



Vitiligo Update

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Vitiligo is an acquired dyschromia of the skin in which there is a loss of epidermal melanocytes. The prevalence of vitiligo is approximately 1% in the United States and 0.1-2% worldwide. The exact pathogenesis of vitiligo remains elusive and is likely multifactorial. After completing this update, participants should be able to discuss the epidemiology of vitiligo and summarize the proposed mechanisms for development of this disease. In addition, they should be able to discuss physical findings, approach to the patient, and some of the therapeutic modalities for this disorder.

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Vitiligo occurs worldwide, with a prevalence of $\leq 2\%$. In the United States, its estimated incidence is 1%. The disease usually begins in childhood or young adulthood with a peak onset at 10-30 years. All races are affected, and both sexes are equally affected; however, a female preponderance has been reported. This discrepancy may potentially be skewed by increased reporting of cosmetic concerns by female patients. Vitiligo can be psychologically devastating for the affected patient. This is especially true in patients with darker skin because of the great contrast between the color of vitiliginous skin and surrounding normal skin. Vitiligo can affect quality of life, self-esteem, marriage, and employment, especially in darker-skinned individuals and in certain cultures because of confusion with leprosy and other contagious skin diseases. Loss of pigment may be viewed by patients as a threat to racial identity.

Etiopathogenesis

Vitiligo is multifactorial and polygenic. The precise pathogenesis remains elusive; however, several theories have been proposed to explain the loss of epidermal melanocytes in this disorder. Proposed mechanisms fall under the rubrics of autoimmune, biochemical, oxidant-antioxidant, neural, and viral. Studies have also pointed to a significant role of genetic susceptibility to vitiligo.

Genetics of Vitiligo

Vitiligo is inherited in a non-Mendelian pattern and is characterized by incomplete penetrance, multiple susceptibility

loci, and genetic heterogeneity. Inheritance may involve genes associated with melanin biosynthesis, response to oxidative stress, and regulation of autoimmunity. Because of the frequent association of vitiligo with autoimmune diseases, there have been investigations of possible HLA associations in vitiligo. Several haplotypes have been associated with vitiligo in more than one study.^{1,2}

The catalase gene has been implicated in the pathogenesis of vitiligo. Most likely a C/T single nucleotide polymorphism in exon 9 of the catalase gene is responsible.³ Reduced catalase enzyme activity has been demonstrated in the epidermis of lesional and nonlesional skin in patients with vitiligo.⁴ Catalase is a peroxisomal enzyme found in nearly all organisms exposed to oxygen that catalyzes the decomposition of hydrogen peroxide to water and oxygen. Therein, it serves to prevent cell damage by highly reactive oxygen radicals.

Role of the Immune System

The association of vitiligo with autoimmune conditions is well established. Thyroid disorders, particularly Hashimoto's thyroiditis and Graves' disease, are commonly associated with vitiligo, as are other endocrinopathies, such as Addison's disease and diabetes mellitus. Alopecia areata, pernicious anemia, systemic lupus erythematosus, inflammatory bowel disease, rheumatoid arthritis, psoriasis, and autoimmune polyglandular syndrome also are associated, though the significance of some of these associations is debated. The most compelling argument for an autoimmune pathogenesis is the demonstration of circulating autoantibodies to melanocytes in the serum of patients with vitiligo. Autoantibodies directed specifically against melanocyte cell surface antigens have the ability to kill melanocytes *in vivo* and *in vitro*. The levels of these autoantibodies seem to correlate with disease extent and activity. One of the autoantigens identified is VIT 40.¹ Tyrosinase and TRP-1 and -2 have been identi-

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fied as autoantigens as well, but data supporting this claim have been conflicting.⁵ Some patients with vitiligo have antibodies to melan A/MART-1, a melanocyte differentiation antigen.⁶ SOX transcription factors, which are involved in the differentiation of tissue derived from the neural crest, have been identified as melanocytic antigens in vitiligo associated with the polyendocrine syndrome.⁷ Antiorgan antibodies, such as antibodies to thyroglobulin, thyroid microsomes, and gastric parietal cells, also are frequently elevated in patients with vitiligo as compared with healthy control patients.¹ Speculation abounds that codon-54 polymorphism in the mannose-binding lectin 2 gene may play a role in susceptibility to vitiligo. Mannose-binding lectin is a calcium-dependent lectin that causes predisposition to infections and autoimmune diseases.⁸

Oxidant-Antioxidant Role in Vitiligo

Oxidative stress may also play an important pathogenic role in vitiligo. Several studies suggest that accumulation of free radicals toxic to melanocytes leads to their destruction. Cultured melanocytes and the serum of patients with vitiligo often have increased nitric oxide levels, suggesting that nitric oxide could lead to autodestruction of melanocytes. Compared with control patients, the red cells of vitiligo patients have lower levels of glutathione, which helps prevent free radical mediated injury.⁹ Thus, vitiligo patients may be subject to a greater level of oxidative stress.

Neural Theory

Segmental vitiligo often occurs in a dermatomal pattern. This observation led to a neural hypothesis that proposes certain chemical mediators released from nerve endings may cause decreased melanin production. Elevated neuropeptide Y levels have been demonstrated in skin affected by vitiligo.¹⁰ Decreased sweating occurs in some patches of segmental vitiligo, and some patients have been shown to have mild degenerative or regenerative changes in axons and Schwann cells in the depigmented areas.

Viral

Cytomegalovirus (CMV) DNA has been identified in skin biopsy specimens of some patients with vitiligo, which raises the question of whether there is viral-induced damage to melanocytes in subsets of patients with vitiligo.¹¹ The possible involvement of other viruses, such as hepatitis C, HIV, and Epstein-Barr virus has been suggested by some authors.^{12,13}

Convergence Theory

Although all the aforementioned hypotheses are attractive, it is likely that vitiligo is a result of the convergence of several of these pathologic pathways. Most experts agree that vitiligo may indeed be a syndrome rather than a single entity.

Clinical Findings

Patients present with 1 to several amelanotic macules that appear chalk- or milk-white in color. There is no epidermal

change and usually no erythema; however, very occasionally, inflammation can be seen at the advancing edge of lesions. Lesions are often symmetric and usually enlarge centrifugally in size with time. The increase in size corresponds with a substantial loss of functioning epidermal and, sometimes, hair follicle melanocytes. Lesions are typically well demarcated, but the borders may be scalloped. Lesions are accentuated with Wood's lamp examination. Initial lesions occur most frequently on the hands, forearms, feet, and face, although they may appear anywhere, including the mucous membranes. Facial vitiligo often favors a periorificial distribution.¹⁴

Classification of Vitiligo

Vitiligo is classified as segmental, acrofacial, generalized, and universal or by pattern of involvement as focal, mixed, and mucosal types.

- Focal vitiligo is usually a solitary macule or a few scattered macules in 1 area, most commonly in the distribution of the trigeminal nerve, although the neck and trunk are also commonly involved. This form occurs more commonly in children.
- Segmental vitiligo presents as unilateral macules in a dermatomal or quasi-dermatomal distribution. This type tends to have an early age of onset and, unlike the other types, is not associated with thyroid disease or other autoimmune diseases. Alteration of neural peptides has been implicated in the pathogenesis. More than one half of patients with segmental vitiligo have poliosis.
- Acrofacial vitiligo presents as depigmentation of the distal fingers and periorificial areas.
- Generalized vitiligo is also termed vitiligo vulgaris. This is the most common pattern. Depigmented patches are widely and usually symmetrically distributed.
- Universal vitiligo presents as depigmented macules and patches over most of the body and can be associated with multiple endocrinopathy syndrome (Fig. 1).
- Mucosal vitiligo involves only the mucous membranes (Fig. 2).

In patients of darker skin type, there is great contrast between depigmented and normal skin as shown in Figs. 3 and 4. This is often psychologically devastating.

Clinical Variants

Trichrome vitiligo is characterized by both depigmented and hypopigmented macules in addition to normally pigmented skin. The natural evolution of the hypopigmented areas is progression to full depigmentation. Quadrichrome vitiligo refers to the additional presence of marginal or perifollicular hyperpigmentation. This variant is recognized more frequently in darker skin types, particularly in areas of repigmentation. Pentachrome vitiligo has also been reported with additional blue-gray hyperpigmented macules, representing areas of melanin incontinence. Occasionally, patients with vitiligo may present with an unusual variant called the con-



Figure 1 Universal vitiligo in an Asian woman.

fetti type. These patients have several tiny, discrete, hypomelanotic macules. Inflammatory vitiligo is characterized clinically by erythema at the margins of vitiligo macules.

Differential Diagnosis

Several diseases can be mistaken for vitiligo, including but not limited to *Tinea versicolor*, piebaldism, idiopathic guttate hypomelanosis, and progressive macular hypomelanosis. *Tinea versicolor* is a superficial yeast infection that can lead to loss of pigment in darker-skinned individuals. It presents as light-colored macules typically on the upper trunk and chest, with a fine dry surface scale. Piebaldism is an autosomal-dominant disorder in which there is an absence of melanocytes from the affected areas of the skin. It usually presents at



Figure 2 Mucosal involvement of the lip with vitiligo in an African-American man.

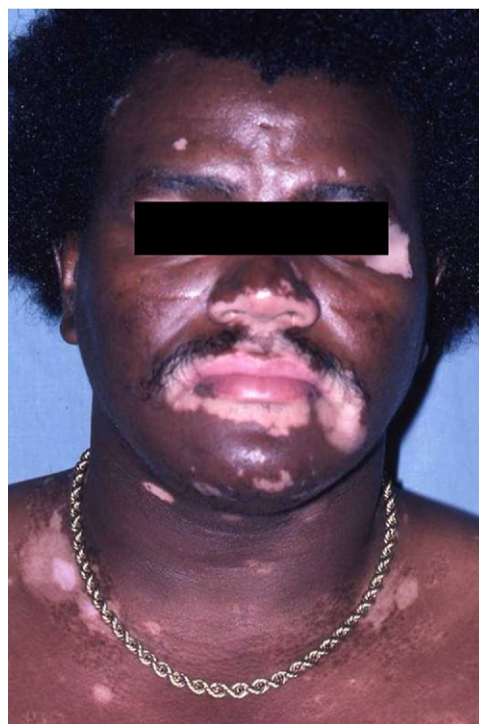


Figure 3 Disfiguring facial involvement with vitiligo in an African-American man.

birth with depigmented areas that are usually near the midline on the front, including a white forelock. Idiopathic guttate hypomelanosis presents with multiple small discrete white macules on the trunk or on sun-exposed areas of the limbs. Progressive macular hypomelanosis is a common disorder that is often misdiagnosed. It is most common in African-American patients originating from tropical countries. It is characterized by ill-defined, nummular, nonscaly hypopigmented macules on the trunk, often confluent in and around the midline and rarely extending to the proximal extremities and head and neck.¹⁴

Laboratory Tests

The diagnosis of vitiligo is based primarily on clinical findings. However, given the association between vitiligo and other autoimmune diseases (a history of autoimmune disease in a family member is obtained in 32% of patients), several screening laboratory tests are helpful, including thyroid-stimulating hormone, antinuclear antibody, and complete blood count. Clinicians should also consider testing for serum antithyroglobulin and antithyroid peroxidase antibodies, especially if patient and family history indicates so. Antithyroid peroxidase antibodies, in particular, are regarded as a sensitive and specific marker of autoimmune thyroid disorders (Table 1).

Histology

Lesional skin of vitiligo patients lacks melanocytes. A superficial dermal lymphocytic infiltrate may be observed at the margin of vitiliginous skin, particularly in early lesions. This

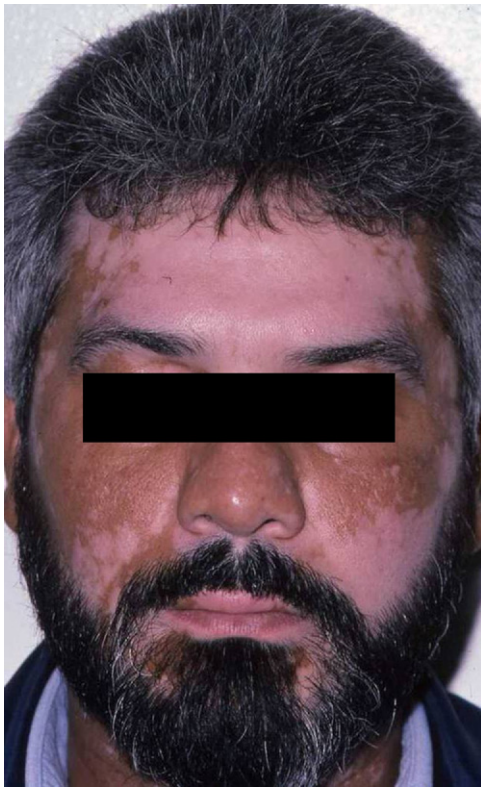


Figure 4 Disfiguring facial involvement with vitiligo in a Hispanic man.

finding is consistent with cell-mediated immune processes destroying melanocytes.¹⁵

Approach to the Patient with Vitiligo

In the guidelines for diagnosis and management of vitiligo by Gawkrödger et al,¹⁴ the algorithm was based on studies of various levels of evidence. Levels of evidence were defined as follows:

- 1++ High-quality meta-analyses, systematic reviews of randomized controlled trials (RCTs), or RCTs with a very low risk of bias
- 1+ Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
- 1- Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
- 2++ High-quality systematic reviews of case-control or cohort studies; and
- High quality case-control or cohort studies with a very low risk of confounding, bias, or chance and a high probability that the relationship is causal
- 2+ Well-conducted case-control or cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relationship is causal
- 2- Case-control or cohort studies with a low risk of confounding, bias, or chance and a significant risk that the relationship is not causal

- 3. Nonanalytical studies, for example, case reports, case series
- 4. Expert opinion.¹⁴

Vitiligo can be a psychologically devastating disease that has a significant impact on quality of life and self-esteem. Vitiligo may cause social isolation and significant depression. Some assessment of the impact of vitiligo on the patient's quality of life should be made at the initial consultation (level of evidence 2+A).

Women are more severely affected with respect to quality of life, being more likely to be depressed about their appearance and more likely to internalize stigmatization and attribute an internal cause (level of evidence 3). Psychological effects appear to be more prominent when visible body areas are affected (level of evidence 3). Vitiligo has an impact similar to that of psoriasis on a patient's quality of life. Psychological interventions should be offered as a way of improving coping mechanisms in patients with vitiligo. Group therapy and individual therapy were both shown to be of benefit in the works of Papadopolous et al.¹⁶ Also, parents of affected children should be offered psychological counseling (level of evidence 4).¹⁴

There are several treatment options available to vitiligo patients. Most treatments are intended to restore pigment to the skin. Each treatment has advantages and disadvantages. No treatment is appropriate for every patient with vitiligo.

Sunscreens

Sunscreens help prevent sunburn and in effect lessen photo-damage, which decreases the chance that an isomorphic response of Koebner will occur. In addition, sunscreens decrease tanning of the uninvolved skin and therefore lessen the contrast with vitiliginous lesions.

Cosmetics

Many patients find cosmetic cover-ups to be a valuable treatment option. Areas of depigmentation, especially on the face, neck, or hands can be covered with conventional make-up, self-tanning products, or other topical dyes. Advantages of cosmetics are that they offer limited cost, minimal side effects, and ease of application. In children and adults of skin types I and II, it is appropriate to consider whether the initial approach may be to use no active treatment other than cosmetics and sunscreen (level of evidence 4).¹⁴

Topical Corticosteroids

Topical steroids are indicated for the treatment of limited areas of vitiligo and are often the first line of therapy in

Table 1 Screening Laboratory Tests in Patients With Vitiligo

Thyroid-stimulating hormone
Complete blood count
Antinuclear antibody
Antithyroglobulin antibodies*
Antithyroid peroxidase antibodies*

*If patient and/or family history indicates.

pediatric patients, although most experience is anecdotal. Lesions on the face seem to have the best response and lesions on the neck and extremities with the exception of the fingers and toes also have a favorable response.¹⁷ It is unclear why lesions on the face have a better response rate. Proposed theories are that the facial skin has greater permeability to the corticosteroids, a larger number of residual melanocytes in the uninvolved skin, greater follicular reservoirs, or melanocyte damage that is more easily reversed. Lesions on the face often repigment diffusely, whereas lesions elsewhere more commonly repigment in a dot-like follicular pattern.

In children and adults with recent onset of vitiligo, treatment with a potent or very potent topical steroid should be considered for a trial period of no more than 2 months (level of evidence 1).¹⁴ Studies by both Kandil¹⁸ and Clayton¹⁹ show that the use of an ultrapotent or potent topical steroid can repigment vitiligo but only in a small proportion of patients. Clayton found 15-25% repigmentation in 10 of 23 patients and >75% repigmentation in 2 of 23 patients. The other patients showed no repigmentation. Kandi¹⁸ found 90-100% repigmentation in 6 of 23 subjects and 25-90% in 3. Six patients showed "beginning pigmentation." In children and adults with larger lesions, a medium-potency nonfluorinated corticosteroid is often used, likely at the expense of efficacy. Discretion must be exercised when using topical steroids on and around the eyelids, as their use can increase intraocular pressure and exacerbate glaucoma.

Wood's lamp examination can be used to monitor response to treatment. If no response is seen by 3 months, therapy should be discontinued. Maximum re-pigmentation may take 4 months or longer (there is a 30-40% response rate with 6 months of corticosteroid use). More darkly pigmented patients may have a more favorable response to topical corticosteroids than those with lighter complexions. The ease of application, compliance rate, and limited cost are the benefits of using topical corticosteroids for treating limited vitiligo. Recurrence after treatment cessation and corticosteroid side effects are the drawbacks. All patients, especially children, should be monitored closely for side effects.

Topical Immunomodulators

Topical tacrolimus ointment 0.03-0.1% is effective in repigmentation of vitiligo when applied twice daily in patients with localized disease, particularly on the face and neck. Topical tacrolimus is reported to be more effective when combined with UVB or excimer laser therapy.^{20,21} In general, tacrolimus ointment is considered safer for children than topical steroids and should be considered as an alternative. In adults with symmetric types of vitiligo, topical pimecrolimus should be considered as an alternative to the use of a topical steroid; in addition, its side effect profile is better than that of a highly potent topical steroid. This conclusion is based on a small study conducted by Coskun and colleagues²² in which they compared topical pimecrolimus with topical clobetasol. Pimecrolimus resulted in 50-100% repigmentation in 8 of 10 patients. Similar results were seen in 7 of 10 patients treated

with clobetasol. No skin atrophy was seen in the pimecrolimus group, but burning was noted as a side effect.

Topical Calcipotriol

In a randomized, open, left vs right study by Chiaverini et al,²³ the effect of calcipotriol, 0.005% was compared in symmetric target lesions in 24 patients with localized and generalized vitiligo. After 3-6 months, no repigmentation was noted in 21 of 23 patients. One had 5% repigmentation and 2 had repigmentation with and without calcipotriol. The use of topical calcipotriol as a monotherapy is not recommended (level of evidence 2+).¹⁴

Pseudocatalase

Levels of catalase, an enzyme that is normally found in skin that decreases damage from free radicals, have been reported to be low in the skin of vitiligo patients. A replacement therapy using an analog of normal human catalase, pseudocatalase, in combination with narrow band UVB phototherapy has been reported to repigment some vitiligo patients and prevent disease progression.²⁴⁻²⁶

Systemic Therapies

Systemic immunosuppressive drugs have many potential side effects that are difficult to justify for a disease such as vitiligo. However, systemic corticosteroids have been used as pulse therapy with variable results and may prevent rapid depigmentation in active disease. In an open study conducted by Radakovic-Fijan et al,²⁷ of 25 adults with active generalized types of vitiligo treated with oral dexamethasone 10 mg twice weekly for 24 weeks, 22 of 25 had disease-progression arrest. Side effects were common and included weight gain, acne, menstrual irregularity, and hypertrichosis. Systemic immunosuppressive drugs to arrest progression of vitiligo cannot be recommended due to an unacceptable risk of side effects (level of evidence 2+A).¹⁴ There has been a case report of repigmentation in a patient with vitiligo being treated for psoriasis with efalizumab.²⁸ Biologics may be a potential therapeutic modality for vitiligo; however, their side effect profile may preclude their use.

Phototherapy

Topical or oral 8-methoxy psoralen combined with UVA irradiation (PUVA) is effective for treating vitiligo,²⁹ although frequent treatments over several months are required. After exposure to UVA, psoralens covalently bind to DNA and inhibit cell replication. How this then leads to repigmentation of vitiligo lesions is poorly understood. PUVA stimulates tyrosinase activity and melanogenesis in unaffected skin. PUVA is also local immunosuppressive, and decreased expression of vitiligo-associated melanocyte antigens has been reported.

In vitiligo, melanocytes in the bulb and infundibulum of the hair follicle are often destroyed, but the lower and middle portion of the follicle as well as the outer root sheath are spared. PUVA stimulates follicular melanocytes to migrate into the epidermis and repopulate the surrounding vitiligi-

nous skin, possibly because of the release of cytokines and chemoattractants from the epidermal keratinocytes.

If <20% of the body surface of a patient's skin is involved, topical PUVA is sometimes used. However, unwanted side effects are common and include cosmetically displeasing hyperpigmentation of skin surrounding areas of vitiligo as the result of inadvertent psoralen application, severe phototoxicity, and severe pruritus. Oral psoralens are used for patients with more extensive involvement or in patients who do not respond to topical PUVA.

Careful selection of patients with vitiligo for PUVA therapy is very important. Although 70-80% of patients experience some repigmentation with PUVA, <20% of patients achieve total repigmentation. In general, vitiligo on the trunk, proximal extremities, and face responds well to PUVA, but lesions on the distal extremities respond poorly. As with corticosteroids, patients with a darker complexion tend to respond better to PUVA, possibly because they tolerate greater PUVA exposures.³⁰

Narrow-band UVB (NBUVB) irradiation is another option for patients with vitiligo and is currently considered by many to be the first choice for most patients.¹⁴ In patients with extensive generalized vitiligo, NBUVB was more effective than topical PUVA (67% vs. 46% response rate, respectively).³¹ This comparison is not an appropriate one, however, because topical PUVA is indicated for <20% skin surface involvement with vitiligo and NBUVB is indicated for >20% skin surface involvement. A better comparison would have been between NBUVB and oral PUVA therapy which is used for >20% skin surface involvement with vitiligo. NBUVB should be used in preference to oral PUVA in view of evidence of greater efficacy and safety (level of evidence 1+).¹⁴ If no improvement is seen within 6 months, NBUVB therapy should be discontinued. In one study, 53% of children experienced more than 75% repigmentation after NBUVB therapy, and 6% showed complete repigmentation. Again, better pigmentation was achieved on the face, trunk, and proximal extremities than on the distal extremities and groin. Phototherapy should generally be reserved for patients who can't be adequately controlled by more conservative treatments, who have widespread vitiligo, or who have localized vitiligo with a significant impact on quality of life.¹⁴

Excimer Laser

Excimer (308 nm) laser has been studied in several trials for its efficacy in treating vitiligo. Therapy has been found to be most effective when used 3 times per week. Treatment periods of more than 12 weeks are necessary to obtain satisfactory repigmentation. The initial dose is 50-100 mJ per square cm. As with standard phototherapy, excimer laser produced the best treatment results on the face. The least responsive areas were the hands and feet.³²

Depigmentation

Monobenzyl ether of hydroquinone (monobenzone) is the only agent available in the United States and Europe for depigmenting residual normal skin in patients with extensive

vitiligo. Monobenzone is a phenolic toxin that destroys epidermal melanocytes after protracted use. Monobenzone can therefore produce a uniform depigmented state that is more acceptable for many patients than the contrast between normal and affected skin. Monobenzone is available as a 20% cream and can be compounded to concentrations up to 40%. The individual using monobenzone should avoid direct contact with others for 1 hour after application, as contact may cause depigmentation of others' skin.³³ Monobenzone may also be irritating and allergic sensitization may occur. This treatment should generally be reserved for adults who have severe vitiligo with >50% depigmentation or extensive depigmentation on the face or hands that cannot be repigmented or for adults who choose not to seek repigmentation and can accept the permanence of never being able to tan (level of evidence 4).¹⁴ The acceptance of appearance after depigmentation by the patient is almost universal regardless of the race or original skin color of the patient.

Surgical Modalities

Surgical treatments should be reserved for cosmetically sensitive sites in which there have been no new lesions, no Koebnerization and no extension of the lesion in the previous 12 months (level of evidence 1+).¹⁴ In a study by Kim and Kang³⁴ in which they performed suction blister transfer, relapse was seen in 40% of patients with progressive disease as opposed to 10% with stable disease. There are fortunately several very successful surgical treatments available, including split thickness grafts, suction blister grafts, mini punch grafts, and melanocyte transplant. A detailed discussion of these modalities is beyond the scope of this update but can be reviewed elsewhere.

Conclusions

Vitiligo can be a very psychologically devastating disease. This is especially true in patients with skin of color. Vitiligo carries with it myriad psychosocial implications. In dealing with vitiligo patients, it may be of use to take a multidisciplinary approach and involve psychology or psychiatry consultation early in the treatment course. Treatments for vitiligo have various response rates and it may be necessary to use rotational therapy to diminish side effects and to gain better repigmentation response.

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