. There was 50% clearance of hyperpigmentation in 79% of patients and >75% clearance in 32% [117]. Side effects included transient blistering and erythema, but no worsening of hyperpigmentation was observed [117]. Use of pulse-in-pulse mode IPL in 25 Korean patients with FST III–V demonstrated >50% improvement in PIH in the majority of patients, without any adverse events [7]. A study of 530-nm variable pulsed light device (VPL), in which only 3 of 18 patients had PIH, showed fair results in patients with this condition. Worsening of hyperpigmentation was reported [135].

5.3 Chemical Peels for PIH

Superficial chemical peels are commonly used for the treatment of PIH (Table 4) [136]. While numerous studies have demonstrated the efficacy and safety of superficial chemical peels in skin of color, careful consideration of the type, concentration, and length of chemical peel is needed to avoid irritation, which may result in worsening of PIH. Medium-depth peels (e.g., TCA 35–50%) are associated with higher risk of postprocedure PIH than superficial peels and, therefore, should be used with caution in patients with skin of color. Deep peels (e.g., phenol peels) are generally contraindicated in FST IV–VI because of both pigmentary risks and the risk of keloids or hypertrophic scars [61, 137–140].

GA is an alpha-hydroxy acid isolated from sugarcane that causes epidermolysis and desquamation of the skin, the depth of which depends on the concentration, vehicle, quantity, and duration of the peel [137]. In an open-label, randomized study of 35 Indian patients (FST III–V) treated with serial 20–50% GA peels plus Modified Kligman's Formula (MKF) versus MKF alone, those who had undergone the peels demonstrated significantly better improvement in hyperpigmentation than those who used MKF only [136]. Those in the peel group exhibited a mean decrease in HASI of 11.16 ± 3.43 at week 12 and 17.72 ± 2.62 at week 21 (baseline HASI 19.29 ± 2.9). Those who received MKF (baseline HASI 16.66 ± 4.3) only demonstrated 5.15 ± 6.14 and 11.53 ± 5.65

improvement at 12 and 21 weeks, respectively. Similar results were seen in an earlier pilot study wherein weekly application of 50 or 68% GA peels combined with a daily topical regimen (tretinoin 0.025%, hydroquinone 2%, GA 10%) was associated with a significant decrease in HASI and colorimetric analysis [138]. In both studies, use of a combination topical therapy for 2–4 weeks before treatment, with discontinuation 2 days before the procedure, was associated with superior efficacy of the chemical peel [136, 138].

SA is a beta-hydroxy acid derived from the bark of willow trees that functions as a keratolytic and comedolytic agent [137]. Results using SA peels in the treatment of PIH have been mixed. An early study of 20–30% serial SA peels plus hydroquinone 4% in 25 patients with skin of color, five of whom had PIH, demonstrated moderate to significant improvement in hyperpigmentation and skin texture in all patients. The use of twice-daily hydroquinone 4% for 2 weeks before the first chemical peel and following each peel likely contributed to the positive results in this study [61]. A recent non-blinded, comparative study of 20–30% SA peel plus topical tretinoin 0.1% versus both treatments alone similarly demonstrated significantly better improvement in PIH with combination treatment [141]. In both of these studies, there appeared to be an additive benefit of SA peel and topical therapy due to the combined effects of exfoliation (by SA) and inhibition of tyrosinase (by hydroquinone and tretinoin) [61, 141].

Studies on SA peel without a concurrent topical regimen have failed to establish the efficacy of this treatment. An open-label study of 24 Koreans with acne treated with 30% SA every 2 weeks for six total treatments demonstrated numeric improvement in hyperpigmentation based on colorimetric assessment of lightness (L^*), but the increase in L^* did not reach statistical significance [142]. Similarly, a randomized, open-label, split-face study of 20–30% SA in ten patients with skin of color (African American and Indian) demonstrated no difference in pigmentation based on blinded investigator rating of photographs [5]. Patients, who were not blinded to the treatment, reported statistically significant improvement in PIH on the chemical peel side.

Side effects of superficial and medium-depth chemical peels include erythema, burning, desquamation, vesiculation, dryness, itching, and crusting [5, 136, 138, 141, 142]. Some of these side effects (e.g., dryness, exfoliation, burning) may be exacerbated by concurrent use of a topical skin care regimen containing tretinoin or hydroquinone [141]. In some cases, irritation of the skin may result in worsening of PIH as well as transient hypopigmentation [5, 136, 138, 141, 142].

6 Conclusion

Overall, evidence suggests that topical and procedural therapies are effective and well-tolerated in the treatment of PIH, especially when used in combination. Nonetheless, both may result in worsened hyperpigmentation if not used cautiously. High concentrations of topical products, particularly hydroquinone and retinoids, may cause irritation of the skin, ultimately resulting in PIH in darker skin types. Similarly, use of lasers and peels can result in iatrogenic hyperpigmentation, particularly when aggressive laser settings or deeper peeling agents are used.

To decrease the risk of worsening PIH, topical medications and chemical peels should be started at lower concentrations (i.e., tretinoin 0.025%, GA or SA 20% peel) and titrated up as tolerated by the patient. Energy-based devices should be started at conservative treatment settings (i.e., low treatment density, low fluence, smaller number of passes) and slowly increased at subsequent sessions.

Randomized clinical studies evaluating the efficacy and safety of topical modalities, chemical peels, and laser devices in the treatment of PIH are lacking. The majority of studies have included small sample sizes and were unblinded. Much of our understanding of laser therapies has come from individual case reports and small case series. Moving forward, inclusion of large patient sample sizes, sub-analyses by skin type, and use of skin spectroscopy for objective measurement of skin pigmentation will be essential for determining the safety and efficacy of commonly used treatments for PIH across diverse ethnic groups. Given the predominance of studies in Asian skin, further research is needed in darker FSTs, particularly in individuals of African ancestry.

Compliance with Ethical Standards

Conflicts of interest Dr. Kaufman and Ms. Aman have no conflicts of interest or financial disclosures to report. Dr. Alexis reports the following conflicts of interest and financial disclosures: grant to institution for clinical trial (Allergan) and honoraria for advisory board/consulting (Galderma and Allergan).

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