Management of Pigmentary Disorders

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Post-inflammatory Hypopigmentation

Post-inflammatory hypopigmentation (PIH) is an acquired consequence of prior skin inflammation, trauma, or exposure to an outside agent that leads to partial or complete loss of pigmentation in the skin. The extent of pigment loss directly correlates with the severity of the inciting process. Though PIH occurs in both sexes and all ethnicities, some individuals are more susceptible to developing PIH than others. It is also more clinically appreciable in dark-skinned individuals. PIH lesions present as hypopigmented macules or patches on virtually any area of the skin from the head to toe in an area of prior skin affliction (Fig. 10.1). Associated overlying epidermal and surface change may or may not be present, dependent upon depth of involvement of the inciting event.

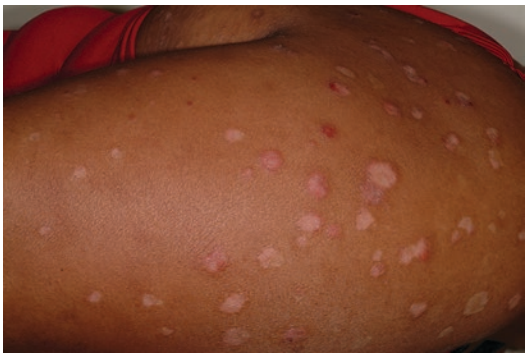

Fig. 10.1 Post-inflammatory hypopigmentation

The specific cause of acquired PIH as a result of skin injury remains to be completely elucidated; however, it is suspected that susceptibility is genetically predetermined in an autosomal dominant fashion with some individuals possessing melanocytes that are more at risk of damage due to stressful events and inflammation [1]. It is hypothesized that PIH occurs mainly due to inhibition of melanogenesis; however, in some conditions, direct destruction of melanocytes leading to permanent hypo- or depigmented lesions can also occur.

There are many underlying skin conditions that result in PIH. These categories include inflammatory skin diseases such as atopic dermatitis, pityriasis alba, psoriasis, sarcoidosis, lichen striatus,

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and pityriasis lichenoides chronica. Cutaneous infections such as secondary syphilis, tuberculosis, leprosy, tinea versicolor, and mycobacteria can also cause lesions of hypopigmentation. Connective tissue disorders like Lichen Sclerosus et. Atrophicus (LS&A) and scleroderma can also present with hypopigmented skin areas. Along with inflammatory skin disease and infection, prior physical trauma can cause PIH lesions, including exposure to various chemicals such as phenols, corticosteroids, monobenzyl ether of hydroquinone (MBEH), and chemical peels, as well as physical trauma through accidental injury, cryotherapy, dermabrasion, and lasers [2–4].

Investigation of hypopigmented lesions to distinguish PIH lesions secondary to injury/trauma or chemical exposure from other more serious diseases or infections that lead to hypopigmentation is vital. Clinical examination should include evaluation of the area with a Wood's lamp to distinguish PIH from depigmented fluorescent lesions of vitiligo, coppery orange fluorescent lesions of progressive macular hypomelanosis, and yellowish fluorescence seen in tinea versicolor. Histopathologic evaluation is also important to rule out underlying conditions that can present with hypopigmented lesions such as lupus, mycosis fungoides (MF), and sarcoidosis that have distinguishing path findings. Histology of PIH lesions is nonspecific and can include a mild to severe lymphohistiocytic infiltrate, reduction in dermal melanin, and scattered melanophages.

Regarding treatment of PIH, it is important to first identify the underlying culprit. Once that has been treated, hypopigmentation will most often gradually resolve on its own over time. Preparations containing both a topical steroid and tar have been reported to aid in repigmentation of PIH lesions, with the steroid addressing residual inflammation and tar inducing melanin production [5, 6]. Topical calcineurin inhibitors have also been reported to treat PIH associated with seborrheic dermatitis in one open label, pilot trial. Pimecrolimus 1% cream was applied to affected areas twice daily for 16 weeks leading to improvement of PIH [7]. Ultraviolet light exposure can also aid in repigmentation of PIH lesions; however, it can also enhance contrast with the surrounding skin as that often also becomes tanned through the same light exposure. Topical 0.1–0.5% 8-methoxypsoralen, coal tar, or anthralin in combination with UVA exposure has been reported to improve PIH. 8-methoxypsoralen compounded in Aquaphor is applied to the affected areas of PIH for 20–30 min, followed by exposure of these areas to UVA light at an initial dose of 0.2–0.5 J/cm^2 1–3 times weekly. The dose is increased by 0.2–0.5 J/cm^2 weekly until improvement is noted, and then the dose is maintained [8, 9]. Reports of improvement in PIH with the 308 nm excimer laser have also been noted to induce pigmentation in hypopigmented scars, with a reported response of 60–70% after 9 weeks of treatments twice weekly. Maintenance treatments will likely be needed every 1–4 months to maintain pigmentation. For extensive cases of PIH, NB-UVB has also been shown to lead to repigmentation of hypopigmented lesions, especially in cases of vitiligo [10]. Cosmetic makeup, self-tanning products, and tattooing may be alternative camouflage options available for some patients. Surgical grafting of tissue or cells can also be considered in vitiligo lesions.

Hypopigmented Mycosis Fungoides

Mycosis fungoides is the most common type of primary cutaneous T cell lymphoma, accounting for up to 60% of all cases [11]. It mainly affects the skin, with minimal systemic involvement until advanced stages. The mean age of onset in most cases is during the fifth decade, with various clinical presentations, including patches, plaques, granulomatous, folliculotropic, and ichthyosiform lesions [12, 13].

One additional subtype, hypopigmented mycosis fungoides (HMF), is a unique variant in that it differs from the other types of cutaneous T cell lymphoma in several ways. First, hypopigmented MF usually presents in the younger population, for which the average age of onset is in the second to third decade of life [14]. It most commonly presents as asymptomatic hypopig-

Fig. 10.2 Hypopigmented mycosis fungoides

mented to slightly scaly patches and plaques mainly localized to the proximal lower body (i.e., buttocks, upper thighs) and trunk (Fig. 10.2). Occasional involvement of the face and upper extremities can occur [15, 16].

Histopathologic findings of HMF include focal parakeratosis, minimal to absent spongiosis, with a lymphocytic infiltrate in the upper dermis with epidermotropism. Pautrier microabscesses are rare. The malignant cell population in HMF is mainly composed of clonal CD8 T cells, which differs from the CD4 T cells most commonly found in classic MF. It is suspected that these neoplastic cells attack and destroy melanocytes leading to their destruction and decreased melanogenesis, contributing to the hypopigmentation of the affected areas (HMF [17, 18]).

Along with a skin biopsy to confirm the diagnosis, patients with HFM should also be evaluated with a complete blood count and peripheral blood smear to identify the presence of Sezary cells, as well as T cell clonal population using flow cytometry.

Since HMF is typically skin limited, treatment is mainly targeted toward the skin only. Limited skin involvement (<10% BSA) can be treated with topical steroids and calcineurin inhibitors, nitrogen mustard, bexarotene, mechlorethamine, and carmustine. For more advanced cases with >10% BSA involvement, combination treatment is often recommended including both topical medications and phototherapy (both UVA and NB-UVB) [19–23]. In one study, more patients reported preference for NB-UVB phototherapy over UVA for treatment of Stage 1A disease, and this is often the preferred treatment for clinicians as well, due to lower side effect profile [24].

Pityriasis Alba

Pityriasis alba (p alba) is a common benign skin condition presenting with round or oval slightly scaly hypopigmented patches most commonly found on the face (especially cheeks) and upper trunk of children and adolescents, ranging from 3 to 16 years old [25–27] (Fig. 10.3). Occasionally, patients may report of mild pruritis, but most times, lesions are asymptomatic. There is no known racial predilection of p alba; however, lesions are more appreciable in patients with darker skin types and can also be accentuated with UV exposure during the summer months.

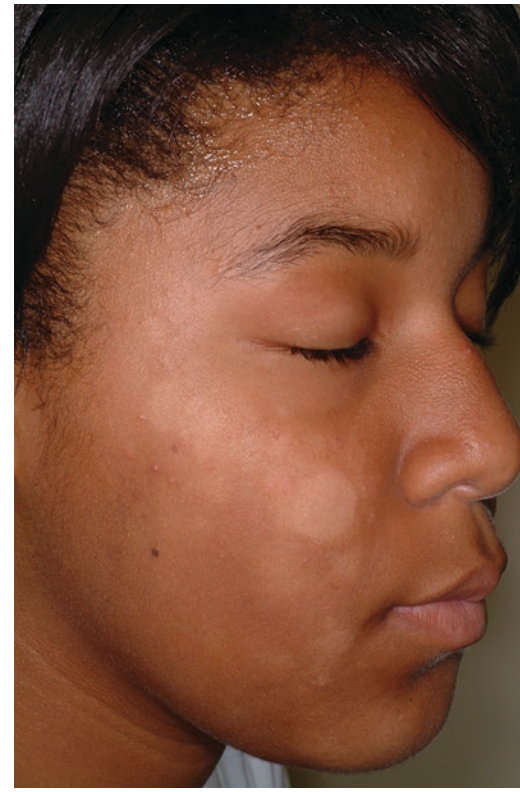

Fig. 10.3 Pityriasis alba

Oftentimes, patients also report a history of atopic dermatitis. Pigmentation of the lesions will spontaneously return over time, usually within 1 year.

Histopathologic findings of p alba include hyperkeratosis, parakeratosis, acanthosis, and spongiosis, with a mild perivascular infiltrate. The hypopigmentation is due to reduced melanin in the basal layer with decreased number of active melanocytes, as well as decreased number and size of melanosomes. The number of total melanocytes, however, is not decreased [28–30]. It is important to rule out underlying causes of hypopigmentation patches in children including tinea versicolor, vitiligo, seborrheic dermatitis, hypopigmented mycosis fungoides, and nevus depigmentosus. This can be done via evaluation of lesions with a Wood's lamp, KOH prep, and skin biopsy.

Treatment of p alba is not required as it most commonly spontaneously resolves over time on its own, though often taking several months to up to 1 year. Gentle skin care with fragrance- and dye-free products should be encouraged. Low-potency topical steroids, calcineurin inhibitors, and topical vitamin D analogs such as calcitriol can be used to reduce associated erythema or pruritis and accelerate repigmentation of the area [31, 32]. The excimer 308 nm laser can also be used for isolated areas to promote repigmentation [33]. Sunscreen should also be applied to the affected and surrounding area to minimize risk of sunburn and decrease darkening of the surrounding skin.

Tinea Versicolor

Tinea versicolor (TV) is a common superficial dermatophyte infection caused by fungi from the *Malassezia* genus. The most common species causing the condition is *M. globosa* followed *M. furfur*. *Malassezia* is commonly found on the skin but becomes pathogenic when it is converted from the yeast to the mycelial form [34]. Worldwide prevalence is 1–4% in temperate climates and 30–40% in tropical areas [35]. Recurrence rate of the TV after discontinuation of treatments can be up to 80% in the first 2 years [36]. There is no known gender or racial predilection; however, the condition might be more visible in darker-skinned individuals. The classic clinical presentation is annular and oval-shaped hypo-/hyperpigmented and even pink scaly plaques occurring most commonly on the trunk, neck, upper arms, and occasionally the face (Fig. 10.4). Often these lesions are asymptomatic; however, patients may also report of mild pruritis [37]. Patients also report that the conditions recur and are most pruritic with heat and moist conditions.

The hypopigmentation that commonly occurs in TV is due to inhibition of tyrosinase by dicarboxylic acid, which is produced by *Malassezia*. In addition, it is also hypothesized that the fungus damages melanocytes and causes accumulation of material in the stratum corneum which blocks ultraviolet light [38]. The hypopigmentation may persist for several months even after the fungus has been cleared.

Malassezia is usually eradicated by T cells in immunocompetent individuals; however, certain environmental conditions support its overgrowth including heat and humidity, as well as the use of oily topical preparations, and genetic predisposition [39].

Diagnosis of TV is most often made clinically due to its classic presentation; however, a KOH preparation of scaling from an active lesion can also reveal fungal elements in the stratum corneum, often referred to as "spaghetti and meatballs." Wood's lamp evaluation can also reveal a bright yellow or gold fluorescence of TV lesions.

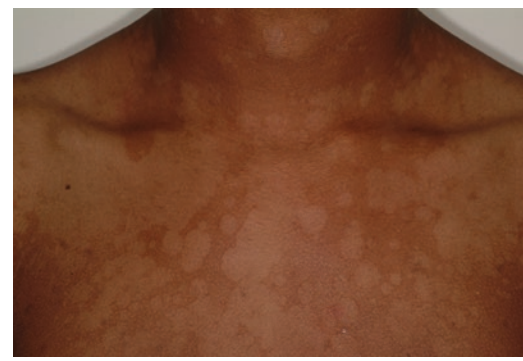

Fig. 10.4 Tinea versicolor

Treatment of tinea versicolor most commonly includes topical antifungal and non-antifungal shampoos and creams. Nonspecific antifungals include selenium sulfide, salicylic acid, zinc pyrithione, and ciclopirox in various preparations including shampoos, lotions, foams, and creams. Direct antifungal creams and shampoos are also used including clotrimazole, ketoconazole, and terbinafine applied daily to twice daily for up to 14 days with up to 80% clearance [37]. In certain recalcitrant cases, oral antifungals might be indicated, including fluconazole and itraconazole. Standard itraconazole dosing is 200 mg per day for 7 days with 80% clearance [40]. Fluconazole dosed at 300 mg/week × 2 weeks leads to 97% cure rate [39]. Pramiconazole is a new oral antifungal that is currently being investigated as a future TV treatment [41]. Prophylactic treatment with weekly or monthly use of a topical or oral antifungals might also be beneficial in patients who often have recurrent episodes of TV. Several case reports have noted a possible role of NB-UVB phototherapy in TV treatment [42].

Progressive Macular Hypomelanosis

Progressive macular hypomelanosis (PMH) is an acquired disorder of hypopigmentation. It classically presents with asymptomatic hypopigmented nonscaly macules and patches on the trunk and upper extremities, with occasional involvement of the face and neck [43] (Fig. 10.5). There is usually no preceding identifiable skin condition in areas of involvement [44]. Pathogenesis of PMH has not been definitively elucidated; however, multiple studies report a causal relationship between the Type III strain of *Propionibacterium acnes*, a Gram-positive anaerobic rod, and the development of PMH. Prior studies have shown that biopsies from PMH hypopigmented skin revealed *P. acnes* in pilosebaceous ducts, which were absent in non-lesional skin. Lesional skin also revealed coppery-orange/red fluorescence, indicating the presence of P. *acnes* [45]. The hypopigmentation within the lesions is thought to be due to both a decrease in melanin production and change in melanosome distribution (favoring aggregated or clustered melanosomes instead of the usually single dispersed pattern), both leading to a decrease in epidermal melanin and subsequent hypopigmentation.

Fig. 10.5 Progressive macular hypomelanosis

Histologic examination of PMH often reveals normal skin, with only very mild decrease in epidermal melanin pigment. PMH is a diagnosis of exclusion after other conditions with similar presentations have been ruled out, including tinea versicolor, mycosis fungoides, seborrheic dermatitis, pityriasis alba, and leprosy. Wood's lamp evaluation can also reveal coral red fluorescence of PMH lesions [44].

Given the presence of *P. acne* bacteria in lesional skin, suggested treatment of PMH often incudes antibacterial medications, including benzoyl peroxide and clindamycin, with various improvements reported, ranging from 30% to 80% over 8–12 months, with no recurrence or relapse up to 2 years after [45]. Spontaneous resolution has also been reported in some cases, usually taking at least 1 year. Other reported successful treatments of PMH include NB-UVB phototherapy with response rate of up to 50–90% of patients having up to 90% repigmentation. The typical protocol is NB-UVB phototherapy twice weekly for at least 3 months to note improvement [46] . In multiple studies, an initial response to treatment is seen after an average of six treatment sessions. Maximum repigmentation typically occurs after 22 sessions. If no improvement is noted after 3–6 months, the treatment should be considered a failure and discontinued. The

mechanism of action for NB-UVB treatment is thought to be due to both a stimulated release of inflammatory markers that help to eradicate *P. acnes* and stimulating residual melanocytes to increase melanin production [47]. Along with phototherapy and antibiotics as treatment for PMH, one case report noted a patient's PMH responding and resolving with low-dose isotretinoin 10 mg/day after 1 month of treatment, which remained clear at 10 months follow-up. The potential mechanism for isotretinoin's treatment of PMH is through its inhibitory effect on sebum production and reduced *P. acnes* colonization, leading to repigmentation [48]. In most cases of PMH, patients are treated with a combination of treatments, including both topical antibiotics and phototherapy for maximum benefit.

Idiopathic Guttate Hypomelanosis

Idiopathic guttate hypomelanosis (IGH) is a benign dermatosis characterized by scattered hypopigmented round to oval macules often identified on the extremities of older individuals with up to 80% of patients over the age of 40 [49, 50] (Fig. 10.6). Lesions are usually asymptomatic and have no overlying surface changes. There is no racial predilection; however, lesions are often more noticeable in darker skin types. The pathogenesis of IGH is unknown, but it is thought to be due to a combination of both genetic and environmental factors. Sun exposure has often been reported as a causative factor; however, this has not been fully elucidated. Genetics has also been identified as a contributing factor, as reports have shown IGH lesions in patients with a positive family history [51]. Repeated trauma has also been proposed as a precipitating cause of IGH lesions, explaining common areas of involvement including the anterior tibia which are often subject to accidental external trauma.

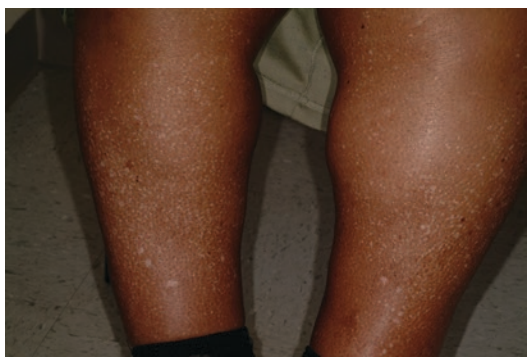

Fig. 10.6 Idiopathic guttate hypomelanosis

The underlying mechanism behind the hypopigmentation in IGH lesions may be due to a slight reduction in the overall total number of melanocytes. Other findings in IGH lesions might also include decreased tyrosinase activity, decreased number of melanosomes, or abnormal keratinocyte uptake of melanosomes [52]. There may also be a mild mononuclear inflammatory infiltrate in some lesion samples. Diagnosis of IGH is most commonly made via clinical observation alone; however, if a biopsy is conducted, it will likely reveal hyperkeratosis, an atrophic epidermis, flattened rete ridges, and a decrease in the number of active melanocytes in the basal layer of the epidermis and decreased melanin production [51].

Given that lesions of IGH are asymptomatic and benign, no treatment is necessary. However, because it is thought that sunlight is a contributing factor, sunscreen and sun protection with physical barriers are important. Other reported treatments to improve IGH lesions have included cryotherapy, topical calcineurin inhibitors, topical retinoids, as well as excimer laser [53–55]. Fractional CO_2 laser and dermabrasion have also been reported as potential treatments for IGH lesions with variable results [56]. A report by Wambier demonstrated repigmentation of IGH lesions after microinfusing 5-fluorouracil to the lesions using tattoo equipment [57].

Vitiligo

Vitiligo is an autoimmune skin disorder characterized by the appearance of depigmented lesions on the skin and mucosal surfaces [58]. It is suggested that 0.5–2% of the world population is affected by vitiligo without a well-established predilection for gender or ethnicity [59].

Regarding age, almost 50% of cases affect the adolescent population before the age of 20 [60]. Vitiligo classically presents with depigmented macules and patches on the skin and mucosal surfaces, with occasional involvement of hair follicles (Fig. 10.7). Factors that have been reported to induce vitiligo lesions include trauma (known as the Koebner phenomenon), stress, sunburn, and pregnancy [61–63]. Chemicals such as 4-tert-butylphenol, rhododendrol, and various hair dyes, which all contain phenol that acts as a tyrosinase inhibitor, can also induce vitiligo-like lesions [64, 65].

The appearance of vitiligo patterns can be classified into localized, segmental, and universal. Localized lesions present as isolated, small depigmented patches that often appear in a symmetric distribution. Acrofacial pattern is a subtype of localized vitiligo where the lesions are mainly confined to the head, hands, and feet. "Lip tip" vitiligo is another localized subtype that involves only the distal fingers, toes, and facial orifices. Segmental vitiligo is a rapidly progressive condition in which a unilateral often linear depigmented patch occurs quickly (often over 6 months) and is associated with rapid leukotrichia (loss of hair pigment), which is a hallmark finding. It most often stabilizes earlier than other types of vitiligo; however, it is a very rare subtype. Segmental vitiligo is less responsive to treatment, and this is thought to be due to involvement of the hair follicles, which leads to a lack of melanocyte repository available for repigmentation. Universal vitiligo is a term reserved for near-complete or complete depigmentation of the skin of greater than 80% body surface area [66, 67].

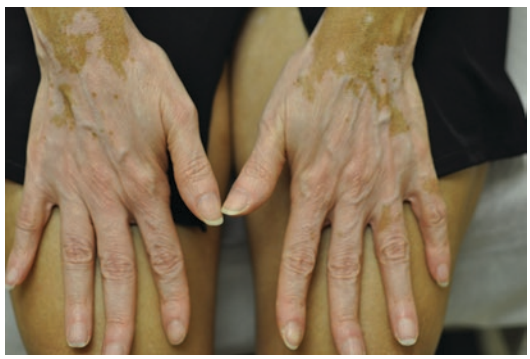

Fig. 10.7 Vitiligo

The pathogenesis of vitiligo is thought to be one of autoimmunity that targets melanocytes for destruction. It has been reported that melanocytes are more susceptible to stress-induced injury because they produce large amounts of the protein melanin which can activate a stress pathway and lead to the production of reactive oxygen species. This in turn leads to the release of inflammatory cells including CD8 T cells that release IFN-gamma and induce the release of CXCL10 and its receptor CXCR3 to recruit additional T cells to attack melanocytes [68–70]. Prior studies have reported vitiligo as inherited in a polygenic pattern, meaning that multiple alleles are involved in the melanocyte's increased susceptibility to injury leading to the condition.

Vitiligo has been associated with various other autoimmune diseases in both the affected patient and their first-degree relatives. Some of these conditions include autoimmune thyroiditis, Type 1 diabetes mellitus, pernicious anemia, rheumatoid arthritis, and lupus [71, 72]. There are also several conditions that present with both vitiligo lesions and changes in the eyes and ears (which also contain melanocytes). Vogt-Koyanagi-Harada syndrome presents with depigmented skin lesions and leukotrichia, as well as ear pain, vertigo, hearing loss, meningitis, and symptomatic uveitis which can lead to blindness [73]. Alezzandrini syndrome often shows similar clinical findings; however, the skin findings typically present with segmental vitiligo [74].

Diagnosis of vitiligo can often be made clinically; however, thorough evaluation of vitiligo lesions is also important. This includes examination with a Wood's lamp exam which will commonly fluoresce with vitiligo lesions as well as a skin biopsy. The biopsy will often show loss of basal melanocytes in the center of the lesion with a possible inflammation with CD4 and CD8 T cells at the border of an active lesion (even without active erythema on clinical exam) [75].

Treatment of vitiligo should focus on two goals: stopping progression of depigmentation and repigmentation of existing lesions.

Identifying active disease is vital, as halting the progression is time sensitive to minimize the extent of disease involvement. There are three findings that should raise suspicion of active disease. These include Koebner phenomenon, inflammatory lesions (i.e., erythematous), and confetti-like lesions. Treatment options of vitiligo include topical medications, phototherapy, surgical interventions, as well as immunomodulation and camouflage [76].

Initial treatment of localized vitiligo includes potent topical steroids and calcineurin inhibitors applied to the affected areas twice daily. In combination, these medications have been shown to be effective in halting inflammation and inducing repigmentation while providing an intermittent break from chronic topical steroid use. In cases where BSA involvement is 5–10% or greater, topical treatment should be combined with phototherapy for maximum results. Vitamin D analogs such as calcipotriene, when combined with phototherapy, may also expedite repigmentation and reduce overall required treatment with phototherapy; however, no studies have shown improvement in repigmentation when calcipotriene is used as a single agent [76].

Phototherapies that have been shown to stabilize disease progression and lead to repigmentation include NB-UVB, PUVA, PUVA plus psoralen, BB-UVB, and excimer. Phototherapy induces apoptosis of T cells in active lesions as well as concomitantly stimulating active melanocytes in perilesional skin and hair follicles, which can lead to repigmentation of the depigmented areas [77]. Response rates for both PUVA and NB-UVB range from 40% to up to 75% with better responses reported in patients with new-onset lesions [78]. In the past, PUVA was the treatment of choice; however, in a review, PUVA was determined to be inferior to NB-UVB, even though PUVA causes more rapid repigmentation [78]. NB-UVB has been found to be more effective in stabilizing disease and causing repigmentation, with one report showing 75% maximum repigmentation rate with NB-UVB at 1 year. Patients are often started at a dose of 100–200 mJ two to three times weekly with the dose gradually increased 10–20% each week until the desired light erythema is appreciated within vitiligo lesions. Once this occurs, the dose should be maintained until this erythema is no longer present. At that point, the dose should again be gradually increased [79–81]. The most responsive areas to phototherapy are often the face and neck, followed by the limbs and trunk. Acral areas show the lowest rates of repigmentation. Excimer 308 nm laser can also induce stability and repigmentation of vitiligo lesions; however, given the limited visual treatment field of the handheld laser, it is often reserved for localized cases when less than 10% BSA is involved. A lack of response to any of the treatments after 6 months indicates nonresponse and should be discontinued. In all types of phototherapy, patients should not apply any topical treatment immediately prior to treatment and should be adamant about sun protection with sunscreen and sun-protective clothing to minimize side effects from additive UV sunlight exposure.

In cases of rapidly progressive disease, oral minipulse steroid therapy is often used. One study reported that low-dose (5 or 7.5 mg) betamethasone or dexamethasone taken on two consecutive days each week for 3–6 months leads to halting of progression, with almost 90% of treated patients having stabilization of disease within 1–3 months [82, 83]. This is most often combined with phototherapy and topical treatment. Other immunosuppressive medications including methotrexate and cyclophosphamide have also been reported as effective treatments in stabilizing vitiligo in limited studies [84–87]. With the use of all immunosuppressive treatment, phototherapy should also be used in combination. Newer medications under current investigation to treat vitiligo include afamelanotide and JAK inhibitors including tofacitinib and ruxolitinib.

With all nonsurgical interventions for the treatment of vitiligo, it is important to be prepared for restarting treatment in the cases of relapse, which occurs in up to 40% of cases within the first year of stopping treatment. One study reported patients that had completed phototherapy treatment continued a maintenance regimen of twice weekly application of tacrolimus ointment to the treated areas on the head and neck. In this

group, 96% of patients reported no relapse; however, 60% of patients using a placebo ointment experienced recurrence of lesions. Therefore, it has been suggested to continue a maintenance regimen of tacrolimus 0.1% ointment to the treated areas twice weekly to minimize the risk of relapse [88].

In addition to topical medications and phototherapy, several surgical treatment options are also available that can provide repigmentation of stable vitiligo lesions. A benefit of surgical intervention over nonsurgical intervention is that when repigmentation occurs in previously affected areas, relapse and recurrence of vitiligo in those areas are uncommon. Surgical options available today include minipunch grafts, suction epidermal grafting, and cellular grafting. These treatments should only be reserved for stable vitiligo cases. Stable vitiligo is defined as a patient without new or expanding lesions for a period of time from 6 months to 2 years. In addition, the patient should not have inflammatory, trichome, or confetti-like lesions, as these also indicate active disease. It is also important to be aware that certain areas are less responsive to surgical interventions, including over the joints (possibly due to repeated trauma and friction) and acrofacial areas, whereas head and neck recipient sites tend to portend the best outcomes.

Tissue grafts involve the transfer of nonaffected pigmented tissue to a depigmented area. In contrast, cellular grafts are reserved for larger surface areas. These grafts are comprised of suspensions of donor site melanocytes and keratinocytes.

There are two types of tissue transplants: minipunch and epidermal suction grants. In performing minipunch graft transplants, 1–1.5 mm punch biopsies from an area of non-affected, pigmented skin are transferred into a prepared recipient, depigmented site. Though the technique is simple, potential complications include irregular surface changes and a risk of scarring and keloid formation at both the donor and recipient sites [89, 90]. Another tissue transfer technique is suction blister epidermal grafting. In this process, blister roofs are created from a normal skin with a suction tool and transferred to the affected skin that has been pretreated with epidermal abrasion. This option has a lower risk of textural changes, scarring, or dyspigmentation; however, the risk of hemorrhagic blisters can be a concern [91].

The other type of surgical transplant in vitiligo is cellular grafting, also known as melanocyte keratinocyte transplant procedure. In most cases, noncultured cellular skin grafts are developed by creating a suspension of melanocytes and keratinocytes from a thin pigmented donor skin graft. The thin grafts are suspended in trypsin to allow separation and removal of the epidermis, which is then manually separated and centrifuged to create a liquid suspension. This product is then resuspended in lactated Ringer's and applied to a recipient depigmented site that has first been prepared with superficial abrasion to encourage absorption of the cellular product. Patients should be careful with the treated areas and remove the covered dressings 4–7 days after treatment [92]. This technique has positive results; however, there are disadvantages, which include the required equipment to create the cellular suspension, which can be costly. When comparing the overall efficacy of all three surgical treatments of vitiligo, noncultured cellular graft suspension has been shown to yield a more aesthetically appealing outcome; however, blister and punch grafts are easier techniques and require minimal extra-expensive equipment or tissue processing procedures.

In cases where vitiligo affects >50% BSA, some patients prefer to depigment the remaining pigmented skin to provide a more even physical appearance. Monobenzylether of hydroquinone (MBEH) is the only drug currently approved by the FDA for the treatment of vitiligo and is used to depigment the skin. Compounded MBEH at 20% concentration is applied to areas of pigmentation twice daily. This treatment often requires 4–12 months of application in order to obtain the desired effects of complete depigmentation. The most common side effect of MBEH is an irritant contact dermatitis. Strict sun exposure should be minimized to prevent perifollicular repigmentation from hair melanocyte reserves. Even after complete depigmented results are achieved, it will likely be necessary to touch up

early-repigmenting areas with MBEH several times per week if necessary [93].

There are also several newer medications currently under current investigation for treatment of vitiligo including afamelanotide and JAK inhibitors such as tofacitinib and ruxolitinib. Afamelanotide is a synthetic analogue of alpha-melanocyte-stimulating hormone. One study used this synthetic hormone in conjunction with NB-UVB to treat vitiligo patients in a double blind, multicenter study. Those patients who received both treatments together reported repigmentation rates of almost 50% compared to 33% of patients only receiving NB-UVB phototherapy in the study. Commonly reported side effects associated with afamelanotide include nausea, itching, and generalized hyperpigmentation [94, 95]. Additional future studies need to be conducted to further elucidate this potential treatment option.

Tofacitinib and ruxolitinib are JAK inhibitors that are also currently being investigated as potential treatments for vitiligo. The mechanism behind JAK inhibitors affecting vitiligo is based on the known increase in interferon gamma-CXCL10 identified in vitiligo lesions. JAK inhibitors directly inhibit interferon signaling, allowing for melanocyte stabilization, survival, and increased melanin production, leading to repigmentation. One study reported that after oral ingestion of tofacitinib, which is a JAK1/3 inhibitor, the patient's serum CXCL10 level was lower than the initial value, possibly providing insight that JAK inhibitors affect vitiligo patients through inhibition of interferon gamma-CXCL10. This finding might be a way to quantitatively evaluate a patient's disease activity and response to treatment in the future. Topical forms of ruxolitinib in small studies have also begun to show promising results; however, additional replicative studies are necessary to validate results [96–99].

In addition to pharmacologic, phototherapy, and surgical interventions in vitiligo, several studies have hypothesized a potential role of various vitamin supplementation to improve repigmentation, including vitamin C, D, E, folate, B12, and zinc. This is thought to be due to their anti-oxidative properties which can decrease the effect of reactive oxygen species on their attack of melanocytes. These studies are continuing to be investigated [100].

Finally, discussing camouflage techniques with makeup, self-tanners, and possible permanent pigment tattooing should be discussed with patients [101, 102]. Various support groups for vitiligo patients exist, and it is important to provide education and support resources for all patients, as this disease can affect them not only physically but also psychologically [103–105].

Post-inflammatory Hyperpigmentation

Post-inflammatory hyperpigmentation (PIH) is an acquired pigmentary disorder that results after an inflammatory reaction such as acne vulgaris, psoriasis, atopic dermatitis, allergic or irritant contact dermatitis, trauma to the skin, or laser/light therapy [106–111]. It can present anywhere on the body, as it is a result of an existing inflammatory process or injury. Lesions appear as tan-brown to dark brown macules or patches, though they can even be a dark gray or blue-gray color when the inciting event occurs within dermis (Fig. 10.8) [110]. PIH is most common in Fitzpatrick skin types III–IV and is due to hyperreactive melanocytes known as hypermelanosis [106, 108, 110]. Melanocytes react to the initiating inflammatory process and become hypertrophic, secreting more melanin [109]. PIH can be divided into two categories: epidermal hypermelanosis and dermal hypermelanosis. The exact pathogenesis of epidermal hypermelanosis is not well understood but is thought to be due to melanocyte response to inflammatory markers, whereas dermal hypermelanosis occurs when melanophages accumulate at the site of injury and destroy basal keratinocytes [110]. The severity of PIH is determined by the degree of inflammation, patient's skin type, involvement of the dermo-epidermal junction, and the stability of melanocytes [111].

PIH is more common in darker skin types including African American, Hispanic/Latino, Asian, Native American, Pacific Islander, and

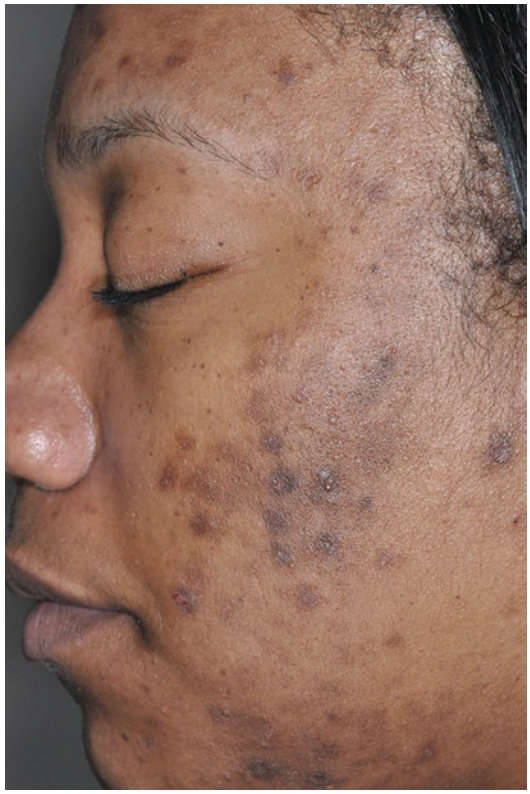

Fig. 10.8 Post-inflammatory hyperpigmentation

Middle Eastern and is the second most common diagnosis in African Americans [109, 112]. A clinical history and exam can usually support a diagnosis of PIH without need for further workup. Some physicians have found utility in the Wood's lamp which can be useful in determining the location of excess pigment. Wood's lamp can reveal if pigment is located in the epidermis or dermis, which is important when determining the best treatment option. New advances using polarized light photography, colorimetry, and diffuse reflectance spectroscopy (DRS) can assist in diagnosis by producing quantitative information about the affected areas [6]. Biopsy is rarely used but can give a definitive answer when there is question about the diagnosis. Histopathology will reveal superficial dermal melanophages and increased epidermal melanin without basal cell vacuolization [111].

There are many treatment options available for PIH which range from topical to systemic to surgical therapies. The first steps in management include prevention and adequate management of the underlying skin disorder, proper sun protection, and behavior modification to encourage patients not to scratch affected areas. Photoprotection can prevent worsening of the hyperpigmentation, and patients should use a daily broad-spectrum sunscreen and wear protective clothing when possible [108, 110, 112].

Topical depigmenting agents are the first-line option for epidermal PIH and can be used as monotherapy or in combination with other agents [108, 109]. Common topical depigmenting agents include hydroquinone, azelaic acid, kojic acid, and retinoids. Hydroquinone is the gold standard for treating PIH and works by inhibiting tyrosinase. More specifically, it is a phenolic compound that blocks the conversion of dihydroxyphenylalanine (DOPA) to melanin [108, 110]. It is often used by mixing it with retinoids, corticosteroids, or antioxidants to obtain maximum results. It has been shown that hydroquinone 4% can be used twice daily for up to 6 months with good results [107]. Some adverse events reported include contact dermatitis, permanent leukoderma, and hypopigmentation of the unaffected skin also known as the "halo effect." One of the more concerning adverse events is exogenous ochronosis where homogentisic acid accumulates in the dermis causing permanent hyperpigmentation [110, 113]. Similar to hydroquinone, mequinol is a derivative of hydroquinone and is found to be less irritating than its counterpart. The exact pathway is unknown, but it is thought to also be a tyrosinase inhibitor [108].

Retinoids are effective in treating PIH through their skin-lightening effects. Retinoids are vitamin A derivatives and work through cell proliferation, differentiation, induction of apoptosis, and expression of anti-inflammatory properties. The most commonly seen side effect is mild to moderate irritation [106, 108].

Other topical agents with varying effects include azelaic acid, kojic acid, arbutin, niacinamide, vitamin C, and licorice root extract. Azelaic acid aids in depigmentation by tyrosinase inhibition along with selective antiproliferative mechanisms against hyperactive

melanocytes [108]. Kojic acid is a fungal metabolite species found in *Penicillium*, *Aspergillum*, and *Acetobacter* and works as a tyrosinase inhibitor to aid in its skin-brightening effects [106, 108]. Arbutin is found naturally in bearberry, pear, cranberry, or blueberry leaves; it is derived from hydroquinone but has less side effects [108]. Niacinamide is the active form of vitamin B3 and works by decreasing melanosome transfer to keratinocytes. It has not been widely used in PIH, but studies show great promise due to its benefit in treating hyperpigmentation found in melasma. Vitamin C or ascorbic acid is a naturally occurring antioxidant that works in depigmentation by interacting with the active sites of tyrosinase and reducing dopaquinone oxidation which is an important product in the melanin synthesis pathway. Lastly, licorice root extract has anti-inflammatory and anti-tyrosinase activity with minimal side effects for the patient [104].

Chemical peels using glycolic acid or salicylic acid are effective in treating and reducing the appearance of PIH [99, 104]. Glycolic acid is a naturally occurring alpha-hydroxy acid found in sugar cane and works through epidermolysis. Salicylic acid is a beta-hydroxy acid found in willow tree bark that works by causing keratolysis. Both glycolic and salicylic acid have shown great safety and efficacy for PIH management [104]. Laser/light therapy has also shown utility in the treatment of PIH. A systemic review looking at the use of lasers for PIH therapy found that Q-switched Nd:YAG is the most effective laser in reducing the appearance of lesions [108]. Cosmetic camouflage can be used by patients to conceal pigmented lesions, improve appearance, and positively impact quality of life [104].

Melasma

Melasma is an acquired pigmentary disorder of unknown etiology. It classically presents with hyperpigmented brown to dark brown macules with "moth-eaten" or scalloped borders that are typically located on the face, mainly on the malar cheeks, centrofacial area, and mandibular areas (Fig. 10.9). Occasional involvement of the upper chest or extremities can be seen [114, 115]. Prior associations with exposure to ultraviolet radiation (UVR), increased estrogen levels, genetic predisposition, and phototoxic drugs [107, 113] have been theorized as underlying culprits or exacerbating factors. It is less commonly associated with ovarian dysfunction, thyroid disease, and liver disease [107]. UVR is known to worsen melasma, and increased exposure leads to the production of alpha-melanocyte-stimulating hormone (MSH), interleukin (IL)-1, and corticotrophin which stimulate melanin production [107]. However, visible light may also induce skin pigmentation of affected areas [116]. Estrogen is thought to induce melasma as it develops frequently during pregnancy, use of oral contraceptives (OCPs), and with hormone replacement therapy (HRT) [109]. The four different classifications of melasma are epidermal, dermal, mixed epidermal-dermal, and intermediate. Epidermal is attributed to increased melanin production in the epidermis and is the most common and easiest type to treat. Dermal is characterized by melanin-laden macrophages in the dermis and is the least responsive to treatment. Mixed epidermal-dermal is a combination of the two, and the intermediate type is more commonly found in darker skin types, Fitzpatrick skin types V–VI [113].

Fig. 10.9 Melasma

Melasma occurs predominately in women and can be seen in all ethnic groups; however, it is more common in Fitzpatrick skin types IV–VI. Exact prevalence is unknown but has been reported as 4–10% in Latin America and more specifically up to around 50% of women of Mexican descent of childbearing age [113, 114]. The true prevalence worldwide is not known yet [117]. Melasma can be diagnosed clinically and rarely requires a skin biopsy. Histopathology will show pigment accumulation in the epidermis, dermis, or both as well as melanin-laden macrophages [115]. The Melasma Area Severity Index (MASI) was created to evaluate the severity of melasma. Clinicians assess the forehead, malar cheeks, and chin for the presence of lesions and add up scores based on the area involved, darkness of the lesions, and homogeneity. The higher the score, the more severe the condition [113].

The goal for treatment of melasma is to slow the proliferation of melanocytes and to stop melanosome formation. Photoprotection is key to preventing worsening of dark lesions, and it is recommended for all patients to wear a broad-spectrum sunscreen. Discontinuation of OCPs or HRT may result in clearance of melasma since estrogen is thought to be involved in its presentation. Treatment of melasma in pregnancy is usually held until after delivery because of its increased resistance to treatment. Further, melasma may resolve after delivery of the baby [109].

Hydroquinone is the gold standard for treatment and can be used as monotherapy or combined with other lightening agents [113, 117]. Hydroquinone inhibits melanin production through the inhibition of tyrosinase, which is the rate-limiting step in melanin synthesis. In the United States, there is a triple combination cream that consists of 4% hydroquinone, 0.01% fluocinolone acetone, and 0.05% tretinoin and is often used for initial treatment for melasma. Patients should be made aware of the common side effects including skin atrophy and irritant reactions, and therefore the combination cream should be used for no longer than 6 months [109, 114]. Tretinoin reduces pigmentation by inhibiting tyrosinase and stops melanin production. Some side effects include mild irritation and increased pigmentation [109, 117]. Adapalene is a synthetic retinoid that often causes less irritation than tretinoin and may be appropriate for long-term therapy. Azelaic and kojic acid have similar effects in inhibiting tyrosinase and have been shown to improve the appearance of melasma. Side effects include acneiform eruptions and mild irritation [109, 113]. Cysteamine is a newer topical agent that aids in treating hyperpigmentation through inhibition of tyrosinase and peroxidase in the melanin synthesis pathway. It has also been found to remove dopaquinone, bind and remove iron and copper, and increase glutathione, all which lead to the lightening of melasma [118]. Oligopeptides are a new class of tyrosinase inhibitors that are being studied for the treatment of melasma and may be a good alternative to hydroquinone due to its decreased side effects. Chemical peels with salicylic acid have also been found to be effective in management [114].

There have been some new research studies looking at the utility of laser/light therapy for the management of melasma, which have produced good results. Carbon dioxide fractional ablative lasers are ablative treatment that non-selectively destroys the epidermis. The laser is fractional so the amount of epidermal injury is decreased, and there is less risk of dyspigmentation. Quality-switched neodymium-doped yttrium aluminum garnet laser (Nd:YAG) targets melanin specifically and can be used with low, short pulses to reduce the side effect of hypopigmentation. 1550 nm fractional non-ablative laser has shown promise but is still being investigated for the treatment of melasma [114].

Tranexamic acid (TA) and methimazole are oral agents that may be useful in depigmenting lesions in melasma. Tranexamic acid works in hyperpigmentation by decreasing melanocyte-stimulating hormone; however, more studies are needed to evaluate the effectiveness. The major side effect associated with this therapy is the risk of deep venous thrombosis, so patients will need to be carefully screened before starting this treatment for a history or increased risk of thromboembolic events [115]. Methimazole is an oral antithyroid medication that when used topically depigments the skin without effecting the thyroid gland [117]. More studies are needed to determine the long-term effects of this treatment.

The Pigmentary Disorders Academy (PDA) created a treatment algorithm for melasma that has been used to guide therapy. According to the PDA, first-line treatment should be topical therapy with primarily triple or dual combination depigmenting agents that include hydroquinone. Second-line options include chemical peels, either alone or in combination with topical lightening therapy. Per PDA, lasers and light sources should be used only in select cases for melasma.

Lichen Planus Pigmentosus

Lichen planus pigmentosus (LPP) is a rare, uncommon variant of lichen planus and is more prevalent in skin of color [111, 119, 120]. Lesions often appear in a symmetrical pattern as violaceous, gray to black macules and patches which are typically present on the face [111] (Fig. 10.10). There is a variant of LPP called LPP inversus which is typically found in the flexural skin folds and intertriginous areas, primarily the axillae [120]. The frequency and etiology of this disease are unknown but may be associated with UVR, hepatitis C virus, and various topical agents [120–122]. As far as pathogenesis, LPP is similar to lichen planus (LP) in that it has an abnormal immune response, where CD8 T cells attack epidermal keratinocytes and lead to pigmentary incontinence [123]. LPP occurs mainly in females in their third to fourth decades of life. LPP presents as dark brown macules that are present in sun-exposed areas and flexural folds [119]. Pathology will show epidermal basal cell layer vacuolation, a few necrotic keratinocytes, and a lichenoid lymphocytic infiltration [111].

There is currently no gold standard option for the treatment of LPP. Management options include use of topical medications like hydroquinone, corticosteroids, calcineurin inhibitors, keratolytics, vitamin A derivatives, and chemical peels [124]. The most commonly used topical agent is tacrolimus. Systemic corticosteroids can be used for severe cases and should be tapered over time; dapsone and isotretinoin can also be used for severe cases [123]. Laser therapy has been shown to improve the appearance of LPP, and more research is needed on this area.

Erythema Dyschromicum Perstans

Erythema dyschromicum perstans (EDP) is a dermatosis of unknown etiology and is commonly seen in darker skin types, especially the Latin American population [124, 125]. The other name for EDP is ashy dermatosis [111]. EDP presents as blue-gray macules and patches and may have a pale area around the lesion which is considered a halo effect [124] (Fig. 10.11). Lesions may also have active

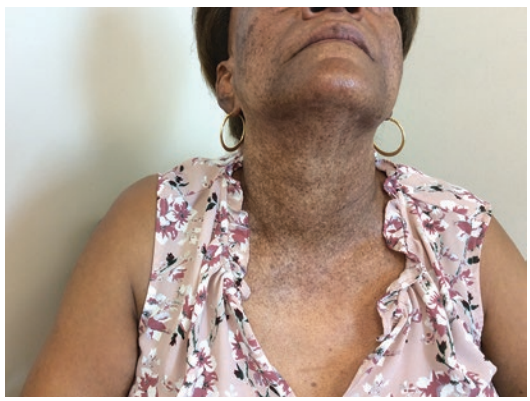

Fig. 10.10 Lichen planus pigmentosus

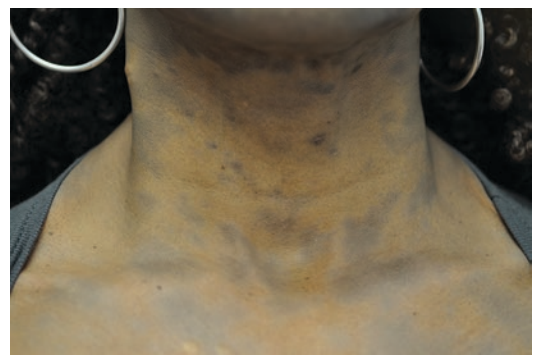

Fig. 10.11 Erythema dyschromicum perstans

erythematous borders that disappear and leave oval gray macules and patches. LPP often affects sun-protected areas, though may involve the trunk, the upper extremities, and the neck [111]. Pigmentary changes can be chronic, and there is no widely accepted treatment available. Pathology will reveal a lichenoid dermatitis with basal layer vacuolization and will also appear similar to LP.

There is no widely accepted therapy for EDP, and there has been a history of varying effectiveness of topical treatments. Promising results have been reported with laser therapy used in conjunction with topical tacrolimus which targets the exact location of the pigment in EDP [125]. Clofazimine is a hypochlorous acid that decreases inflammation and has been reported to be a good treatment option for some patients [126].

Drug-Induced Hyperpigmentation

There are some common medications that are known to cause hyperpigmentation (Table 10.1) [126–129]. These lesions classically present as hyperpigmented macules and patches, often on sun-exposed areas, though they can be found on any part of the body (Fig. 10.12). Drug-induced hyperpigmentation can either resolve after dis-

Table 10.1 Common drugs associated with skin hyperpigmentation

Drug name	Mechanism of action	Classification	Presentation
Minocycline	Tetracycline that inhibits protein synthesis and bacterial growth by binding to the 30S ribosomal subunit	Antibiotic	Type I: black blue discoloration in old scars Type II: common lower extremities Type III: generalized dark, brown pigment
Zidovudine	Nucleoside reverse transcriptase inhibitor (NRTI); inhibits thymidine kinase	Antiretroviral therapy	Diffuse melanonychia; mucocutaneous hyperpigmentation
Bleomycin	Glycopeptide antibiotic; inhibits DNA, RNA, protein synthesis in G2 and M phase	Antineoplastic	Transverse melanonychia; hyperpigmentation over joints and palmer creases
Busulfan	Alkylating agent; interferes with DNA intercalation and RNA transcription	Antineoplastic	Generalized hyperpigmentation
Chlorpromazine	Antagonizes dopamine D2 receptors in the brain	Antipsychotic	Slate-gray discoloration in sun-exposed areas
Oral contraceptives	Combination pills with estrogen and progestin or progestin-only pills	Hormonal contraceptive	Melasma; increased pigment of the nipples
Hydantoins	Stabilizes neuronal membranes and decreases seizure activity by increasing efflux of sodium ions	Anticonvulsant	Slate-gray discoloration in sun-exposed areas
Cyclophosphamide	Interferes with malignant cell growth by cross-linking tumor cell DNA	Antineoplastic	Diffuse hyperpigmentation of the skin and mucous membranes; pigment involved nails
Amiodarone	Inhibits adrenergic stimulation and affects sodium, potassium, and calcium channels	Anti-dysrhythmics	Slate-gray to violaceous discoloration in sun-exposed areas
Clofazimine	Bacteriocidal effects on *Mycobacterium*; also exerts anti-inflammatory properties	Antitubercular agent	Violet, brown to blue discoloration
Hydroxychloroquine sulfate	Unknown; may impair complement-dependent antigen-antibody reactions	Antimalarial	Gray to blue/black pigmentation usually on the lower extremities, face, and sclera
Procarbazine	Inhibits protein, DNA, and RNA synthesis	Antineoplastic	Generalized hyperpigmentation
Doxorubicin	Intercalates between DNA base pairs and impairs topoisomerase II function	Antineoplastic	Hyperpigmentation over small hand joints; involves palmer creases

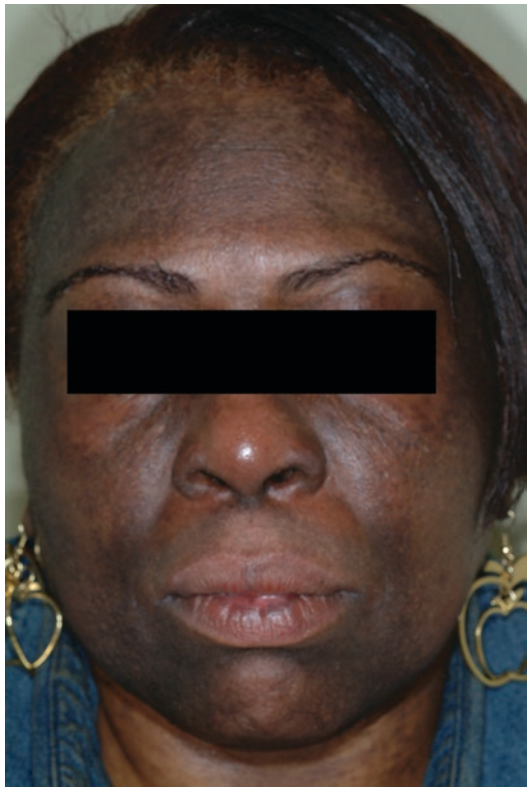

Fig. 10.12 Drug-induced hyperpigmentation

continuation of the medication or can persist for months to years. Minocycline is a common culprit for inducing hyperpigmentation and is known to accumulate in the skin and mucous membranes as well as the teeth and nails. There are three types of hyperpigmentation associated with minocycline. Type 1 appears after an inflammatory process and typically presents on the sun-exposed skin of the face as a blue-black color. Type 2 appears on normal skin and is normally present on the shins and upper extremities. Type 3 is more generalized and presents as a dark brown color. There have also been many reported cases discussing neoplastic agents leading to skin hyperpigmentation. For treatment of drug-induced hyperpigmentation, the first line of action is to stop the offending agent. Skin-lightening agents have been also used to treat the lesions but are commonly ineffective because most drug-induced pigment is located in the dermis, which cannot be reached by topical lightening agents. Laser therapy using the Q-switched Nd:YAG laser and Q-switched ruby laser have shown some promising results [126].

Table 10.2 briefly describes other common metabolic and miscellaneous causes of hyperpigmentation [130–150] (Fig. 10.13).

Metabolic and Other Miscellaneous Causes of Hyperpigmentation (Table 10.2)

Table 10.2 Miscellaneous causes of hyperpigmentation

Diagnosis	Etiology	Epidemiology	Presentation	Histology	Management
Hyperpigmentation due to Addison's disease [24–28]	Increased production of adrenocorticotropic hormone (ACTH) which is a type of melanocortin 1 receptor agonist that is highly expressed on melanocytes	Seen in majority of adult patients and 67% of pediatric patients	Generalized bronze hyperpigmentation more prevalent in the axilla, areolas, perineum, and palmer creases. Can also involve mucosal surfaces	Increase amount of melanin in basal epidermal keratinocytes and moderate melanophages	Treat the underlying disease with replacement of deficient glucocorticoids and mineralocorticoids
Hyperpigmentation due to hyperthyroidism [28, 29]	Not well understood but likely due to melanocyte stimulation from thyroid hormones	Present in 2% of patients with hyperthyroidism; common in Graves' disease	Localized or generalized hyperpigmentation common in the creases of palms, soles, and mucosal surfaces. Fine hair; mild alopecia	Increased melanosis of the basal layer and greater deposition of hemosiderin in the dermis	Treat the underlying disease
Hyperpigmentation due to chronic renal disease [24, 30–32]	May be due to increased production of urochrome pigments, carotenoids, and melanocyte-stimulating hormone	Common in patients receiving hemodialysis	Generalized hyperpigmentation of gray to yellow to brown skin color	Basement membrane thickening, endothelial cell activation, and chronic inflammatory infiltrate	Treat the underlying disease, adequate photoprotection
Hemochromatosis [33]	Increased melanogenesis and iron deposit accumulation in the skin	Occurs in 70% of affected patients	Generalized bronze hyperpigmentation mainly affecting the face and hands	Increased melanin in the epidermis and melanophages in the dermis. Iron deposits in deeper part of the dermis	Treat the underlying cause with phlebotomy or chelation
Diabetic dermopathy [34, 35]	Likely due to microangiopathic complications of diabetes, but the exact mechanism is unknown	Affects 70% of adults with diabetes mellitus. Most common cutaneous manifestation in diabetics	Small, oval, red-brown atrophic macules and patches more commonly seen on the lower extremity. Atrophy or scarring can be present after resolution	Atrophy of rete ridges, pigmentation of basal cells, and moderate hyperkeratosis and dermal perivascular plasma cells	Appropriate wound care to prevent infection and aid in healing. The lesions are asymptomatic and often resolve spontaneously without treatment. Patients should be worked up for diabetes

(continued)

Table 10.2 (continued)

Diagnosis	Etiology	Epidemiology	Presentation	Histology	Management
Hyperpigmentation due to B12 deficiency [36–38]	Not fully understood but may be related to reduced glutathione-stimulating hormone leading to increased tyrosinase activity; high levels of biopterin which increases phenylalanine utility; defect in the transport of melanin and incorporation into keratinocytes	Common in B12 deficiency and more prevalent in patients with darker skin tones	Generalized hyperpigmentation more pronounced on the extremities and flexural folds. Less commonly in the oral mucosa and nails	Epidermal thinning, vacuolization of keratinocytes, increased number of melanocytes and melanophages in the dermis	Repletion of vitamin B12 orally, intravenously, or intramuscularly
Acanthosis nigricans [34, 39–41]	Elevated insulin concentrations lead to activation of IGF-1 receptors of keratinocytes and fibroblasts leading to proliferation	Most commonly associated with insulin resistance and people of Hispanic, African, or Native American descent. Common in children and in patients with a family history of diabetes mellitus	Diffuse, velvety hyperpigmented plaques found in the axillae, neck, inframammary folds, and inguinal folds	Thickened stratum corneum with thickened, elongated dermal projections and hyperkeratosis	Weight loss, retinoids, adapalene, calcipotriol, and laser therapy. Important to identify any underlying condition by obtaining basic labs and evaluating the patient's risk

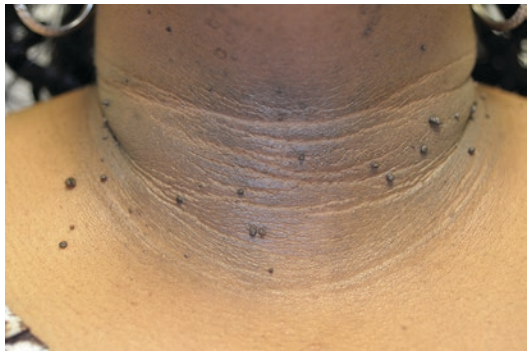

Fig. 10.13 Acanthosis nigricans

References

1. Vachiramon V, Thadanipon K. Postinflammatory hypopigmentation. Clin Exp Dermatol. 2011;36:708–14.
2. Verma S, Patterson JW, Derdeyn AS, et al. Hypopigmented macules in an Indian man. Arch Dermatol. 2006;142:1643–8.
3. Rowley MJ, Nesbitt LT Jr, Carrington PR, Espinoza CG. Hypopigmented macules in acantholytic disorders. Int J Dermatol. 1995;34:390–2.
4. Yang CC, Lee JY, Won TW. Depigmented extramammary Paget's disease. Br J Dermatol. 2004;151:1049–53.
5. Halder RM, Richards GM. Management of dyschromias in ethnic skin. Dermatol Ther. 2004;17:151–7.
6. High WA, Pandya AG. Pilot trial of 1% pimecrolimus cream in the treatment of seborrheic dermatitis in African American adults with associated hypopigmentation. J Am Acad Dermatol. 2006;54:1083–8.
7. Ruiz-Maldonado R, Orozco-Covarrubias ML. Postinflammatory hypopigmentation and hyperpigmentation. Semin Cutan Med Surg. 1997;16:36–43.
8. Grimes PE, Bhawan J, Ki J, et al. Laser resurfacing induced hypopigmentation: histologic alterations and repigmentation with topical photochemotherapy. Dermatol Surg. 2001;27:515–20.
9. Alexiades-Armenakas MR, Bernstein LJ, Friedman PM, Geronemus RG. The safety and efficacy of the 308-nm excimer laser for pigment correction of hypopigmented scars and striae alba. Arch Dermatol. 2004;140:955–60.
10. Suvanprakorn P, Dee-Ananlap S, Pongsomboon C, Klaus SN. Melanocyte autologous grafting for treatment of leukoderma. J Am Acad Dermatol. 1985;13:968–74.
11. Bisherwal K, Singal A, Pandhi D, Sharma S. Hypopigmented mycosis fungoides: clinical, histological, and immunohistochemical remission induced by narrow-band ultraviolet B. Indian J Dermatol. 2017;62(2):203–6.
12. Fatemi N, Abtahi-Naeini B, Sadeghiyan H, Nilforoushzadeh MA, Najafian J, Pourazizi M. Mycosis fungoides in Iranian population: an epidemiological and clinicopathological study. J Skin Cancer. 2015;306543:1–6.
13. Amorim G, Nieeyer-Corbellini J, Quintella DC, Cuzzi T, Ramos-e-Silva M. Hypopigmented mycosis fungoides: a 20-case retrospective series. Int J Dermatol. 2018;54:306–12.
14. Yamashita T, Abbade LP, Marques ME, et al. Mycosis fungoides and Sezary syndrome: clinical, histopathological and immunohistochemical review and update. An Bras Dermatol. 2012;87:817–28.
15. Sanches JA Jr, Moricz CZM, Neto CF. Lymphoproliferative processes of the skin. Part 2-Cutaneous T-cell and NK-cell lymphomas. An Bras Dermatol. 2006;81:7–25.
16. Rodney IJ, Kindred C, Angra K, Qutub ON, Villanueva AR, Halder RM. Hypopigmented mycosis fungoides: a retrospective clinicohistopathologic study. J Eur Acad Dermatol Venereol: JEADV. 2017;31:808–14.
17. Tan EST, Tang MBY, Tan SH. Retrospective 5-year review of 131 patients with mycosis fungoides and sezary syndrome seen at the National Skin Centre, Singapore. Australas J Dermatol. 2006;47:248–52.
18. Furlan FC, Sanches JA. Hypopigmented mycosis fungoides: a review of its clinical features and pathophysiology. An Bras Dermatol. 2013;88:954–60.
19. Castano E, Glick S, Wolgast L, et al. Hypopigmented mycosis fungoides in childhood and adolescence: a long-term retrospective study. J Cutan Pathol. 2013;40:924–34.
20. Laws PM, Shear NH, Pope E. Childhood mycosis fungoides experience of 28 patients and response to phototherapy. Pediatr Dermatol. 2014;31:459–64.
21. Breathnach SM, McKee PH, Smith NP. Hypopigmented mycosis fungoides: report of five cases with ultrastructural observations. Br J Dermatol. 1982;106:643–9.
22. Boulos S, Vaid R, Aladily T, Ivan D, Talpur R, Duvic M. Clinical presentation, immunopathology, and treatment of juvenile-onset mycosis fungoides: a case series of 34 patients. J Am Acad Dermatol. 2014;71:1117–26.
23. Kanokungsee S, Rajatanavin N, Rutnin S, Vachiramon V. Efficacy of narrowband ultraviolet B twice weekly for hypopigmented mycosis fungoides in Asians. Clin Exp Dermatol. 2012;37:149–52.
24. Carter J, Zug KA. Phototherapy for cutaneous T cell lymphoma: online survey and literature review. J Am Acad Dermatol. 2009;60:39–50.
25. Miazek N, Michalek I, Pawlowska-Kisiel M, Olszewska M, Rudnicka L. Pityriasis alba- common disease, enigmatic entity: up-to-date review of the literature. Pediatr Dermatol. 2015;32(6):786–91.
26. Jadotte YT, Jannige CK. Pityriasis alba revisited: perspectives on an enigmatic disorder of childhood. Cutis. 2011;87:66–72.

27. Wells BT, Whyte HJ, Kierland RR. Pityriasis alba: a ten-year survey and review of the literature. Arch Dermatol. 1960;85:183–9.
28. Givler DN, Givler A. Pityriasis, alba. StatPearls [Internet]. Treasure Island: StatPearls Publishing; 2018.
29. Vargas-Ocampo F. Pityriasis alba: a histologic study. Int J Dermatol. 1993;32:870–3.
30. In SI, Yi SW, Kang HY, et al. Clinical and histopathological characteristics of pityriasis alba. Clin Exp Dermatol. 2009;34:591–7.
31. Kang HY, Choi YM. FK506 increases pigmentation and migration of human melanocytes. Br J Dermatol. 2006;155:1037–40.
32. Lin RL, Janniger CK. Pityriasis alba. Cutis. 2005;76:21–4.
33. Al-Mutairi N, Hadad AA. Efficacy of 3058-nm xenon chloride excimer laser in pityriasis alba. Dermatol Surg. 2012;38:604–9.
34. Kallini J, Riaz F, Khachemoune A. Tinea versicolor in dark-skinned individuals. Int J Dermatol. 2014;53:137–41.
35. Hald M, Arendrup M, Svejgaard E, Lindskov R, Foged E, Saunte D. Evidence- based Danish guidelines for the treatment of Malassezia-related skin diseases. Acta Derm Venerol. 2015;95:12–9.
36. Hu S, Bigby M. Pityriasis versicolor. Arch Dermatol. 2010;146(10):1132–9.
37. Gupta AK, Foley KA. Antifungal treatment for pityriasis versicolor. J Fungi. 2015;1:13.
38. Karray M, McKinney W. Tinea, versicolor. StatPearls [Internet]. Treasure Island: StatPearls Publishing; 2018.
39. Gupta AK, Lane D, Paquet M. Systematic review of systemic treatments for tinea versicolor and evidence-based dosing regimen recommendations. J Cutan Med Surg. 2014;18(2):79–90.
40. Kose O, Bulent H, Riza A, Kurumlu A. Comparison of a single 400 mg dose versus a 7-day 200mg daily dose of itraconazole in the treatment of tinea versicolor. J Dermatol Treat. 2002;13:77–9.
41. Faergemann J, Todd G, Pather S, Vawda ZFA, Gillies JD, Walford T, Barranco C, Quiring JN, Briones MA. Double-blind, randomized, placebo-controlled, dose-finding study of oral pramiconazole in the treatment of pityriasis versicolor. J Am Acad Dermatol. 2009;61:971–6.
42. Balevi A, Ustuner P, Kaksi S, Ozdemir M. Narrowband UV-B phototherapy: an effective and reliable treatment alternative for extensive and recurrent pityriasis versicolor. J Dermatol Treat. 2018;29(3):252–5.
43. Want K, Nassef Y, Sahu J, Hermes H, Schwartz L. Facial involvement in progressive macular hypomelanosis. Cutis. 2018;101(4):297–300.
44. Pertersen RL, Scholtz C, Jensen A, Bruggemann H, Lomholt H. Propionibacterium acnes phylogenetic type III is associated with progressive macular hypomelanosis. Eur J Microbiol Immunol. 2017;7:37–45.
45. Thng S, Long V, Chuah S, Ta VW. Efficacy and relapse rates of different treatment modalities for progressive macular hypomelanosis. Indian J Dermatol Venerol Leprol. 2016;82(6):673–6.
46. Kim MB, Kim GW, Park HJ, Kim HS, Kim SH, Kim BS, Ko HC. Narrowband UVB treatment of progressive macular hypomelanosis. J Am Acad Dermatol. 2012;66(4):598–605.
47. Sim JH, Lee DJ, Lee JS, Kim YC. Comparison of the clinical efficacy of NBUVB and NBUVB with benzoyl peroxide/clindamycin in progressive macular hypomelanosis. J Eur Acad Dermatol Venereol: JEADV. 2011;25:1318–23.
48. Kim J, Lee DY, Lee JY, Yoon TY. Progressive macular hypomelanosis showing excellent response to oral isotretinoin. J Dermatol. 2012;39(11): 937–8.
49. Brown F, Crane JS. Idiopathic guttate hypomelanosis. StatPearls [Internet]. Treasure Island: StatPearls Publishing; 2018. p. 1–4.
50. Mazioti M. Idiopathic guttate hypomelanosis: a mini review. J Pigmentary Disord. 2015;2(10):1–4.
51. Falabella R, Escobar C, Giraldo N, Rovetto P, Gill J. On the pathogenesis of idiopathic guttate hypomelanosis. J Am Acad Dermatol. 1987;16:35–44.
52. Kakepis M, Katoulis A, Katsambas A, et al. Idiopathic guttate hypomelanosis: an electron microscopy study. J Eur Acad Dermatol Venerol. 2015;29:1435–8.
53. Gordon J, Reed KE, Sebastian KR, Ahmed AM. Excimer light treatment for idiopathic guttate hypomelanosis: a pilot study. Dermatol Surg. 2017;43:553–7.
54. Kumarasinghe SP. 3–5 cryotherapy is effective in idiopathic guttate hypomelanosis. J Dermatol. 2004;31:437–9.
55. Asawanonda P, Sutthipong T, Prejawal N. Pimecrolimus for idiopathic guttate hypomelanosis. J Drugs Dermatol. 2010;9:238–9.
56. Hexsel DM. Treatment of idiopathic guttate hypomelanosis by localized superficial dermabrasion. Dermatol Surg. 1999;25:917–8.
57. Wambier CG, Wambier SPDF, Soares MTPS, Breunig J, Cappel MA, Landau M. 5-fluorouracil tattooing for idiopathic guttate hypomelanosis. J Am Acad Dermatol. 2018;78:e81–2.
58. Bishnoi A, Parsad D. Clinical and molecular aspects of vitiligo treatments. Int J Mol Sci. 2018;19(1509):1–15.
59. Ezzedine K, Silverberg N. A practical approach to the diagnosis and treatment of vitiligo in children. Pediatrics. 2016;138(1):e20154126.
60. Agarwal S, Gupta S, Ojha A, Sinha R. Childhood vitiligo: clinicoepidemiologic profile of 268 children from the Kumaun region of Utarakhand, India. Pediatr Dermatol. 2013;30(3):348–53.
61. Rodrigues M, Ezzedine K, Hamzavi I, Pandya A, Harris J. New discoveries in the pathogenesis and classification of vitiligo. J Am Acad Dermatol. 2017;77:1–13.

62. Mason CP, Gawkrodgor DJ. Vitiligo presentation in adults. Clin Exp Dermatol. 2005;30:344–5.
63. Manolache L, Benea V. Stress in patients with alopecia areata and vitiligo. J Eur Acad Dermatol Venereol. 2007;21:921–8.
64. Tokura Y, Fujiyama T, Ikeya S, et al. Biochemical, cytological and immunological mechanisms of rhododendrol-induced leukoderma. J Dermatol Sci. 2015;77:146–9.
65. Ghosh S, Mukhopadhyay S. Chemical leukoderma: a clinic-aetiological study of 864 cases in the perspective of a developing country. Br J Dermatol. 2009;160:40–7.
66. Ezzedine K, Lim HW, Suzuki T, Katayama I, Hamzavi I, Lan CC, Goh BK, Anbar T, de Castro CS, Lee AY, et al. Revised classification/nomenclature of vitiligo and related issues: the vitiligo global issues consensus conference. Pigment Cell Melanoma Res. 2012;25(3):E1–E13.
67. Ezzedine K, Le Thuaut A, Jouary T, Ballanger F, Taieb A, Bastuji-Gari S. Latent class analysis of a series of 717 patients with vitiligo allows the identification of two clinical subtypes. Pigment Cell Melanoma Res. 2014;27(1):134–9.
68. Toosi S, Orlow SJ, Manga P. Vitiligo-inducing phenols activate the unfolded protein response in melanocytes resulting in upregulation of IL6 and IL8. J Invest Dermatol. 2012;132:2601–9.
69. Richmond JM, Frisoli ML, Harris JE. Innate immune mechanisms in vitiligo: danger from within. Curr Opin Immunol. 2013;25:676–82.
70. Schallreuter KU, Moore J, Wood JM, et al. In vivo and in vitro evidence for hydrogen peroxide(H2O2) accumulation in the epidermis of patients with vitiligo and its successful removal by a UVB-activated pseudocatalase. J Investig Dermatol Symp Proc. 1999;4:91–6.
71. Alkhateeb A, Fain PR, Thody A, Bennett DC, Spritz RA. Epidemiology of vitiligo and associated autoimmune diseases in Caucasian probands and their families. Pigment Cell Res. 2003;16:208–14.
72. Silverberg JI, Silverberg NB. Clinical features of vitiligo associated with comorbid autoimmune disease: a prospective survey. J Am Acad Dermatol. 2013;69(5):824–6.
73. Sakata VM, Da Silva FT, Hirata CE, De Carvalho JF, Yamamoto JH. Diagnosis and classification of Vogt-Koyanagi-Harada disease. Autoimmun Rev. 2014;13:550–5.
74. Alezzandrini AA. Unilateral manifestations of tapeto-retinal degeneration, vitiligo, poliosis, grey hair and hypoacousia. Ophthalmologica. 1964;147:409–19.
75. Faria AR, Tarle RG, Dellatorre G, Mira MT, Castro CC. Vitiligo- part 2- classification, histopathology and treatment. An Bras Dermatol. 2014;89(5):784–90.
76. Goh BK, Pandya AG. Presentations, signs of activity, and differential diagnosis of vitiligo. Dermatol Clin. 2017;35:135–44.
77. Rodrigues M, Ezzedine K, Hamzavi I, Pandya A, Harris J. Emerging treatments for vitiligo. J Am Acad Dermatol. 2017;77:17–29.
78. De Francesco V, Stinco G, Laspina S, Parlangeli ME, Mariuzzi L, Patrone P. Immunohistochemical study before and after narrow band (311nm) UVB treatment in vitiligo. Eur J Dermatol. 2008;18:292–6.
79. Njoo MD, Bos JD, Westerhof W. Treatment of generalized vitiligo in children with narrow-band (TL-01) UVB radiation therapy. J Am Acad Dermatol. 2000;42(2 Pt 1):245–53.
80. Mohammad TF, Al-Jamal M, Hamzavi IH, et al. The vitiligo working group recommendations for narrowband ultraviolet B light phototherapy treatment of vitiligo. J Am Acad Dermatol. 2017;76:879–88.
81. Li R, Qiao M, Wang X, Zhao X, Sun Q. Effect of narrow band ultraviolet B phototherapy as monotherapy or combination therapy for vitiligo: a meta-analysis. Photodermatol Photoimmunol Photomed. 2017;33:21–31.
82. Bhatnagar A, Kanwar AJ, Parsad D, De D. Psoralen and ultraviolet A and narrow-band ultraviolet B in inducing stability in vitiligo, assessed by vitiligo disease activity score: an open prospective comparative study. J Eur Acad Dermatol Venereol. 2007;21:1381–5.
83. Linthorst Homan MW, Spuls PI, Nieuweboer-Krobotova L, et al. A randomized comparison of excimer laser vs narrow-band ultraviolet B phototherapy after punch grafting in stable vitiligo patients. J Eur Acad Dermatol Venereol. 2012;26(6):690–5.
84. Kanwar AJ, Mahajan R, Parsad D. Low-dose oral mini-pulse dexamethasone therapy in progressive unstable vitiligo. J Cutan Med Surg. 2013;17:259–68.
85. Singh A, Kanwar AJ, Parsad D. Mahajan. Randomized controlled study to evaluate the effectiveness of dexamethasone oral minipulse therapy vs oral minocycline in patients with active vitiligo vulgaris. Indian J Dermatol Venereol Leprol. 2014;80(1):29–35.
86. Singh H, Kumaran MS, Bains A, Parsad D. A randomized comparative study of oral corticosteroid minipulse and low-dose oral methotrexate in the treatment of unstable vitiligo. Dermatology. 2015;231:286–90.
87. Gokhale BB. Cyclophosphamide and vitiligo. Int J Dermatol. 1979;18:92.
88. Iannella G, Greco A, Didona D, Didona B, Granata G, Manno A, Pasquariello B, Magliulo G. Vitiligo: pathogenesis, clinical variants and treatment approaches. Autoimmun Rev. 2016;15:335–43.
89. Radmanesh M, Saedi K. The efficacy of combined PUVA and low-dose azathioprine for early and enhanced repigmentation in vitiligo patients. J Dermatol Treat. 2006;17:151–3.
90. Cavalie M, Ezzedine K, Fontas E, Montaudie H, Castela E, Bahadoran P, Taieb A, Lacour JP, Passeran T. Maintenance therapy of adult vitiligo with 0.1% tacrolimus ointment: a randomized, double

blind placebo-controlled study. J Invest Dermatol. 2015;135(4):970–4.
91. Feetham HJ, Chan JL, Pandya AG. Characterization of clinical response in patients with vitiligo undergoing autologous epidermal punch grafting. Dermatol Surg. 2012;38:14–9.
92. Agrawal K, Agrawal A. Vitiligo: repigmentation with dermabrasion and thin split-thickness skin graft. Dermatol Surg. 1995;21:295–300.
93. Gupta S, Ajith C, Kanwar AJ, Kumar B. Surgical pearl: standardized suction syringe for epidermal grafting. J Am Acad Dermatol. 2005;52:348–50.
94. Huggins RH, Henderson MD, Mulekar SV, et al. Melanocyte-keratinocyte transplantation procedure in the treatment of vitiligo: the experience of an academic medical center in the United States. J Am Acad Dermatol. 2012;66:785–93.
95. Nordlund JJ, Forget B, Kirkwood J, Lerner AB. Dermatitis produced by applications of monobenzone in patients with active vitiligo. Arch Dermatol. 1985;121:1141–4.
96. Lim HW, Grimes PE, Agbai O, et al. Afamelanotide and narrowband UV-phototherapy for the treatment of vitiligo: a randomized multicenter trial. JAMA Dermatol. 2015;151:42–50.
97. Passeron T. Medical and maintenance treatments for vitiligo. Dermatol Clin. 2017;35:163–70.
98. Rashighi M, Harris JE. Interfering with the IFN-gamma/CXCL 10 pathway to develop new targeted treatments for vitiligo. Ann Transl Med. 2015; 3:343.
99. King BA, Craiglow BG. Tofacitinib citrate for the treatment of vitiligo: a pathogenesis-directed therapy. JAMA Dermatol. 2015;151(10):1110–2.
100. Harris JE, Rashighi M, Nguyen N, et al. Rapid skin repigmentation on oral ruxolitinib in a patient with coexisting vitiligo and alopecia areata (AA). J Am Acad Dermatol. 2016;74:370–1.
101. Ramien ML, Ondrejchak S, Gendron R, et al. Quality of life in pediatric patients before and after cosmetic camouflage of visible skin conditions. J Am Acad Dermatol. 2014;71(5):935–40.
102. Tedeschi A, Dall'Oglio F, Micali G, Schwartz RA, Janniger CK. Corrective camouflage in pediatric dermatology. Cutis. 2007;79(2):110–2.
103. Rothstein B, Joshipura D, Saraiya A, et al. Treatment of vitiligo with the topical Janus kinase inhibitor ruxolitinib. J Am Acad Dermatol. 2017;76:1054–60.
104. Grimes P, Nashawati R. The role of diet and supplements in vitiligo management. Dermatol Clin. 2017;35:235–43.
105. De Cuyper C. Permanent makeup: indications and complications. Clin Dermatol. 2008;26:30–4.
106. Shokeen D. Postinflammatory hyperpigmentation in patients with skin of color. Cutis. 2016;97(1):E9–E11.
107. Nouveau S, Agrawal D, Kohl M, Bernard F, Misra N, Nayak CS. Skin hyper pigmentation in Indian population: Insights and best practice. Indian J Dermatol. 2016;61(5):487–95.
108. Davis E, Callender V. Postinflammatory hyperpigmentation: a review of the epidemiology, clinical features, and treatment option in skin of color. J Clin Aesthet Dermatol. 2010;3(7):20–31.
109. Lynne C, Kraft J, Lynde C. Topical treatments for melasma and post inflammatory hyper pigmentation. Skin Therapy Lett. 2006;11(9):1–6.
110. Callender VD, Surin-Lord SS, Davis EC, Maclin M. Postinflammatory hyperpigmentation etiologic therapeutic considerations. Am J Clin Dermatol. 2011;12(2):87–99.
111. Silpa-archa N, Kohl I, Chaowattanapanit S, Lim H, Hamzavi I. Postinflammatory hyperpigmentation: a comprehensive review. J Am Acad Dermatol. 2017;77(4):591–605.
112. Liz N, Vafaie J, Kihiczak N, Schwartz R. Postinflammatory hyperpigmentation: a common but troubling condition. Int J Dermatol. 2004;43:362–5.
113. Cestari T, Arellano I, Hexsel D, Ortonne JP, Latin American Pigmentary Disorders Academy. Melasma in Latin America: options for therapy and treatment algorithm. Eur Acad Dermatol Venereol. 2009;23:760–72.
114. Oma A, Hamzavi I, Jagdeo J. Laser treatments for postinflammatory hyperpigmentation: a systemic review. JAMA Dermatol. 2017;153(2):199–206.
115. Ball Arefiew KL, Hantash BM. Advances in the treatment of melasma: a review of the recent literature. Dermatol Surg. 2012;38(7):971–84.
116. Passeron T. Melasma pathogenesis and influencing factors-an overview of the latest research. J Eur Acad Dermatol Venereol. 2013;27(1):5–6.
117. Ogbechie-Gode OA, Elbuluk N. Melasma: an up-to-date comprehensive review. Dermatol Ther. 2017;7:305–18.
118. Mansouri P, Farshi S, Hashemi Z, Kasraee B. Evaluation of the efficacy of cysteamine 5% cream in the treatment of epidermal melasma: a randomized double-blind placebo-controlled trial. British Journal of Dermatology. 2015;173:209–17.
119. Rodrigues M, Panda A. Melasma: clinical diagnosis and management options. Aust J Dermatol. 2015;56:151–63.
120. Bourra H, Leila B. Lichen planus pigmentosus. Pan Afr Med J. 2013;15:55.
121. Ghosh A, Coondoo A. Lichen planus pigmentosus: the controversial consensus. Indian J Dermatol. 2016;61(5):482–6.
122. Vachiramon V, Suchonwanit P, Thadanipon K. Bilateral linear lichen planus pigmentosus associated with hepatitis C virus infection. Case Rep Dermatol. 2010;2:169–72.
123. Weston G, Payette M. Update on lichen planus and its clinical variants. Int J Women's Dermatol. 2015;1(3):140–9.
124. Robles-Medez JC, Rizo-Frias P, Herz-Ruelas ME, Pandya AG, Candiani JO. Lichen planus pigmentosis and its variants: review and update. Int J Dermatol. 2017;57(5). Wiley Online Library.

125. Osswald SS, Proffer LH, Sartori CR. Erythema dyschromicum perstans: a case report and review. Cutis: Chatham. 2001;68(1):25–8.
126. Mulinari-Brenner FA, Guilherme MR, Werner B. Frontal fibrosing alopecia and lichen planus pigmentosus: diagnosis and therapeutic challenge. An Bras Dermatol. 2017;92(5):79–81.
127. Wolfshohl JA, Geddes ERC, Stout A, Friedman PM. Improvement of erythema dyschromicum perstans using a combination of the 1,550-nm erbium-doped fractionated laser and topical tacrolimus ointment. Laser Surg Med. 2016;49(1). Wiley Online Library.
128. Pandya A, Guevara IL. Disorders of hyperpigmentation. Dermatol Clin. 2000;18(1):91–8.
129. Skorin L. Minocycline-induced hyperpigmentation of the skin, sclera, and palpebral conjunctiva. Can J Opthalmol. 2017;52:e79–81.
130. Bahloul E, Jallouli M, Garbaa S, Marzouk S, Masmoudi A, Turki H, et al. Hydroxychloroquine-induced hyperpigmentation in systemic disease prevalence, clinical features and risk factures: a cross-sectional study of 41 cases. Lupus. 2017;26:1304–8.
131. Cohen PR, Eichenfield DZ. Amitriptyline-induced cutaneous hyperpigmentation: case report and review of pscychotropic drug-associated mucocutaneous hyperpigmentation. Dermatol Online J. 2016;22(2):6.
132. Lause M, Kamboj A, Faith EF. Dermatologic manifestations of endocrine disorders. Transl Pediatr. 2017;6(4):300–12.
133. Michels A, Michels N. Addison disease: early detection and treatment principles. Am Fam Physician. 2014;89(7):563–8.
134. Neiman LK, Chanco Turner ML. Addison's disease. Clin Dermatol. 2006;24:276–80.
135. Fernandez-Flores A, Cassarino DS. Histopathologic findings of cutaneous hyperpigmentation in Addison disease and immunostain of the melanocytic population. Am J Dermatopathol. 2017;39:924–7.
136. Banba K, Tanaka N, Fujioka A, Tajima S. Hyperpigmentation caused by hyperthyroidism: differences from the pigmentation of Addison's disease. Clin Dermatol. 1999;43:196–8.
137. Leonhardt JM, Heymann WR. Thyroid disease and the skin. Dermatol Clin. 2002;20(3):473–81.
138. Amatya B, Agrawal S, Dhali T, Sharma S, Pandey SS. Pattern of skin and nail changes in chronic renal failure in Nepal: a hospital-based study. J Dermatol. 2008;35:140–5.
139. Becker S, Walter S, Witzke O, et al. Edema, hyper pigmentation, induration: 3 skin signs heralding danger in patients on maintenance hemodialysis. Medicine. 2016;95(12):1–6.
140. Onelmis H, Sener S, Sasmaz S, Ozer A. Cutaneous changes in patient with chronic renal failure on hemodialysis. Cutan Ocul Toxicol. 2013;31(4): 286–91.
141. Fistarol SK, Itin PH. Disorders of pigmentation. J German Soc Dermatol. 2010;8:187–202.
142. Levy L, Zeichner JA. Dermatologic manifestation of diabetes. J Diabetes. 2012;4:68–76.
143. Morgan AJ, Schwartz RA. Diabetic dermopathy: a subtle sign with grave implications. J Am Acad Dermatol. 2008;58(3):447–51.
144. Vera-Kellter C, Andino-Navarrete R, Navajas-Galimany L. Vitamin B12 deficiency and its numerous skin manifestations. Actas Dermosifiliogr. 2015;106:762–4.
145. Brescoll J, Daveluy S. A review of vitamin b12 deficiency in dermatology. Am J Clin Dermatol. 2015;16:27–33.
146. Demir N, Dogan M, Koc A, Kaba S, Bulan K, Ozkol HU, et al. Dermatological findings of vitamin B12 deficiency and resolving time of these symptoms. Cutan Ocul Toxicol. 2014;33(1):70–3.
147. Higgins SP, Freemark M, Prose NS. Acanthosis nigricans: a practical approach to evaluation and management. Dermatol Online J. 2008;14(9). Retrieved from https://escholarship.org/uc/item/7mf6g290.
148. Abraham C, Rozmus CL. Is acanthosis nigricans a reliable indicator for risk of type 2 diabetes in obese children and adolescents? A systematic review. J Sch Nurs. 2012;28(3):195–205.
149. Brickman WJ, Binns HJ, Jovanovis BD, Kolesky S, Mancini AJ, Metzger BE. Acanthosis nigricanss: A common finding in overweight youth. Pediatr Dermatol. 2007;24(6):601–6.
150. Schwartz RA. Efficacy of topical 0.1% adapalene gel for the use in the treatment of childhood acanthosis nigricans: a pilot study. Dermatol Ther. 2015;28:266.