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Review Article

Guidelines for the management of vitiligo

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Abstract Vitiligo is an acquired disorder of depigmentation affecting 0.1%-2% of the world's population without discrimination of race, age and gender. The disease is characterized by white patches, often symmetrically distributed, which usually increase in size with time, corresponding to a considerable loss of functioning epidermal and sometimes hair follicle melanocyte. There are many treatment options available for the disease. Standardized guidelines for treating this disease in Asian skin are not readily available which leads to no set criteria for treating this cosmetically disfiguring problem. These guidelines have been prepared for dermatologists considering all the latest evidence based data available. Vitiligo is diagnosed clinically, although in some cases biopsy is required. Lesions on face and neck respond well to the treatment. However, segmental and acral types respond poorly to treatment. In the assessment of patient before starting therapy it is important to consider age, pre-existing diseases, in particular autoimmune disorders and previous medications. Topical corticosteroids and/or topical immunomodulators for localized vitiligo and phototherapy for generalized vitiligo are considered as first line therapies. As the treatment often extends over a long period of time, patients are frequently frustrated by the failure of previous treatments, so psychological stress is common and thus psychotherapy has also positive role. These comprehensive guidelines for the diagnosis and management of vitiligo in coloured skin aims to give high quality clinical advice, based on the best available evidence and expert consensus.

Key words
Vitiligo ,guidelines, management

Introduction

Vitiligo is a skin disorder characterized by multiple patches of depigmentation causing significant social and psychological distress.[1] Disease can appear at any age but more frequently seen in individuals less than 20years of age. It affects about 0.1%-2% of general population and familial incidence is about 30%.[2] The disease show no regards for race, gender or socioeconomic background of affected individuals.[3] Vitiligo can be a psychologically devastating disease, especially in darker skinned individuals, in whom it is more easily noticeable.[4,5] The exact cause of the disease is not yet known, but several hypothesis suggest that genetic predisposition, autoimmunity and increased vulnerability of melanocyte to destructive effects of toxic metabolites play an important role in disease causation.[6] Despite several therapeutic modalities, the treatment of vitiligo still remains unsatisfactory and is a therapeutic challenge for dermatologists.[7] Conventional treatment options are topical steroids, phototherapy (UVB 280-320nm), photochemotherapy (PUVA i.e. Psoralen plus UVA 329nm-400nm). Recently excimer laser and topical calcipotriol are also being used.

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Pathogenesis

The actual pathogenesis of vitiligo is not known but has been attributed to autoimmune (AI) causes, oxidative stress, and/or sympathetic neurogenic disturbance.[8] It remains uncertain

what causes damage to melanocytes and their consequent disappearance in affected skin. There are several pathophysiologic theories as explained earlier, but no one is exclusive, and it is likely that each of them partially contribute. The current thought is that vitiligo represents a group of varied pathophysiologic disorders with a similar phenotype. The convergence theory explains that stress, accumulation of toxic compounds, infection, autoimmunity, mutations, altered cellular environment, and impaired melanocyte migration can all contribute to pathogenesis.[9] Autoimmune mechanisms are the likely cause of generalized vitiligo, while a more localized phenomenon as focal or segmental vitiligo is likely to be a result of neurohumoral mechanisms.[10] New theories, such as melanocytorrhagy and decreased melanocyte survival, are also under consideration.[11,12]

Cutaneous manifestations

Vitiligo is a disorder of pigmentation manifesting as symmetrically distributed white macules and patches. It can occur at any age and has no gender bias. It is typically asymptomatic. Vitiligo is classified into three types: localized, generalized, and universal.[13,14] Localized vitiligo is further subtyped into focal, segmental(SV) (dermatomal or Blaschko-linear), and mucosal[15]. Generalized vitiligo may be further subclassified as acrofacial, vulgaris or mixed. Universal vitiligo involves more than 80% of the skin. Generalized vitiligo is the most common type, and vulgaris is the most common subtype. The common sites for vitiligo vulgaris are the fingers and wrists, axillae, groin and body orifices, such as the mouth, eyes, and genitals.[15,16,17] SV usually begins in childhood[18,19] and most commonly affects trigeminal dermatome and tends to remain stable.[16,18] Generalized vitiligo may begin later in life, and at sites which are sensitive to pressure, friction, and/or trauma. It is typically progressive with occasional flares. Hair is affected in later stages. There is a frequently associated personal or family history of autoimmune disorders.[19] Koebnerization and nonsegmental subtypes are associated with disease progression in patients not receiving therapy.[20,21] Rare types of vitiligo include ponctué which manifests as discrete, confetti-like amelanotic macules which occur on normal or hyperpigmented skin.[22] Trichrome vitiligo is also a rare type, represents a tan zone of varying width between normal and depigmented skin.[23]

Associated diseases

Vitiligo may be associated with other autoimmune disorders especially autoimmune thyroid disorders as hypothyroidism and hyperthyroidism. They may present in as many as 24% of pediatric vitiligo patients,[24-26] although the onset is typically delayed by more than a decade.[27] Other associated AI disorders include diabetes, pernicious anemia, and psoriasis.[28] Vitiligo may also be associated with ophthalmologic and auditory abnormalities such as uveitis, iritis and hearing loss.[29,30,31] Moreover, vitiligo is also known to be associated with several syndromes, including autoimmune polyendocrinopathy candidiasis- ectodermal dysplasia syndrome, Vogt-Koyanagi-Harada syndrome, Alezzandrini's syndrome, and Schmidt syndrome.[32-38]

Diagnosis

The diagnosis of vitiligo is usually made clinically. Wood's lamp may be of use in determining extent and activity of vitiligo, as well as monitoring response to therapy and the progress of lesions over time.[15,39] Recommended evaluation checklist for the management of patients with nonsegmental is given in **Box 1** and **2**.[40]

Box 1 *Checklist for assessment of vitiligo patient*

- Skin phototype
- Duration of disease (progressive or regressive, stable over the last 6 months)
- Premature hair greying
- Age at onset
- Genitals involvement
- Type and duration of previous treatments and ongoing treatment
- Previous spontaneous repigmentation
- Koebner phenomenon
- History of autoimmune disease in family including vitiligo
- Thyroid function tests (in adults), polyglandular syndromes may be suspected in such cases
- Photographs may be required for monitoring treatment response.
- Comorbid conditions and their treatment list
- Psychological status and quality of life of the patients

Box 2 *Diagnosis of vitiligo*

1. Special cases
   - Anti-thyroid peroxidase antibodies
   - Antithyroglobulin antibodies
   - TSH and other tests if needed to assess thyroid function
   - Additional autoantibodies (only if patient's history, family history and/or laboratory parameters point to a strong risk of additional autoimmune disease)
   - Endocrinologist/immunologist advice if multiple autoimmune syndrome considered
2. Uncertain diagnosis
   - Punch biopsy from lesional and nonlesional skin

Management

Younger patients, those with recent onset of the disease, darker skin types, and lesions of the face, neck, and trunk tend to respond best to the treatment. Segmental type of vitiligo is non progressive, but it does not respond well to the treatment. Family history of vitiligo, mucosal involvement and typically acral lesions are associated with the disease progression and are resistant to treatment. **Table 1** shows a summary whereas various treatment options are discussed in upcoming sections.

(i) Corticosteroids

Topical corticosteroids (TCS) are most effective as monotherapy[41] and produce the best clinical outcomes especially when combined with light therapy.[42] In children and adults, topical corticosteroid can be advised for the patients with limited, extrafacial involvement for a period no longer than 3 months, according to a daily application therapy.[15,40] An alternate day application therapy (15 days per month for 6 months with a strict assessment of response based on photographs preferably) is a better option.[40] As potent topical corticosteroids appear to be at least as effective as very potent topical corticosteroid so, the first category should be the safest choice.[43] Systemic absorption and skin atrophy is a concern when large areas of skin are involved, regions with thin skin and children who are treated for a prolonged time with potent steroids. In such cases, topical corticosteroids with negligible systemic effects, such as mometasone furoate or methylprednisolone aceponate should be preferred.[40] Systemic corticosteroids therapy is not considered useful for repigmenting stable vitiligo. However, they can arrest activity of the disease.[17] Weekend oral mini-pulse (OMP) starting with low doses (2.5 mg daily) of dexamethasone for fast-spreading vitiligo can be considered, with a good tolerance profile. The optimal duration of OMP therapy needed to stop vitiligo progression is between 3 and 6 months. Methylprednisolone 40-60mg intramuscular or dexamethasone in stat doses is also recommended for halting rapidly progressive vitiligo. Moreover, it must be kept in mind that because of the potential side-effects of these agents (**Box 3**), their use as first line drugs is not justified in vitiligo.[44,45]

Table 1 Treatment algorithm for vitiligo.

First line therapy	*Second line therapy*	*Third line therapy*	*Fourth line therapy*
Non segmental vitiligo			
1. Topical steroids alone or with topical vitamin D3 analogues. 2. Avoidance of triggering and aggravating factors. 3. NB-UVB therapy if >20% BSA involved *Alternative*. 1. Topical calcineurin inhibitors. 2. Short course of systemic steroids in rapidly progressive cases. 3. Combination with systemic /topical therapies, including reinforcement with UVB therapy.	1. NB-UVB with topical calcineurin topical steroids e inhibitors or 2. PUVA therapy *Alternative:* 1. Oral steroids mini-pulse therapy for 3-4 months. 2. Immunosuppressants for recalcitrant cases.	1. 308nm excimer laser. *Alternative:* 2. 308nm laser with calcineurin inhibitors	1. Surgical options as blister grafts, split skin grafts, punch grafts. 2. Depigmentation techniques (hydroquinone monobenzyl ether, 4-methoxyphenol alone or associated with Q-switched ruby laser) in nonresponding cases or widespread disease (> 50%).
Segmental vitiligo Treat as nonsegmental vitiligo, additionally helium neon laser can be used for better results. Surgical treatment is also helpful.			
General recommendation Camouflage and psychotherapy should be offered at all stages.			

Box 3 *Adverse effects of corticosteroids*

Local adverse effects

i) Epidermal atrophy
ii) Telangiectasia
iii) Striae distensae
iv) Steroid folliculitis
v) Acne

Systemic adverse effects

1. Insomnia
2. Agitation
3. Menstrual disturbances
4. Weight gain
5. Hypertrichosis
6. Hypertension
7. Diabetes
8. Cataract
9. Adrenal insufficiency

Box 4 *Adverse effects of calcineurin inhibitors*

- Mild burning or irritations
- Reactivation of herpes simplex
- Skin hyperpigmentation
- Main limitation in use of TIM is its cost

(ii) Calcineurin inhibitors

Topical immunomodulators (TIM) can be safely used in adults and children with vitiligo as an alternative to topical steroids for new, actively spreading, lesions on thin skin.[46-49] The topical safety profile of calcineurin inhibitors (TCI) is better as compared to potent topical steroids, especially concerning risks of skin atrophy. Tacrolimus and pimecrolimus are topical ascomycin immunomodulating macrolactams (TIM) and act as TCI, affecting the activation and maturation of T cells and subsequently inhibiting the production of cytokines, such as tumour necrosis factor (TNF)-α. Moreover, they also enhance melanocyte migration and differentiation. The use of TIM should be restricted to selected areas, in particular the head and neck region. Twice-daily applications are recommended. The treatment should be prescribed initially for 6 months, which can be prolonged to 12 months safely.[50,51,52] Common Adverse effects are mentioned in **Box 4**.[53]

(iii) Vitamin D3 analogues

Vitamin D3 analogues act via

immunomodulatory effects and enhancement of melanocyte development and melanogenesis in vitiligo.[54,55] As monotherapy, these agents are inferior to topical corticosteroids.[56] They are safe for use in both children and adults and are most beneficial when combined with topical CSs.[56] The impact of calcipotriene on light phototherapy is contentious and requires further research. While some studies suggest that there is no benefit of adding calcipotriene to NBUVB phototherapy, and that calcipotriene may actually delay repigmentation.[57-59] It should not be used immediately before or after light phototherapy. The recommended use is as maximum 100 g weekly of the combination of calcipotriene 0.005% and betamethasone 0.05%, limiting application to less than 30% of the body surface area and not exceeding 4 consecutive weeks of therapy with the ointment (8 weeks for the cream and solution).[60] Except mild irritation vitamin D3 analogues are generally safe.

(iv) Phototherapy

Ultraviolet light has been used to treat patients with vitiligo since many years. The exact mechanism of action is not known. It acts via both immunosuppressive and melanocyte stimulatory effects. In vitro trials have shown that both UVA and UVB phototherapies promote melanocyte migration and proliferation and produce a favourable environment for melanocyte growth, and also inhibit autoimmunity.[61] Narrowband ultraviolet B light phototherapy is superior to ultraviolet A light phototherapy for the treatment of vitiligo[62,63]. Phototherapy should be reserved for patients who fail topical therapy or who have extensive vitiligo at the onset.[15] Psoralen plus ultraviolet A light phototherapy may increase the incidence of both melanoma and nonmelanoma skin cancer, so should be used with caution.[60]

(a) NB-UVB

NB-UVB is indicated for generalized NSV. 311-nm NBUVB phototherapy has outdated PUVA phototherapy in the treatment of vitiligo because it was shown to be clinically more effective. NBUVB induces tyrosinase, an enzyme required for melanin production, and increases the presentation of HMB45 on the surface of melanosomes.[64] Total body treatment is suggested for lesions involving more than 15-20% of the body area. It has also been considered as treatment for actively spreading vitiligo. Targeted phototherapies are indicated for localized vitiligo and also for small lesions of recent onset and in childhood vitiligo, to avoid side-effects due to total body irradiation with UVB, and in all cases where contraindications exist for total body irradiation with conventional NB-UVB. Patients with vitiligo have traditionally been regarded as skin type I and so should be treated with very low initial NB-UVB doses (150-250 mJ/cm^2). Treatment is recommended as two to three sessions per week lasting between 10 weeks and 2 years. In children, an average of 34 treatments was required to achieve 50% repigmentation.[65] There is as yet no consensus as to the optimum treatment duration of NBUVB.[60] Treatment may be stopped if no repigmentation occurs within the first 3 months or in case of unsatisfactory response (<25% repigmentation from the baseline) after 6 months of treatment. Phototherapy is usually continued as long as there is ongoing repigmentation or over a maximum period of 1 or 2 years.[40] Maintenance irradiation is not recommended, but regular follow-up examinations are suggested for detection of relapse. NB-UVB gives better results when combined with topical steroids or topical immunomodulators.[1,6]

(b) Photochemotherapy

Oral PUVA is being currently used in adult patients with generalized vitiligo as a second-line therapy. UVA phototherapy is almost always given in combination with the photosensitizer psoralen. PUVA phototherapy induces hypertrophy of melanocytes and hyperactive melanosomes.[66] It also increases melanocyte production in hair follicles, and induces keratinocyte release of factors that stimulate melanocyte growth, and may reduce the presence of vitiligo-associated melanocyte antigens on melanocyte membranes.[67] Clinically, this results in perifollicular repigmentation.[68] PUVA is approved by the FDA for the treatment of vitiligo,[60] but high doses of UVA alone (15 J/cm2) has also induced repigmentation in various trials on vitiligo patients.[69] Repigmentation rates were higher with PUVA on head and neck ,however response was lower on extremities.[70,71] As compared to NB-UVB it has the disadvantage of lower efficacy and higher short- and long-term risks.[60] It is not recommended in children aged under 10-12 years because of the risk of retinal toxicity.[72]. For oral PUVA, 8-methoxypsoralen (8-MOP 0.6-0.8 mg/ kg), 5-methoxypsoralen (5-MOP 1.2-1.8mg/kg) or trimethylpsoralen (0.6 mg/kg) is given orally 1-3 h before exposure to UVA.[60] Patients should be motivated to continue PUVA therapy for at least 6 months before being considered nonresponsive.[45] Darker skin types show maximal responses to PUVA. As with NB-UVB, 12-24 months of continuous therapy may be necessary to acquire maximal repigmentation. The maximum recommended lifetime exposure to PUVA should be limited to 1000 J/cm^2 or 200 treatments.[60] For topical PUVA, psoralens should be formulated in creams at very low concentration (0.001%) should be applied 30 min before UVA exposure, with possible further concentration increments. The advantage of topical therapy is that fewer treatments are needed and considerably smaller cumulative UVA doses are required, consequently results in less systemic and ocular phototoxicity.[15,40]

Box 5 *Adverse effects of phototherapy and PUVA*

UVB
- Considered safe
- Erythema
- Burning
- Reactivation of herpes simplex
- Photoageing
- Carcinogenesis

PUVA
- Erythema
- Burning
- Pruritus
- Pigmentation
- Hypertrichosis
- Actinic keratosis
- Lentigines
- Retinal toxicity
- Gastritis
- Photoageing
- Melanoma

Non-melanoma skin cancer

Combination treatments

1. *Topical steroids and phototherapy* The combination of TCS and UVB sources NB-UVB (311-312nm) and excimer lasers (308nm) are more effective in difficult cases. Potent topical steroids applied once a day (3 weeks out of 4) can be used on vitiligo lesions for the first 3 months of phototherapy.[73]
2. *TCI and phototherapy* There is good evidence that the combination of TCI and UV radiation is effective and provides better results than the two treatments used alone.[1,74,75]
3. *Vitamin D analogues and phototherapy* The use of vitamin D analogues in combination with UV radiation is not recommended as the benefit of the

combination therapy appears to be at best very limited.[76]

4. *TCS and TIM/vitamin D3 analogues* This combination provides better results in vitiligo.[76]
5. *Phototherapy after surgery* There is now a good level of evidence that phototherapy (NB-UVB or PUVA) should be used for 3 or 4 weeks after surgical procedures to enhance repigmentation.[77,78]

(v) Lasers

The mechanism of action is thought to be similar to conventional light therapy, but lasers allow targeted treatment, less total body irradiation, and fewer side effects on healthy skin. The monochromatic excimer laser (308 nm) allows for the targeted treatment of specific lesions and yields better results than conventional light therapy.[79] Mild erythema and pruritus are reported.[80] It is recommended as one to three times a week for twelve weeks. A new device from Italy, known as Bioskin®, emits focused 311nm UVB phototherapy (microphototherapy). The aim is to improve cosmesis, reduce adverse effects, and decrease the premature aging and risk of skin cancer associated with total body irradiation.[7] Helium neon laser (632.8 nm) therapy is effective for segmental vitiligo. It promotes melanogenesis, melanocyte growth, migration, and survival in the skin.[81]

(vi) Antioxidants

Oxidative stress has recently been implicated in the pathogenesis of vitiligo. Antioxidant supplementation oral or topical can be useful during UV therapy, and also during the reactivation phase of vitiligo. However, further research is required. Pseudocatalase, vitamin E, vitamin C, ubiquinone, lipoic acid, *Polypodium leucotomos*, catalase⁄superoxide dismutase combination, and *Ginkgo biloba* are antioxidants that have been used alone or, more frequently, in combination with phototherapy.[82] The safety profiles of many antioxidants are unknown. Topical catalase/superoxide dismutase causes transient erythema, pruritus, and peeling.[83]

(vii) Surgery

This option should be reserved for patients with SV and other localized forms, or after the documented failure of medical options. Various methods being used are melanocyte transplant techniques such as suction blister grafting, split-thickness grafting, punch grafting, and melanocyte suspension.[81]

(viii) Other interventions

(a) Camouflage Considering the impact of the disease on the patient's personality, camouflage techniques are an important part of the management of the disease. There is a wide choice of self-tanning agents, stains, dyes, whitening lotions, tinted cover creams, compact, liquid and stick foundations, fixing powders, fixing sprays, cleansers, and dyes for pigmenting facial and scalp white hair.[84]

(b) Depigmentation Only patients with extensive vitiligo should be offered this option and only after exploring other possible therapies. Monobenzone is the topical agent used for this purpose. The patient should be advised that monobenzone is a potent depigmenting agent and not a cosmetic skin bleach. Depigmentation can also be obtained by using a Q-switched ruby or alexandrite laser, alone or in combination with topical depigmenting agents. Monobenzone may cause burning, itching, and contact dermatitis.[85] Conjunctival melanosis, pingueculae, and corneal pigment deposition have been reported with monobenzone.[86]

(ix) New concepts in treating vitiligo

Psychotherapy helps the psychosocial effects of vitiligo, but may also cause disease regression.[87] Tumor necrosis factor-α inhibitors are reported to alter disease progression of vitiligo, but this has yet to be studied in clinical trials.[88] A recent study suggests that minocycline may halt disease progression.[89] Immunosuppressants (azathioprine, cyclophosphamide and cyclosporine) may have a role in the treatment of vitiligo. But, still more data are required.[90]

Recommendations

Treatment of vitiligo should be started with less aggressive and cost-effective modalities, reserving more invasive and expensive options for those who fail to respond to first-line therapy. Treatment algorithm is also recommended.

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