Vitiligo

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Introduction

- Vitiligo is a relatively common acquired disorder of pigmentation characterized by the development of well-defined white macules on the skin. Biopsies of lesional skin reveal a loss of epidermal melanocytes
- Given the contrast between the white areas and normal skin, the disease is most disfiguring in darker skin types and has a profound impact on the quality of life of both children and adults.
- Patients with vitiligo often experience stigmatization, social isolation, and low self-esteem

Epidemiology

- Vitiligo is the most frequent cause of depigmentation.
- Estimated prevalence rates range from 0.1 to 2 percent in both adults and children.
- Vitiligo affects equally males and females, without racial, ethnic, or socio-economic predilections.
- It may appear at any age from early childhood to late adulthood, with peak incidences in the **second and third** decade of life.
- Approximately one-third of patients with vitiligo are children, and 70 to 80 percent of adult patients develop vitiligo prior to age 30 years

Etiology

- The etiology of vitiligo is unknown.
- Patients commonly attribute the onset of their disease to specific triggering events such as physical injury or illness, sunburn, emotional stress, or pregnancy, but there are no data supporting a causative role for these factors.
- The frequency of comorbid autoimmune diseases is significantly elevated in patients with vitiligo and in their first-degree relatives, suggesting an autoimmune etiology for this disorder

Pathogenesis

- Multiple theories have been proposed for melanocyte destruction in vitiligo.
- These include genetic, autoimmune, neural, biochemical, oxidative stress, viral infection, and melanocyte detachment mechanisms.
- Although the autoimmune and oxidative stress theories are best supported by research data, none of the proposed theories are in themselves sufficient to explain the diverse vitiligo phenotypes.
- The so-called "convergence theory" suggests that multiple mechanisms may contribute to the disappearance of melanocytes in vitiliginous skin and that vitiligo may indeed represent a disease spectrum

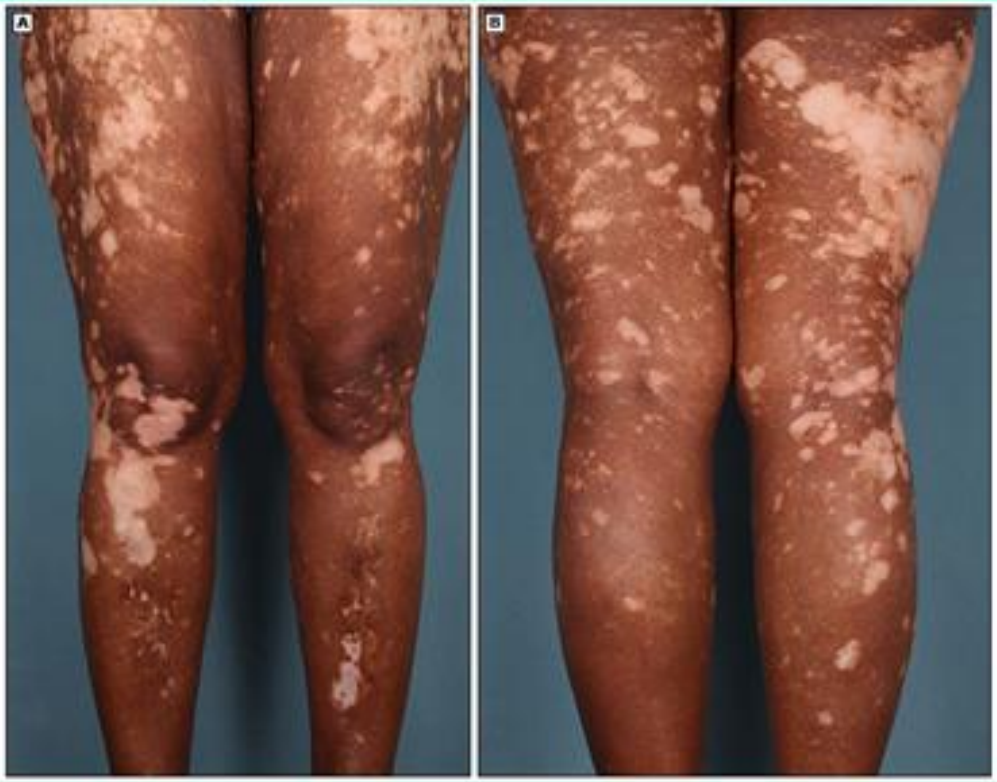
Pathogenesis

- **Genetics** — Family clustering of vitiligo suggests a genetic basis for the disease . Genetic studies indicate a non-Mendelian, multifactorial, polygenic inheritance pattern .
- Twenty-five to 50 percent of persons with vitiligo have affected relatives, and approximately 6 percent have siblings with the disorder
- **Autoimmunity** — Historically, vitiligo has been associated with several autoimmune diseases, including Hashimoto's thyroiditis, Graves' disease, type 1 diabetes mellitus, alopecia areata, pernicious anemia, rheumatoid arthritis, autoimmune polyglandular syndrome, and psoriasis.

Clinical Features

- Vitiligo typically presents with asymptomatic depigmented macules and patches, milk or chalk white in color, that lack clinical signs of inflammation
- Severe sunburn, pregnancy, skin trauma, and/or emotional stress may precede the disease onset.
- Lesions can appear at any age and anywhere on the body, with a predilection for the face and areas around the orifices, genitals, and hands.
- They vary in size from a few millimeters to many centimeters and usually have convex borders well-demarcated from the surrounding normal skin.

Vitiligo



Numerous white macules on the legs of this patient with generalized vitiligo.

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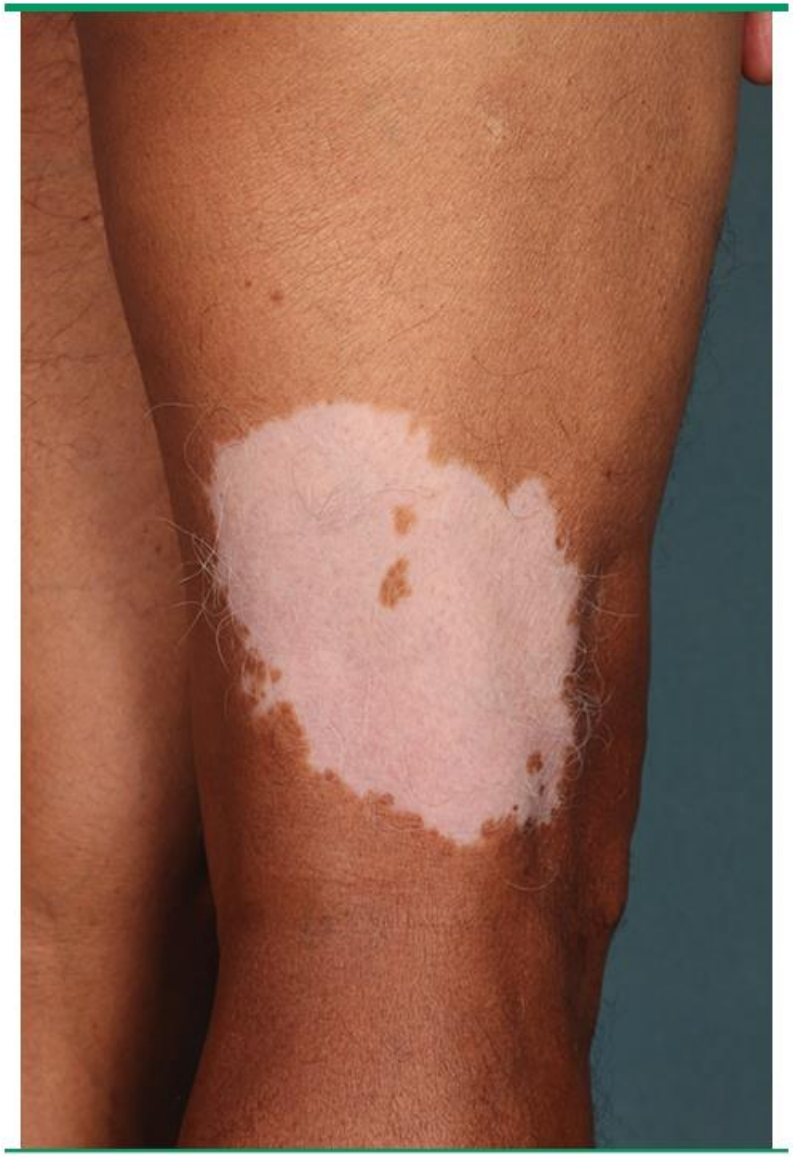
Clinical Features

- Depigmented hairs are often present in lesional skin. While such hairs indicate a reduction or loss of the follicular reservoir for repigmentation, their presence does not invariably preclude the repigmentation of a lesion
- **Poliosis**, a decrease or absence of melanin or color in head hair, eyebrows, and/or eyelashes, may also be a manifestation of vitiligo
- Premature graying of scalp hair may occur in patients with vitiligo and in their families

Vitiligo



A large vitiligo patch is present on the leg of this patient. Note the depigmented hairs in the lesional skin.

Courtesy of Pearl E Grimes, MD.

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Vitiligo

A depigmented patch of vitiligo is present on the periocular skin. Note associated loss of pigment in the eyebrow and eyelashes.

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Clinical classification

- A detailed classification scheme for vitiligo has been proposed in 2012 by the Vitiligo Global Issues Consensus Conference
- Vitiligo is classified in two broad categories:
  - **Non Segmental vitiligo (NSV), (the most common)**
  - **Segmental vitiligo (SV)**
- NSV is further divided into subtypes based upon the distribution of skin lesions (ie, generalized, acral or acrofacial, mucosal, localized, universal, and mixed pattern).

Classification of vitiligo

Type of vitiligo	Subtypes	Clinical features
Nonsegmental vitiligo	Generalized	▪ Symmetric, bilateral, depigmented macules in a random distribution over the entire body surface ▪ Onset usually before age 30 years ▪ Evolving over time
	Acral or acrofacial	▪ Only extremities and/or face involved
	Focal	
	Mucosal	▪ Multiple mucosal sites involved ▪ Usually associated with generalized vitiligo
	Universal	▪ Usually involves 80 to 90% of the body surface area
Segmental vitiligo	Monosegmental Bisegmental Plurisegmental	▪ Unilateral, asymmetric distribution of white macules that match a cutaneous segment (dermatomal distribution) ▪ Monosegmental most common ▪ Early age of onset ▪ Rapid stabilization
Mixed	Combination of nonsegmental and segmental vitiligo	
Rare variants	Vitiligo minor	▪ Incomplete depigmentation ▪ More common in dark-skinned individuals
	Follicular vitiligo	
Unclassified	Multifocal asymmetrical Single mucosal site involved	

Data from:

1. *Kovacevic M, Stanimirovic A, Vucic M, et al. Mixed vitiligo of Blaschko lines: a newly discovered presentation of vitiligo responsive to combination treatment. Dermatol Ther 2016 [Epub ahead of print].*
2. *Ezzedine K, Lim HW, Suzuki T, et al. Revised classification/nomenclature of vitiligo and related issues: The Vitiligo Global Issues Consensus Conference. Pigment Cell Melanoma Res 2012; 25:E1.*

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Vitiligo

(A) Nonsegmental facial vitiligo before treatment.
(B) Complete repigmentation after treatment with topical tacrolimus for three months.

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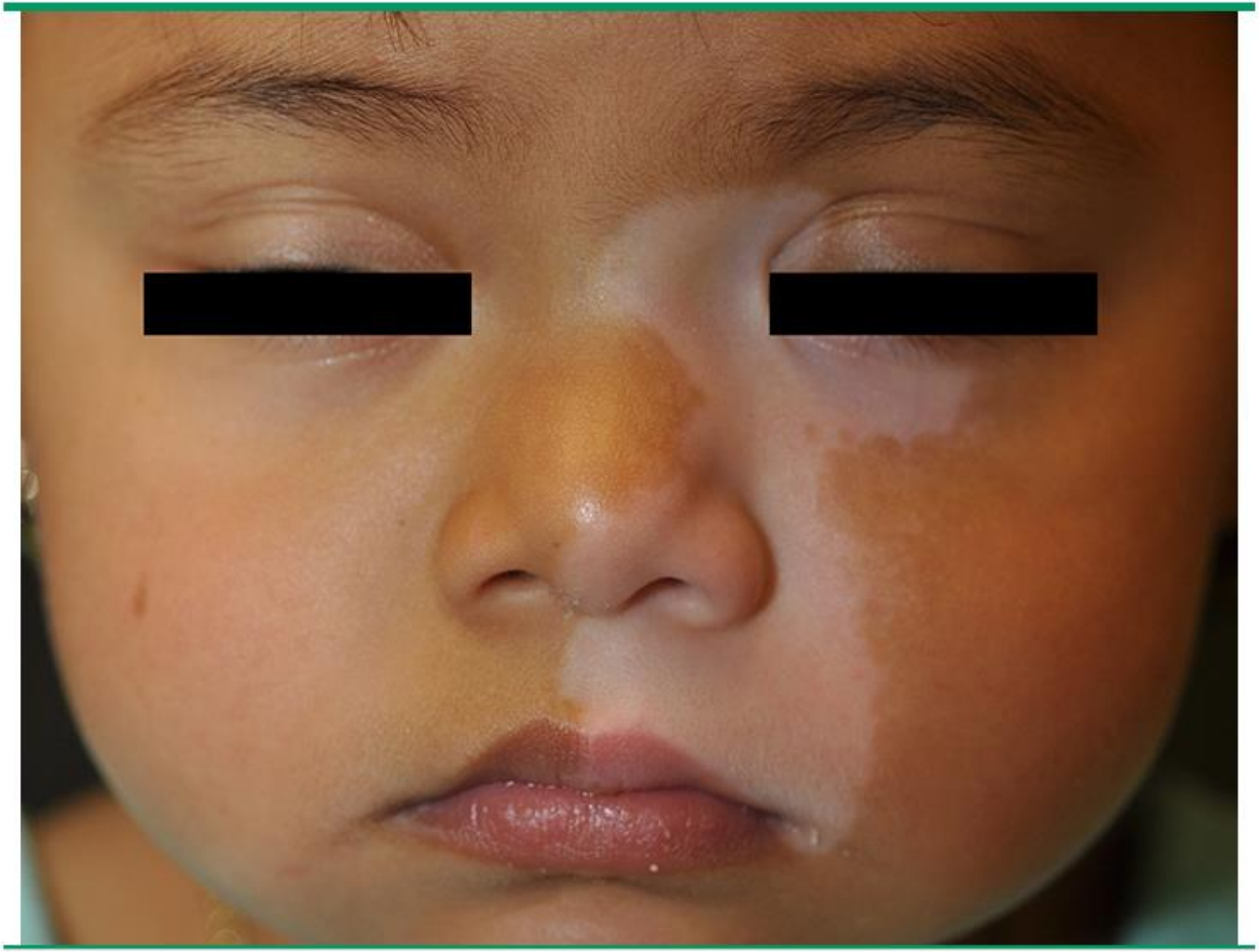
Segmental vitiligo



Segmental vitiligo in a child. Note the typical involvement of only one side of the face.

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Clinical Course

- The clinical course of vitiligo is **unpredictable**. Lesions can remain stable or progress slowly for years.
- In most cases, the extent and distribution of lesions change during the course of a person's lifetime by centrifugal expansion of current lesions and/or the appearance of new lesions.
- Progression is more common in patients who have a family history of nonsegmental vitiligo, a longer duration of disease, and mucosal involvement, but the rate of progression in the individual patient is unpredictable
- Flare-ups are common and may be separated by stable periods. Stable vitiligo is most common in children and adolescents, regardless of ethnicity and skin type . Lesions can be considered stable if no change is detected by serial photography in a 12-month period

Diagnosis

Clinical — The diagnosis of vitiligo is in most cases straightforward, based upon the clinical finding of acquired, discrete, well-demarcated, uniformly white macules with convex borders surrounded by normal skin in the absence of inflammation or textural changes. Elements of history that are helpful for the diagnosis include:

- Age at onset of lesions
- Factors or events that may have preceded onset
- Symptoms associated with the lesions
- Progression or spread of lesions
- Changes observed in lesions over time
- Presence of concomitant diseases
- Current medications
- Occupational history/exposure to chemicals
- Family history of vitiligo and autoimmune diseases

Diagnosis

Diagnostic aids — The diagnosis of vitiligo may be facilitated by the use of a Wood's lamp (a handheld device emitting ultraviolet A light at approximately a 365 nm wavelength), especially in individuals with pale skin . Under the Wood’s light, the depigmented areas emit a bright blue-white fluorescenc

Laboratory studies — Given the relatively high frequency of the association of vitiligo with autoimmune thyroid disease, it is reasonable to screen all patients with vitiligo, and especially those with generalized disease and extensive involvement of the body surface, for thyroid function e and appear sharply demarcated

Management

- **Factors that may influence the approach to treatment include**
- Age at onset of lesions
- Type of vitiligo (segmental, nonsegmental)
- Mucosal involvement, Koebner phenomenon
- Rate of progression or spread of lesions
- Previous episodes of repigmentation
- Type and response to previous treatments
- Family history of vitiligo and/or autoimmune diseases
- Presence of concomitant diseases
- Current medications and supplements
- Occupation, exposure to chemicals
- Effects of disease on the quality of life

Management

- Factors that may influence the approach to treatment include
- Each leg represents 18 percent of the TBSA.
- Each arm represents 9 percent of the TBSA.
- The anterior and posterior trunk each represent 18 percent of the TBSA.
- The head represents 9 percent of the TBSA

Management

- Goals of treatment
  - The goals of treatment for vitiligo should be set with the individual patient or parents in the case of children, based upon the patient's age and skin type, the extent, location, and degree of disease activity, and the impact of the disease on the patient's quality of life. An open discussion with the patient about the limitations of treatment may be helpful to create realistic expectations.

Management

- Nonsegmental vitiligo has an unpredictable course, and treatment is often challenging.
- Multiple therapies, including topical agents, light therapies, and autologous grafting procedures, have demonstrated efficacy for repigmentation of vitiligo.
- The response to treatments is generally slow and may be highly variable among patients and among different body areas in the same patient.
- The best outcomes are often achieved in darker skin types (Fitzpatrick IV to VI), although satisfactory results are often seen also in lighter skin types (Fitzpatrick II, III).
- Facial and truncal lesions respond well to treatment, while acral areas are extremely difficult to treat

Therapies for stabilization and repigmentation of vitiligo

Stabilization	Repigmentation
Oral corticosteroids	Topical corticosteroids
NB-UVB phototherapy	Calcineurin inhibitors
Minocycline	Vitamin D analogues
Methotrexate	NB-UVB phototherapy
Vitamin supplementation	Psoralen photochemotherapy
	Targeted phototherapy
	Experimental agents Afamelanotide Prostaglandin F2-alpha analogues

NB-UVB: narrowband ultraviolet B.

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Management

- For patients who experience rapid progression of vitiligo, with depigmented macules spreading over a few weeks or months, we suggest low-dose oral corticosteroids as first-line therapy for the stabilization (cessation of spread) of the disease.
- Oral prednisone is given at the dose of 5 to 10 mg per day in children and 10 to 20 mg per day in adults for a maximum of two weeks. If needed, treatment can be repeated in four to six weeks

Management

- Vitiligo involving <10 percent of the TBSA
  - **Localized disease** — In patients with nonsegmental stable vitiligo (no increase in size of existing lesions and absence of new lesions in the previous three to six months) that involves <10 percent of the total body surface area (TBSA) and is limited to the face, neck , trunk, or extremities, mid- to high-potency topical corticosteroids.
  - High-potency and mid-potency topical corticosteroids are applied to the involved skin once and twice daily, respectively. Agents with negligible systemic or local side effects, such as mometasone furoate, are preferred

Management

- Topical corticosteroids can be used safely for two to three months, interrupted for one month, and then resumed for an additional two or three months. Others suggest a discontinuous scheme (eg, once-daily application for 15 days per month for six months
- Adverse effects related to a prolonged use of topical corticosteroids, including folliculitis, mild atrophy, telangiectasia, and hypertrichosis, have been reported, generally in a small number of patients, in nearly all studies.
- Systemic absorption resulting in adrenal suppression is a concern when large areas of skin and areas with thin skin are treated for a prolonged time with potent steroids, especially in children

Super-high potency (group 1)	Clobetasol propionate	
High potency (group 2)	Betamethasone dipropionate Clobetasol propionate 0/025	Ointment/cream
High potency (group 3)	Triamcinolone acetonide 0/5 Betamethasone valerate 0/1	Ointment/cream
Medium potency (group 4)	Triamcinolone acetonide 0/1	
Lower-mid potency (group 5)	Fluocinolone acetonide 0/025	
Low potency (group 6)	Fluocinolone acetonide Triamcinolone acetonide	
Least potent (group 7)	Hydrocortisone (base, ≥2%)	

Management

- **Topical calcineurin inhibitors**
- Tacrolimus and pimecrolimus are topical immunomodulatory agents that affect the T-cell and mast-cell function and inhibit the synthesis and release of multiple proinflammatory cytokines, including interferon-gamma, tumor necrosis factor-alpha, interleukin (IL)-4, IL-5, and IL-10 .
- In contrast with topical corticosteroids, topical calcineurin inhibitors do not induce skin atrophy, striae, or telangiectasias and are increasingly used for the treatment of facial vitiligo

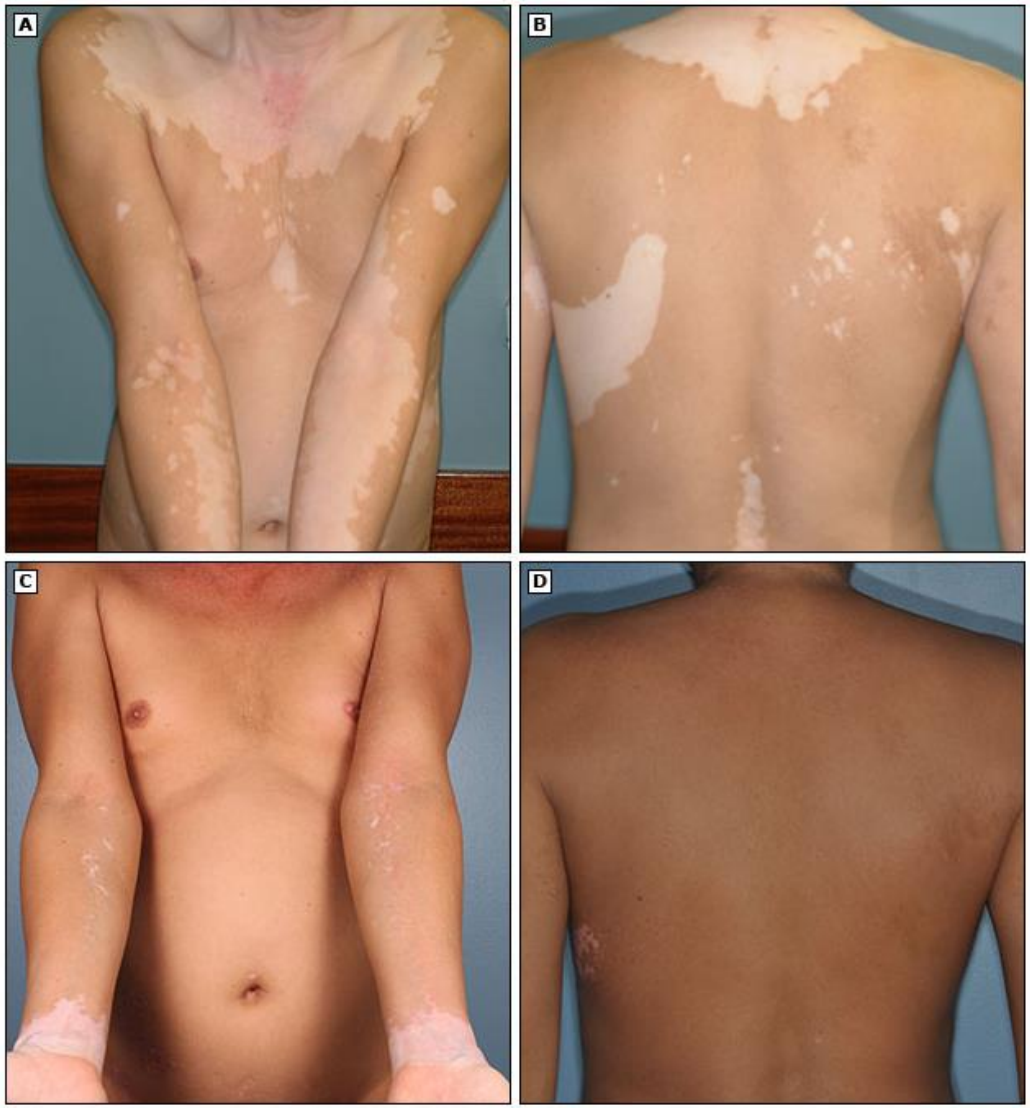
Management

- Although the increased risk of skin cancer among transplant patients treated with systemic calcineurin inhibitors is well recognized, the use of topical calcineurin inhibitors does not seem to be associated with an increased risk for skin or systemic malignancies.
- However, based upon animal studies documenting an increased risk of lymphoma and skin cancers associated with topical or systemic exposure to calcineurin inhibitors and to reports of cancer cases in children who used topical pimecrolimus or tacrolimus for atopic dermatitis, in 2006 the US Food and Drug Administration placed a boxed warning on the prescribing information for these medications.
- **Labeling also recommends that these agents should not be used in combination with ultraviolet (UV) light therapy**

Management

- Phototherapy
- Narrowband ultraviolet B phototherapy — NB-UVB involves the use of UV lamps with a peak emission of approximately 311 nm
- These shorter wavelengths provide higher-energy fluences and induce less cutaneous erythema. NB-UVB induces local immunosuppression and apoptosis; stimulates the production of melanocyte-stimulating hormones, basic fibroblasts, growth factor, and endothelin I; and increases melanocyte proliferation and melanogenesis
- Due to its lack of systemic toxicity and its good safety profile in both children and adults, NB-UVB phototherapy has emerged as the initial treatment of choice for patients with vitiligo involving >10 percent of the body surface area (BSA). NB-UVB can be used for both stabilization and repigmentation of vitiligo

Repigmentation of vitiligo with narrowband UVB phototherapy



(A and B) Before and (C and D) after narrowband UVB phototherapy, 68 treatments.

UVB: ultraviolet B.

Courtesy of Pearl E Grimes, MD.

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Management

- Phototherapy
- PUVA photochemotherapy —
- Historically, photochemotherapy with topical or systemic PUVA radiation was the "gold standard" treatment for the repigmentation of vitiligo but has been largely replaced by NB-UVB phototherapy.
- PUVA is associated with substantial adverse effects, including phototoxicity and gastrointestinal discomfort, and requires patients to use ocular protection for 12 to 24 hours following treatment. In addition, the long-term risk of skin cancer is well established for PUVA

Management

- **Unproven topical therapies**
- The benefit of topical vitamin D3 analogues in the treatment of vitiligo is controversial. A few small randomized trials evaluated the role of calcipotriol and tacalcitol in combination with psoralen plus ultraviolet A (PUVA), narrowband ultraviolet (NB-UV), or natural sunlight for the treatment of nonsegmental vitiligo with conflicting results

Management

- **Complementary and alternative therapies** —
- Oral supplementation with antioxidants and vitamins is often used as an adjunctive treatment for vitiligo, usually in combination with phototherapy. However, there is limited evidence from high-quality studies to support their use

Management

- **Complementary and alternative therapies** —
- **Vitamins** – A few small uncontrolled studies have reported stabilization and repigmentation in vitiligo patients treated with UVB phototherapy and high-dose vitamin supplementation, vitamin C, vitamin B12, and folic acid

Management

- **Complementary and alternative therapies** —
- **Alpha-lipoic acid** – Alpha-lipoic acid is an organosulfur compound derived from octanoic acid. The efficacy of alpha-lipoic acid in vitiligo was demonstrated in one randomized trial including 35 patients with nonsegmental vitiligo. In this study, twice-daily oral supplementation with alpha-lipoic acid, vitamin E, polyunsaturated fatty acids, and cysteine monohydrate combined with NB-UVB twice weekly for six months resulted in significantly more patients (47 versus 18 percent) achieving >75 percent repigmentation compared with phototherapy alone. In addition, repigmentation occurred earlier with lower cumulative UVB dose.

Management

- **Complementary and alternative therapies** —
- ***Ginkgo biloba*** – Extracts from the *Ginkgo biloba* leaf have long been used in traditional Chinese medicine to treat various conditions, including cutaneous, neurologic, and vascular disorders. The two main groups of active constituents responsible for *G. biloba's* medicinal effects are terpene lactones (ginkgolides and bilobalides) and ginkgo flavone glycosides, which are present in varying concentrations in the leaf of the ginkgo tree

Management

- **Depigmentation** — Since the 1950s, monobenzyl ether of hydroquinone (monobenzone) has been used as a depigmenting agent for patients with extensive vitiligo
- Monobenzone causes permanent destruction of melanocytes and induces depigmentation locally and remotely from the sites of application. Thus, the use of monobenzone for other disorders of pigmentation is contraindicated.
- The major side effects of monobenzone therapy are irritant contact dermatitis and pruritus, which usually respond to topical and systemic steroids. Other side effects include severe xerosis, alopecia, and premature graying

Thanks

Potency group*	Corticosteroid	Vehicle type/form	Trade names (United States)	Available strength(s), percent (except as noted)
Super-high potency (group 1)	Betamethasone dipropionate, augmented	Ointment, optimized	Diprolene	0.05
		Lotion	Diprolene	0.05
		Gel	Diprolene	0.05
	Clobetasol propionate	Ointment	Temovate	0.05
		Cream	Temovate	0.05
		Cream, emollient base	Temovate E	0.05
		Gel	Temovate	0.05
		Lotion	Clobex	0.05
		Foam aerosol	Olux-E	0.05
		Foam aerosol (scalp)	Olux	0.05
		Shampoo	Clobex	0.05
		Solution (scalp)	Temovate, Cormax	0.05
		Spray aerosol	Clobex	0.05
	Diflucortolone valerate (not available in United States)	Ointment, oily cream	Nerisone Forte (United Kingdom, others)	0.3
	Fluocinonide	Cream	Vanos	0.1
	Flurandrenolide	Tape (roll)	Cordran	4 mcg/cm^2
	Halobetasol propionate	Ointment	Ultravate	0.05
		Cream	Ultravate	0.05
		Lotion	Ultravate	0.05