# Vitiligo: A Review

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**Abstract**

Vitiligo, a common depigmenting skin disorder, has an estimated prevalence of 0.5–2% of the population worldwide. The disease is characterized by the selective loss of melanocytes which results in typical nonscaly, chalky-white macules. In recent years, considerable progress has been made in our understanding of the pathogenesis of vitiligo which is now clearly classified as an autoimmune disease. Vitiligo is often dismissed as a cosmetic problem, although its effects can be psychologically devastating, often with a considerable burden on daily life. In 2011, an international consensus classified segmental vitiligo separately from all other forms of vitiligo, and the term vitiligo was defined to designate all forms of nonsegmental vitiligo. This review summarizes the current knowledge on vitiligo and attempts to give an overview of the future in vitiligo treatment.

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## Introduction

Vitiligo, a depigmenting skin disorder, is characterized by the selective loss of melanocytes, which in turn leads to pigment dilution in the affected areas of the skin. The characteristic lesion is a totally amelanotic, nonscaly, chalky-white macule with distinct margins. Considerable recent progress has been made in our understanding of the pathogenesis of vitiligo, and it is now clearly classified as autoimmune disease, associated with genetic and environmental factors together with metabolic, oxidative stress and cell detachment abnormalities [1, 2]. Vitiligo should not be dismissed as a cosmetic or insignificant disease, as its effects can be psychologically devastating, often with a considerable burden on daily life [3].

In 2011, an international consensus classified vitiligo into two major forms: nonsegmental vitiligo (NSV) and segmental vitiligo (SV) [2]. The term vitiligo was defined to designate all forms of NSV (including acrofacial, mucosal, generalized, universal, mixed and rare variants). Distinguishing SV from other types of vitiligo was one of the most important decisions of the consensus, primarily because of its prognostic implications.

## Epidemiology

Vitiligo is the most common depigmenting skin disorder, with an estimated prevalence of 0.5–2% of the population in both adults and children worldwide [4–7]. One of the earliest and largest epidemiological surveys to have been reported was performed on the Isle of Bornholm, Denmark, in 1977, where vitiligo was reported to affect 0.38% of the population [4]. Vitiligo affects ethnic groups and people of all skin types with no predilection [1, 8, 9]. However, there seem to be large geographic differences.

For example, a study in the Shaanxi Province of China reported a prevalence as low as 0.093% [10], whereas regions of India had rates as high as 8.8% [11, 12]. This high value could be due to the inclusion of cases with chemical and toxic depigmentation [12], or because these data might reflect the prevalence of a single skin institute in Delhi [11]. Moreover, the disparity in the prevalence data may be due to higher reporting of data in places where social and cultural stigma are common, or where lesions are more evident in darker-skinned individuals [12]. An extensive in-depth review of prevalence data from more than 50 worldwide studies has demonstrated that the prevalence of vitiligo ranges from a low of 0.06% to a high of 2.28% [7]. A meta-analysis assessing the prevalence of vitiligo which included a total of 103 studies found that the pooled prevalence of vitiligo from 82 population- or community-based studies was 0.2% and from 22 hospital-based studies 1.8% [13]. SV accounts for 5–16% of overall vitiligo cases [14, 15]; however, its incidence and prevalence are not well established. The prevalence of SV ranges from 5 to 30% in published reports [14, 16–18]. This variability in epidemiological data could be accounted for by differences in disease classification due to the lack of consensus in previous years, inconsistent reporting by patients and varied populations.

Males and females are equally affected, although women and girls often seek consultation more frequently, possibly due to the greater negative social impact than for men and boys [6, 19]. NSV develops at all ages but usually occurs in young people between the ages of 10 and 30 years [12, 20, 21]. Twenty-five percent of vitiligo patients develop the disease before the age of 10 years, almost half of patients with vitiligo develop the disease before the age of 20 years and nearly 70–80% before the age of 30 years [12, 22]. Most populations have mixed age-of-onset groups and double peaks as has been noted [23]. SV tends to occur at a younger age than NSV [21]: before the age of 30 years in 87% of cases and before the age of 10 years in 41.3% [14]. In the report of Hann and Lee [14], the mean age of onset was 15.6 years. The earliest reported onset was immediately after birth, whereas the latest was 54 years. Most cases were less than 3 years in duration at referral, ranging from 2 months to 15 years [14].

## Pathogenesis

Vitiligo is a multifactorial disorder characterized by the loss of functional melanocytes [2, 24–27]. Multiple mechanisms have been proposed for melanocyte destruction in vitiligo. These include genetic, autoimmune responses, oxidative stress, generation of inflammatory mediators and melanocyte detachment mechanisms. Both innate and adaptive arms of the immune system appear to be involved. None of these proposed theories are in themselves sufficient to explain the different vitiligo phenotypes, and the overall contribution of each of these processes is still under debate, although there is now consensus on the autoimmune nature of vitiligo. Several mechanisms might be involved in the progressive loss of melanocytes, and they consist either of immune attack or cell degeneration and detachment. The "convergence theory" or "integrated theory" suggests that multiple mechanisms may work jointly in vitiligo to contribute to the destruction of melanocytes, ultimately leading to the same clinical result [1, 8, 24, 28, 29].

NSV and SV were believed to have distinct underlying pathogenetic mechanisms due to their different clinical presentations, with the neuronal hypothesis or somatic mosaicism favored for the segmental form [30]. However, more recent evidence points towards an overlapping inflammatory pathogenesis for both SV and NSV. Both seem to involve a multistep process, which involves initial release of proinflammatory cytokines and neuropeptides elicited by external or internal injury, with subsequent vascular dilatation and immune response [1, 31, 32].

Some authors have suggested that the nervous system contributes to vitiligo pathogenesis, referred to as the "neural hypothesis." This hypothesis relied on the unilateral distribution pattern of SV [27]. However, the distribution pattern of SV is not entirely similar to any other skin disease, and it is rarely, if ever, dermatomal [31, 33]. Furthermore, there is not enough evidence to support such a hypothesis. Moreover, melanocyte-specific T-cell infiltrations identical to NSV were found in SV further suggesting that it is also mediated by autoimmunity [34].

### Genetics of Vitiligo

Strong evidence from multiple studies indicates the importance of genetic factors in the development of vitiligo, although it is clear that these influences are complex. Epidemiological studies have shown that vitiligo tends to aggregate in families [9, 35–37]; however, the genetic risk is not absolute. Around 20% of vitiligo patients have at least 1 first-degree relative with vitiligo, and the relative risk of vitiligo for first-degree relatives is increased by 7- to 10-fold [37]. Monozygotic twins have a 23% concordance rate, which highlights the importance of additional stochastic or environmental factors in the development of vitiligo [37]. Large-scale genome-wide association studies performed in European-derived

whites and in Chinese have revealed nearly 50 different genetic loci that confer a vitiligo risk [38–46].

Several corresponding relevant genes have now been identified. They are involved in immune regulation, melanogenesis and apoptosis; they are associated with other pigmentary, autoimmune and autoinflammatory disorders [38–48]. Several loci are components of the innate and adaptive immune system and are shared with other autoimmune disorders, such as thyroid disease, type 1 diabetes and rheumatoid arthritis [42, 47, 49, 50].

Tyrosinase, which is encoded by the *TYR* gene, is an enzyme that catalyzes the rate-limiting steps of melanin biosynthesis [51]. Tyrosinase is a major autoantigen in generalized vitiligo [52–54]. A genome-wide association study has discovered a susceptibility variant for NSV in *TYR* in European white people that is rarely seen in melanoma patients [43]. It seems that there is a mutually exclusive relationship between susceptibility to vitiligo and susceptibility to melanoma, suggesting a genetic dysregulation of immunosurveillance against the melanocytic system [38, 43, 47]. The *NALP1* gene on chromosome 17p13, encoding the NACHT leucine-rich repeat protein 1, is a regulator of the innate immune system. It has been linked to vitiligo-associated multiple autoimmune disease, a group of diseases including various combinations of vitiligo, autoimmune thyroid disease, and other autoimmune and autoinflammatory syndromes [42]. On another hand, the production of large amounts of protein during melanin synthesis increases the risk of misfolding of those proteins, which activates a stress pathway within the cell called the unfolded protein response. *XBP1P1* (the gene encoding X-box binding protein 1) has been associated with vitiligo [49, 55]. It plays a pivotal role in mitigating the unfolded protein response, as well as driving stress-induced inflammation in vivo [39]. Although many of the specific mechanisms arising from these genetic factors are still being explored, it is now evident that vitiligo is an autoimmune disease implicating a complex relationship between programming and function of the immune system, aspects of the melanocyte autoimmune target and dysregulation of the immune response [38].

*Oxidative Stress*

Research into the pathogenesis of vitiligo suggests that oxidative stress may be the initial event in the destruction of melanocytes [56–59]. Indeed, melanocytes from patients with vitiligo were found to be more susceptible to oxidative stress than those from unaffected individuals and are more difficult to culture ex vivo than those from healthy controls [60].

Reactive oxygen species (ROS) are released from melanocytes in response to stress. In turn, this causes widespread alteration of the antioxidant system: An imbalance of elevated oxidative stress markers (superoxide dismutase, malondialdehyde, ROS) and a significant depletion of antioxidative mechanisms (catalase, glutathione peroxidase, glutathione reductase, thioredoxin reductase and thioredoxin, superoxide dismutases, and the repair enzymes methionine sulfoxide reductases A and B) in the skin and in the blood [26, 57, 61–67]. It has been suggested that this imbalance between pro-oxidants and antioxidant in vitiligo is responsible of the increased sensitivity of melanocytes to external pro-oxidant stimuli [57, 58, 68] and, over time, to induce a presenescent status. The generation and buildup of ROS can in turn cause DNA damage, protein oxidation and fragmentation, and lipid peroxidation, thus impairing their cellular function [68, 69].

Both endogenous and exogenous stimuli can potentially generate ROS in vitiligo [29]. The production of melanin itself is toxic to melanocytes. Melanogenesis is an energy-consuming process performed by melanocytes, which generates a pro-oxidant state in the skin [70]. Tyrosine-related protein 1 is an important protein for melanin synthesis. Oxidative stress causes tyrosine-related protein 1 to interact with the calnexin complex, which in turn leads to reduced tyrosine-related protein 1 stability with subsequent production of toxic melanin intermediates [58]. Dihydropteridin reductase is the last enzyme in the recycling process of an essential cofactor 6-tetrahydrobiopterin [71]. Oxidative stress leads to modifications of the active site dihydropteridin reductase which in turn leads to altered biopterin synthesis and recycling [71]. Defective recycling of 6-tetrahydrobiopterin increases production of hydrogen peroxide and decreases catalase levels, which further contributes to cell death.

Mitochondria seem to be the key inducer of ROS, and patients with vitiligo have an altered mitochondrial functionality [72]. An alteration in the mitochondrial transmembrane potential and in the electron transport chain complex causes a marked increase in the expression of mitochondrial malate dehydrogenase activity and a modification of the membrane lipid components. Oxidative stress impairs the function of membrane lipids and cellular proteins [58, 68]. Redox variations of membrane lipids disturb lipid rafts, which disrupt the function of membrane receptors, and electron transfer and ATP production in mitochondria [26, 56, 68, 73]. Furthermore, oxidative stress promotes the expression of the transient receptor potential cation channel subfamily M member

2 and thus facilitates mitochondria dependent apoptosis of melanocytes by increasing calcium influx [74].

Exogenous stimuli can also generate oxidative byproducts [29]. Monobenzone is the most widely used depigmenting agent [75]; it has been shown to induce the release of melanosomal related antigen-containing exosomes following overproduction of ROS from melanocytes [76].

Decreased melanocyte adhesiveness due to oxidative stress has been detected at the borders of vitiligo lesions possibly explaining the Koebner phenomenon [77–79]. Melanocyte-keratinocyte interaction does not require specific adhesive structures such as desmosomes, but simple adhesion molecules such as integrins and cadherins. In nonlesional skin of patients with vitiligo, the expression of e-cadherins is decreased and that of tenascin, an antiadhesion molecule, increased [77, 78]. In vitiligo skin, chronic friction can activate epithelial cells, which in turn convert the mechanical forces into biochemical signals [78], producing intracellular stress and subsequent altered cadherin expression [79].

### Innate Immunity

Innate immunity in vitiligo bridges the gap between oxidative stress and adaptive immunity in vitiligo. It is likely that the activation of innate immune cells occurs early in vitiligo, by sensing exogenously or endogenously induced stress signals released from melanocytes and possibly keratinocyte [25, 76, 80]. As mentioned above, there is an association between vitiligo susceptibility and genetic changes in NALP1, a regulator of the innate immune system [42, 81]. Genomic expression analysis on the skin of patients with vitiligo has highlighted an abnormally heightened innate immunity in the local microenvironment of melanocytes in vitiligo skin, particularly natural killer cells [80]. Indeed, natural killer cells have been found to infiltrate clinically normal skin of patients with vitiligo, suggesting that natural killer cells are early responders to melanocyte stress [80].

Melanocytes seem to communicate stress to the innate immune system through the excretion of exosomes. Human melanocytes were found to secrete exosomes in response to chemically induced stress [76]. These exosomes contain melanocyte-specific antigens, miRNAs, heat shock proteins and other proteins that act as damage-associated molecular patterns [82]. These exosomes deliver vitiligo target antigens to nearby dendritic cells and induce their maturation into efficient antigen-presenting cells [76, 83–85]. Among these damage-associated molecular patterns, inducible heat shock protein 70 is unique as it acts as a chaperone to peptides specific to the origi-

nating host cells that protects cells from undergoing apoptosis [86]. Inducible heat shock protein 70 has been shown to play a central role in vitiligo pathogenesis in a mouse model by inducing dendritic cells to present melanocyte-specific antigens to T cells in lymphoid tissues [83, 87]. This has been proposed to be the key link between innate and adaptive immunity leading to the T cell-mediated autoimmune destruction of melanocytes [88, 89]. A modified version of inducible heat shock protein 70, Hsp70iQ435A, was found to repigment vitiligo lesions in Sinclair swine recently, opening the door to a potential new treatment for vitiligo patients [90, 91].

### Adaptive Immunity

Both humoral and cell-mediated immune abnormalities are implicated in the pathogenesis of vitiligo.

Antibodies to surface and cytoplasmic melanocyte antigens have been identified in the past in the sera of vitiligo patients [92–94]. These antibodies can induce the destruction of melanocytes grown in culture by complement-mediated lysis and antibody-dependent cellular cytotoxicity [92, 93].

Cytotoxic CD8+ T cells that target melanocytes specifically are responsible for the destruction of melanocytes. CD8+ T-cell infiltration of the epidermis and dermis has been demonstrated histologically [95, 96]. Higher numbers of cytotoxic CD8+ T cells are found in the blood of patients with vitiligo compared with healthy controls, and these numbers correlate with vitiligo activity [1, 88, 95–97]. High numbers of CD8+ T cells are found in perilesional skin, and these cells exhibit antimelanocyte cytotoxic reactivity [96]. Infiltrating T cells isolated from biopsies of the perilesional margins show an enrichment of cells that recognize melanocyte antigens. When these cells were isolated and reintroduced in normally pigmented autologous skin, they induced melanocyte apoptosis [98]. By contrast, CD8+ T cell-depleted perilesional T cells were unable to induce cytotoxicity and apoptosis of melanocytes, whereas CD8-purified populations were even more potent [98]. CD8+ T cells also express the skin-homing marker cutaneous lymphocyte antigen [99, 100]. The destruction of melanocytes was found to be associated with the prominent presence of cutaneous lymphocyte antigen-positive T cells at the perilesional site, the majority of which expressed perforin and granzyme-B. So far, some antigenic proteins derived from normal or stressed melanocytes involved in the melanin synthesis have been identified in vitiligo and include gp100, Melan-A/MART-1, tyrosinase, and tyrosinase-related proteins 1 and 2 [101].
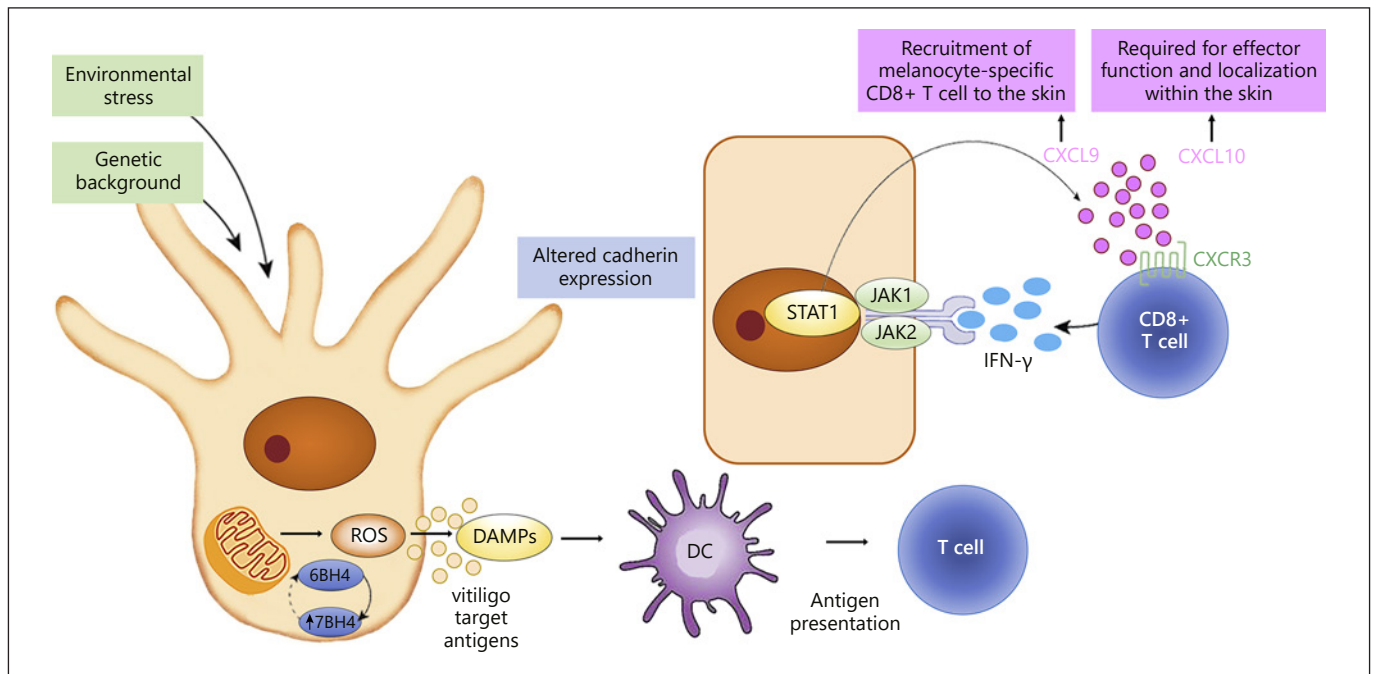
**Fig. 1.** Vitiligo pathogenesis. In vitiligo, melanocytes from patients with vitiligo have decreased adhesiveness and are more susceptible to oxidative stress. Additional environmental stress, in the presence of a susceptible genetic background, causes widespread alterations of the antioxidant system. Mitochondria seem to be the key inducers of ROS, and patients with vitiligo have an altered mitochondrial functionality. Oxidative stress impairs the function of membrane lipids and cellular proteins. Biopterin synthesis and recycling are also altered, leading to further oxidative stress and cell damage. ROS overproduction activates the unfolded protein response and causes melanocytes to secrete exosomes which contain melanocyte-specific antigens, miRNAs, heat shock proteins, and damage-associated molecular patterns. These exosomes deliver vitiligo target antigens to nearby dendritic cells and induce their maturation into efficient antigen-presenting cells. This is followed by cytokine- and chemokine-driven activation of T helper 17 cells and dysfunction of T regulatory cells. The CD8+ T cells from vitiligo lesions produce several cytokines such as IFN-γ. Binding of IFN-γ to its receptor activates the JAK-STAT pathway and leads to CXCL9 and CXCL10 secretion in the skin. Through the cognate receptor CXCR3, CXCL9 promotes the bulk recruitment of melanocyte-specific CD8+ T cells to the skin whereas CXCL10 promotes their localization within the epidermis and their effector function, which increases inflammation through a positive feedback loop. 6BH4, 6-tetrahydrobiopterin; 7BH4, 7-tetrahydrobiopterin; CXCL9, CXC chemokine ligand 9; CXCL10, CXC chemokine ligand 10; CXCR3, chemokine receptor type 3; DAMP, damage-associated molecular pattern; DC, dendritic cell; IFN-γ, interferon-γ; JAK, Janus kinase; ROS, reactive oxygen species; STAT1, signal transducer and activator of transcription 1.

The CD8+ T cells from vitiligo lesions produce several cytokines such as interferon-γ (IFN-γ) and tumor necrosis factor, among other cytokines [98, 102–104]. IFN-γ is central to disease pathogenesis and helps to promote autoreactive CD8+ T-cell recruitment into the skin [102]. The IFN-γ-induced CXC chemokine ligand 9 (*CXCL9*), *CXCL10* and *CXCL11* were the most highly expressed genes in a transcriptional profile of lesional skin of vitiligo patients, whereas other chemokine pathways were not [103]. These IFN-γ-induced CXC chemokines were also reported to be increased in the serum of patients [103]. Analysis of chemokine expression in mouse skin showed that CXCL9 and CXCL10 expression strongly correlates with disease activity, whereas CXCL10 alone correlates with severity, supporting them as potential biomarkers for following disease progression. Likewise, serum CXCL10 in patients with vitiligo also correlates with disease activity and severity and may be a novel biomarker in monitoring disease activity [105, 106]. Neutralization of CXCL10 in mice with established, widespread depigmentation leads to repigmentation, suggesting a critical role for CXCL10 in both the progression and maintenance of vitiligo [103]. Indeed, CXCL9 promotes the bulk recruitment of melanocyte-specific CD8+ T cells to the skin whereas CXCL10 is required for localization within the epidermis where melanocytes reside and effector function [103, 107]. Interestingly, both CXCL9 and CXCL10 share a single receptor, CXCR3. Melanocyte-specific autoreactive T cells in vitiligo patients express CXCR3 in both the blood and in lesional skin [107]. Tar-

geting CXCR3 in a mouse model using depleting antibodies reduces autoreactive T-cell numbers and reverses the disease [108]. Furthermore, keratinocytes were shown to be the major chemokine producers throughout the course of disease in both mouse model and human patients [109]. Functional studies using a conditional signal transducer and activator of transcription (STAT) 1 knockout mouse revealed that keratinocyte-derived chemokines and IFN-$\gamma$ signaling drives vitiligo and proper autoreactive T-cell homing to the epidermis. In contrast, epidermal immune cells such as endogenous T cells, Langerhans cells, and $\gamma\delta$ T cells are not required [109]. IFN-$\gamma$ in turn inhibits melanogenesis and directly induces melanocyte apoptosis [110]. Further functional studies in a mouse model found that IFN-$\gamma$, the IFN-$\gamma$ receptor, STAT1, CXCL10 and CXCR3 are critical for the development of hypopigmentation in vitiligo [102, 103, 107, 111].

Many cytokines that bind type I and type II cytokine receptors use the Janus kinase (JAK) and STAT pathway to achieve their effect [112]. Extracellular binding of cytokines activates their receptors, inducing apposition of JAKs and self-activation by autophosphorylation. Activated JAKs bind STATs, which undergo JAK-mediated phosphorylation leading to STAT dimerization, translocation to the nucleus, DNA binding and regulation of gene expression. In vitiligo, IFN-$\gamma$-bound receptor complex recruits JAK1 and JAK2 kinases, leading to phosphorylation and nuclear translocation of STAT, which in turn transcriptionally activates downstream IFN-$\gamma$-inducible genes. Lesional skin from patients with vitiligo showed much more intense and diffuse JAK1 expression compared with healthy tissue. Moreover, high JAK1 expression was associated with short disease duration and a lower percentage of surviving melanocytes [113, 114]. These results thereby support investigation of therapies that disrupt the pathway targeting IFN-$\gamma$, the IFN-$\gamma$ receptor, the downstream signaling proteins JAK1, JAK2 and STAT1, and the chemokine CXCL10 and its receptor CXCR3 [115–117].

Regulatory T cells (Tregs) are crucial to the development of self-tolerance. Tregs have been found to be less abundant in vitiligo skin and their functional activity compromised [118–120]. The paucity of Tregs in vitiligo skin is likely crucial for perpetual antimelanocyte reactivity in this progressive and chronic disease. Indeed, Tregs show lower expression of transforming growth factor $\beta_1$ in active vitiligo patients [119]. The number of Tregs expressing FoxP3, the transcription factor that downregulates T-cell activation, is reduced significantly in lesional skin [120]. Furthermore, the expression of homing receptor CCL22 was found to be remarkably reduced in vitiligo

**Table 1.** Classification of vitiligo (adapted from Ezzedine et al. [2])

| Type of vitiligo | Subtypes |
| --- | --- |
| NSV | Focal[1] <br> Mucosal <br> Acrofacial <br> Generalized <br> Universal <br> Rare variants of vitiligo (leukoderma punctata, hypochromic vitiligo, follicular vitiligo) |
| SV | Focal[1] <br> Unisegmental <br> Bi- or multisegmental |
| Mixed (NSV + SV) | Concomitant occurrence of SV and NSV <br> According to severity of SV |
| Unclassified | Focal at onset, multifocal asymmetrical nonsegmental, mucosal (one site), |

[1] Can evolve into segmental (SV) or nonsegmental vitiligo (NSV).

skin [121], and conversely, expression of CCL22 can promote Treg skin homing to suppress depigmentation [122].

Functional CD8 tissue-resident memory T cells were found in both stable and active vitiligo, suggesting that those that remain in stable disease could account for the disease reactivation [123].

Figure 1 summarizes the main mechanisms in vitiligo pathogenesis.

## Classification

In 2011, an international consensus classified SV separately from all other forms of vitiligo, and the term vitiligo was defined to designate all forms of NSV [2]. "Mixed vitiligo" in which SV and NSV coexist in one patient, is classified as a subgroup of NSV (Table 1). Distinguishing SV from other types of vitiligo was one of the most important decisions of the consensus, primarily because of its prognostic implications.

NSV includes the acrofacial, mucosal, generalized, universal, mixed and rare variants. Generalized and acrofacial vitiligo are the most common subtypes.

- Generalized vitiligo is characterized by bilateral, often symmetrical, depigmented macules or patches occurring in a random distribution over the entire body surface. It often affects areas that tend to experience pres-

**Fig. 2.** Generalized vitiligo, bilateral, often symmetrical, depigmented macules or patches.



**Fig. 4.** Vitiligo universalis, complete or nearly complete depigmentation of the skin.



**Fig. 3.** Acrofacial vitiligo, depigmented macules limited periorificial areas, distal extremities and/or the face.

sure, friction and/or trauma. It may begin in childhood or early adulthood (Fig. 2).

- Acrofacial vitiligo is characterized by depigmented macules limited to the distal extremities and/or the face. A distinctive feature is depigmentation of the distal fingers and facial orifices. It may later progress to include other body sites and be better classified as generalized or universal [2]. The lip-tip variety is a subcat-

egory of the acrofacial type in which lesions are restricted to the cutaneous lips and distal tips of the digits (Fig. 3).

- Mucosal vitiligo typically involves the oral and/or genital mucosae. It may occur in the context of generalized vitiligo or as an isolated condition. An isolated mucosal vitiligo which remains so after at least 2 years of follow-up is defined as unclassified [2].
- Vitiligo universalis (Fig. 4) refers to complete or nearly complete depigmentation of the skin (80–90% of body surface). It is usually preceded by generalized vitiligo that gradually progresses to complete or near complete depigmentation of the skin and hair.
- Focal vitiligo refers to a small, isolated, depigmented lesion without an obvious distribution pattern and which has not evolved after a period of 1–2 years. It can evolve into SV or NSV [2].
- Mixed vitiligo refers to the concomitant occurrence of SV and NSV [124]. Its clinical features include: (1) the absence of depigmented areas in a segmental distribution at birth and in the first year of life and Wood lamp examination excluding nevus depigmentosus; (2) SV followed by NSV with a delay of at least 6 months; (3) SV affecting at least 20% of the dermatomal segment or presenting a definite Blaschko linear distribution; (4) difference in response to conventional narrow-

**Fig. 5.** Hypochromic vitiligo, hypopigmented macules of the trunk and scalp distributed in a seborrheic pattern.



**Fig. 6.** Monosegmental vitiligo of the left abdomen, depigmented patches are usually confined to a single dermatome, with partial or complete involvement.

band ultraviolet B (NB-UVB) treatment between SV (poor response) and NSV (good response). Leukotrichia and halo nevi at onset may be risk factors for developing MV in patients with SV [125]. The co-occurrence of SV and NSV in a same patient has been viewed as a superimposed segmental manifestation of a generalized polygenic disorder, in which segmental involvement precedes disease generalization and is more resistant to therapy [126, 127].

In a study of latent class analyses, two phenotypes of NSV have been differentiated: the first consists of early onset of disease (before 12 years of age) and is often associated with halo nevi and a familial background of premature hair graying; the second is of late onset and is most often characterized by an acrofacial distribution [23, 128].

Several conditions are difficult to classify into the two classical forms of NSV and SV.

- "Punctate vitiligo" refers to sharply demarcated depigmented punctiform 1- to 1.5-mm macules involving any area of the body [129]. If these lesions do not coexist with classical vitiligo macules, they should be referred to as "leukoderma punctata."
- Hypochromic vitiligo or vitiligo minor is characterized by the presence of hypopigmented macules in a seborrheic distribution on the face and neck associated with hypopigmented macules of the trunk and scalp.

It seems to be limited to individuals with dark skin types (Fig. 5) [130].
- Follicular vitiligo presents with leukotrichia in the absence of depigmentation of the surrounding epidermis [131].

SV refers to depigmented macules distributed in a segmental pattern and is typically associated with leukotrichia and a rapid onset. The characteristic lesion is clinically similar to the macule seen in NSV: a totally amelanotic, nonscaly, chalky-white macule with distinct margins.

The depigmented patches are usually confined to a single dermatome, with partial or complete involvement. In monosegmental vitiligo one or more white depigmented macules are distributed on one side of the body. It is the most common form of SV [14, 132]; however, other distribution patterns are possible whereby the depigmented patch overlaps several ipsi- or contralateral dermatomes, or occurs on large areas delineated by Blaschko's lines.

The head is involved in more than 50% of cases [14, 133]. The most commonly involved dermatome is that of the trigeminal nerve [14, 134, 135]. The next common locations in decreasing order of frequency are the trunk (Fig. 6), the limbs, the extremities and the neck [14, 17, 133, 134].

In SV, the depigmentation spreads within the segment over a period of 6–24 months. After initial rapid spreading in the affected dermatome, the SV patch most often remains stable [14]. Rarely however can it progress again after being quiescent for several years, and if it does so, it usually spreads over the same dermatome. Disease recur-

rence can occur after years of stability [136]. However, in very rare cases, lesions may become generalized, and become part of mixed vitiligo [124, 136].

### Diagnosis

The diagnosis of vitiligo is generally straightforward, made clinically based upon the finding of acquired, amelanotic, nonscaly, chalky-white macules with distinct margins in a typical distribution: periorificial, lips and tips of distal extremities, penis, segmental and areas of friction [6, 8, 137].

The diagnosis of vitiligo does not usually require confirmatory laboratory tests. A skin biopsy or other tests are not necessary except to exclude other disorders [6, 138, 139]. The absence of melanocytes in a lesion can be assessed noninvasively by in vivo confocal microscopy or by a skin biopsy. The histology of the center of a vitiligo lesion reveals complete loss of melanin pigment in the epidermis and absence of melanocytes. Occasional lymphocytes may be noted at the advancing border of the lesions [34, 140].

The diagnosis of vitiligo may be facilitated by the use of a Wood's lamp, a hand-held ultraviolet (UV) irradiation device that emits UVA [141]. It helps identify focal melanocyte loss and detect areas of depigmentation that may not be visible to the naked eye, particularly in pale skin [142]. Under the Wood's light, the vitiligo lesions emit a bright blue-white fluorescence and appear sharply demarcated.

Dermoscopy can be used to differentiate vitiligo from other depigmenting disorders. Vitiligo typically shows residual perifollicular pigmentation and telangiectasia, which are absent in other hypopigmentation disorders [143]. More importantly, it can be useful in assessing disease activity in vitiligo and the stage of evolution: progressive lesions display perifollicular pigmentation, whereas stable or remitting lesions display perifollicular depigmentation [144].

The differential diagnosis of vitiligo is broad (Table 2). Many common and uncommon conditions present with areas of depigmentation that may mimic vitiligo. It is important to differentiate vitiligo from melanoma-associated leukoderma and to prevent its misdiagnosis as vitiligo especially that it may precede melanoma detection. Although clinically similar, antibodies against melanoma antigen recognized by T cells 1 (MART1) in melanoma-associated depigmentation can help differentiate it from vitiligo [145]. Nevus depigmentosus is segmental hy-

**Table 2.** Differential diagnosis of vitiligo

**Chemically-induced leukoderma (occupational)**
Phenols and other derivatives

**Topical or systemic drug-induced depigmentation**
*Genetic syndromes*
Hypomelanosis of Ito
Piebaldism
Tuberous sclerosis
Vogt-Koyanagi-Harada syndrome
Waardenburg syndrome
Hermanski-Pudlak syndrome
Menke's syndrome
Ziprkowski-Margolis syndrome
Griscelli's syndrome

**Postinflammatory hypopigmentation**
Pityriasis alba
Atopic dermatitis/allergic contact dermatitis
Psoriasis
Lichen planus
Toxic drug reactions
Posttraumatic hypopigmentation (scar)
Phototherapy- and radiotherapy-induced

**Neoplasm-related hypomelanoses**
Melanoma-associated leukoderma
Mycosis fungoides
Infection-related hypomelanoses
Leprosy
Pityriasis versicolor
Leishmaniasis
Onchocerciasis
Treponematoses (pinta and syphilis)

**Idiopathic**
Idiopathic guttate hypomelanosis
Progressive (or acquired) macular hypomelanosis

**Congenital**
Nevus anemicus
Nevus depigmentosus

**Others**
Lichen sclerosus et atrophicus
Melasma (caused by contrast between lighter and darker skin)

popigmentation usually present at birth or detectable in the first year of life. It is stable although it may enlarge in proportion to the child's growth. It is a common differential diagnosis of SV, but nevi usually contain a normal number of melanocytes with reduced melanin production [146]. Under Wood's lamp examination, the contrast between lesional and normal skin is less striking than in vitiligo [147].

## Assessment

The management of a patient with vitiligo requires time for a careful initial assessment. The evaluation of the patient with vitiligo entails a detailed history and a complete skin examination to assess disease severity and individual prognostic factors. An assessment form created by the Vitiligo European Task Force summarizes the personal and family history elements and the clinical examination items which may be useful for evaluation [141]. Patients should routinely be asked about family history of vitiligo and premature hair graying and about family or personal history of thyroid disease or other autoimmune diseases [148]. Skin phototype, disease duration, extent, activity, rate of progression or spread of lesions, presence of Koebner's phenomenon, presence of halo nevi, previous treatments including their type, duration and effectiveness, previous episodes of repigmentation, occupational history/exposure to chemicals and effects of disease on the quality of life should all be assessed.

Some areas of the body are more susceptible to Koebner's phenomenon and are related to daily life activities such as hygiene or clothing and occupation [8]. Assessing for the presence of Koebner's phenomenon (vitiligo following mechanical trauma) can prove to be useful in the prevention of vitiligo [8, 149]. A scoring evaluating the probability of Koebner's phenomenon, the K-VSCOR, has been developed and validated [150]. Patients with high scores should be counseled about mechanical stress avoidance.

Many studies have demonstrated the associations of vitiligo with thyroid disorders and other associated autoimmune diseases, such as alopecia areata, rheumatoid arthritis, adult-onset diabetes mellitus, Addison's disease, pernicious anemia, systemic lupus erythematosus, psoriasis and atopic background [9, 128, 151, 152].

Because of the increased risk of autoimmune thyroid disease in NSV, especially Hashimoto's thyroiditis [153], antibodies to thyroid peroxidase should be screened initially, and the thyrotropin levels should be measured regularly, especially in patients with antibodies to thyroid peroxidase at the initial screening. The susceptibility to autoimmune diseases in patients with vitiligo varies with ethnic background and family history of autoimmune diseases [9, 154]. The presence of signs or symptoms of organ-specific autoimmune diseases should prompt an appropriate investigation and referral to specialists [155].

The most extensively characterized clinical markers of active, progressive disease include: Koebner's phenomenon, trichrome lesions, inflammatory lesions and confetti-like depigmentation [27, 156–159].

Finally, an overall assessment of the psychological features and quality of life is warranted as the patient's personality and perceived severity of vitiligo are predictors of quality of life impairment [160, 161]. A vitiligo-specific quality-of-life instrument has been developed and validated [162]. All patients with vitiligo should be offered psychological support and counseling [142].

## Management

The treatment of vitiligo is still one of the most difficult dermatological challenges. An important step in the management of vitiligo is to first acknowledge that it is not merely a cosmetic disease and that there are safe and effective treatments available [163]. These treatments include phototherapy, topical and systemic immunosuppressants, and surgical techniques, which together may help in halting the disease, stabilizing depigmented lesions and stimulating repigmentation [164, 165].

Choice of treatment depends on several factors including: the subtype of the disease, the extent, distribution and activity of disease as well as the patient's age, phototype, effect on quality of life and motivation for treatment. The face, neck, trunk and mid-extremities respond best to therapy, while the lips and distal extremities are more resistant [166]. Repigmentation appears initially in a perifollicular pattern or at the periphery of the lesions. Treatment for at least 2–3 months is needed to determine efficacy of treatment. UV light-based therapy is the most common treatment for vitiligo and, when combined with an additional therapy, is associated with an improved outcome [165].

Management requires a personalized therapeutic approach whereby patients should always be consulted, as most of the therapeutic options are time consuming and require long-term follow-up. Advice on cosmetic camouflage by a cosmetician or a specialized nurse should be offered and can be beneficial for patients with vitiligo affecting exposed areas. These include foundation-based cosmetics and self-tanning products containing dihydroxyacetone which provides lasting color for up to several days.

Several guidelines have been published for the management of vitiligo [142, 167–169]. In 2008, the British Association of Dermatologists published user-friendly clinical guidelines for the diagnosis and management of vitiligo [142] which were established based on the first Cochrane review and expert consensus on vitiligo reflect-
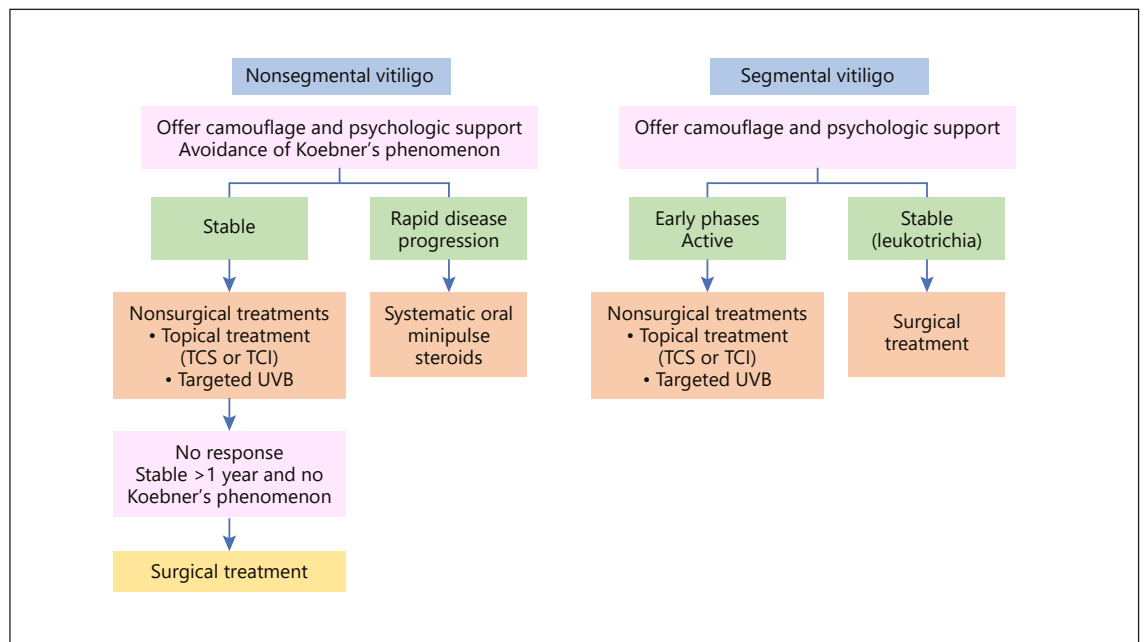
**Fig. 7.** Therapeutic algorithm of vitiligo. TCS, topical corticosteroid; TCI, topical calcineurin inhibitor; UVB, ultraviolet B.

ing patient choice and clinical expertise [169, 170]. The Cochrane reviews of 2010 and 2015 underscored the absence of cure for vitiligo and the inability of current treatment options to restrict the spread of the disease in a lasting way [170–172]. However, most randomized controlled trials (RCTs) included in the review had had fewer than 50 participants. They concluded that due to the heterogeneity in the design of trials and the small numbers of participants, no firm clinical recommendations could be made.

The Vitiligo subcommittee of the European Dermatology Forum has reported guidelines for the management and treatment of vitiligo based on best available evidence combined with expert opinion [167]. Treatments were graded from first- to fourth-line options. First-line treatments consist of topical treatments (corticosteroids and calcineurin inhibitors). Second-line treatments consist of phototherapy (NB-UVB and psoralen and UVA [PUVA]) and systemic steroid treatment. Third-line treatments consist of surgical grafting techniques and fourth-line of depigmenting treatments. A detailed algorithm that summarizes the therapeutic modalities and suggests a stepwise approach is shown in Figure 7.

In NSV, patients can experience a rapid disease progression with depigmented macules spreading over a few weeks or months. This requires urgent intervention with

systemic oral minipulse steroids, a treatment that consists of corticosteroid administration only twice a week [142, 173]. In one study, oral minipulses of betamethasone or dexamethasone (5 mg in single dose) on 2 consecutive days per week for several months led to the halt of vitiligo progression in 32 of 36 patients with active disease after 1–3 months of treatment [173].

Topical corticosteroids (TCS) have been used since the 1950s for their anti-inflammatory and immuno-modulating effects. There are no studies evaluating the optimal duration of treatment with TCS. Some authors suggest its application on a daily basis for 2–3 months, while others suggest a discontinuous scheme (once-daily application for 15 days per month for 6 months [167]). For limited forms of vitiligo, both TCS and topical calcineurin inhibitors (TCIs) are now widely used as first-line treatments [174]. TCIs are generally applied twice daily.

A recent systematic review and meta-analysis assessed the effectiveness of TCI compared with TCS in the treatment of vitiligo. 13 studies were included in the qualitative analysis, and data from 11 studies with a total of 509 vitiligo patients were eligible for meta-analysis. TCIs were noninferior to TCS in reaching at least 50% or at least 75% repigmentation, especially for pediatric patients [175]. Another recent meta-analysis of 46 studies including

1,499 patients showed that TCI monotherapy appears to have significant therapeutic effects on vitiligo and produced at least mild response in 55.0% of the patients, at least moderate response in 38.5% and a marked response in 18.1% after a median treatment duration of 3 months [176]. The treatment responses of TCIs combined with phototherapy were higher than those of TCI monotherapy and those of phototherapy alone, which supports the synergistic effects of this combination therapy. TCI monotherapy could be useful for the treatment of face and neck lesions, particularly in children, when phototherapy is not available. Another meta-analysis on 7 RCTs involving 240 patients suggested that adding TCI on NB-UVB does not yield significantly superior outcomes compared to NB-UVB monotherapy for treatment of vitiligo; except for the face and neck where addition of TCI to NB-UVB may increase treatment outcomes [177].

The Vitiligo Working Group has recently published a unified set of recommendations for NB-UVB phototherapy treatment of vitiligo based on prescribing practices of phototherapy experts from around the world [178]. These included the dosing protocol (initiate dose at 200 mJ/cm$^2$ regardless of constitutive skin type, then increase by 10–20% per treatment), the frequency of administration (optimal 3 times per week), the maximal acceptable doses (1,500 mJ/cm$^2$ for the face, 3,000 mJ/cm$^2$ for the body), the course and the follow-up. They reported that the minimum number of doses needed to determine lack of response was 48 exposures, and that because of the existence of slow responders, ≥72 exposures may be needed to determine lack of response to phototherapy [178].

Due to its good safety profile in both children and adults and lack of systemic toxicity, NB-UVB has emerged as the initial treatment of choice for patients with vitiligo involving >10% of the body surface area. A 2017 meta-analysis of 35 randomized and nonrandomized studies including 1,428 patients compared the repigmentation rates of NB-UVB and PUVA by treatment duration. For NB-UVB, a ≥75% repigmentation was achieved by 19 and 36% of patients at 6 and 12 months of treatment, respectively, compared to 9 and 14% with PUVA. This confirmed the superiority of NB-UVB over PUVA and suggested that phototherapy should be continued for at least 12 months to achieve a maximal response [179].

Targeted phototherapy using 308-nm monochromatic excimer lamps or lasers is useful for the treatment of localized vitiligo. These devices deliver high-intensity light only to the affected areas while avoiding exposure of the healthy skin and lowering the cumulative UVB dose.

A systematic review of 6 randomized trials (411 patients with 764 lesions) found that excimer lamps and excimer lasers are equally effective as NB-UVB in inducing ≥50% and ≥75% repigmentation [180]. Although more frequent weekly treatments lead to more repigmentation, the ultimate repigmentation and final result seems to depend entirely on the overall number of treatment sessions rather than their frequency [181]. As with NB-UVB, TCIs can work synergistically with targeted phototherapy [182, 183]. A meta-analysis which included 8 RCTs comprising a total of 425 patches/patients found that TCIs in conjunction with excimer light/laser are more effective compared with excimer light/laser monotherapy [184].

Surgical methods can be offered as a therapeutic option to patients with SV and those with NSV with stable disease after at least a year of documented nonresponse to medical interventions and absence of Koebner's phenomenon. A minigraft test to assess stability, spread of pigment at the recipient site and no koebnerization at the donor site after 2–3 months can also assist in patient selection. The purpose of the transplantation is to transfer to the vitiliginous skin a reservoir of healthy melanocytes for proliferation and migration into areas of depigmentation [185]. The surgical techniques that are mentioned in the European guidelines [167] include tissue grafts (full-thickness punch, split-thickness and suction blister grafts) and cellular grafts (autologous melanocyte cultures and noncultured epidermal cellular grafts). Other techniques include cultured epidermal suspensions [186, 187] and hair follicle transplantation [188–190]. Tissue grafts use unprocessed pigmented epidermis and dermis, which are transplanted to depigmented areas; they are ideal for treating smaller areas [185]. In contrast, cellular transplants involve more complex processing of the grafts before surgery.

An evidence-based review concluded that split-thickness grafting and blister grafts are the most effective and safe techniques [185]. An old systematic review of randomized trials and observational studies of autologous transplantation methods for vitiligo concluded that split-thickness and epidermal blister grafting were the most effective and safest techniques [191]. Both treatment groups achieved success rates of 90% repigmentation. They could not draw conclusions about the effectiveness of culturing techniques because only a small number of patients have been studied. The benefits of transplantation of autologous melanocyte cultures and epidermal suspensions have been reported in some studies [186, 192, 193]. In an RCT comparing autologous noncultured epidermal cell suspension with suction blister grafts in 41

patients, both treatment groups reached a repigmentation of ≥75% in over 85% of lesions [193]. However, more lesions in the noncultured epidermal cell suspension group (70%) achieved a 90–100% repigmentation compared with those in the suction blister group (27%) [193]. Important advantages of cellular grafting are the possibility of treating large areas and the better cosmetic results than with tissue grafts [194, 195]. Cellular grafts seem to have less frequently associated adverse events than with punch grafting, followed by split-thickness grafting [196].

Depigmenting treatment of residual areas of pigmentation should only be considered in select cases such as: widespread, refractory, and disfiguring vitiligo, or highly visible recalcitrant facial or hand vitiligo [8]. Monobenzyl ether of hydroquinone (monobenzone) has been used as a depigmenting agent for patients with extensive vitiligo since the 1950s [197]. Other skin-bleaching methods include laser treatment (e.g., 755-nm Q-switched alexandrite or 694-nm Q-switched ruby) [198–200] and cryotherapy [75].

Reliable data regarding the treatment of SV are limited since most studies do not differentiate between these types of vitiligo. SV was previously considered to be resistant to treatment. However, recent studies have been reporting promising results; especially during the early stage. Within the first 6 months, patients should be offered potent TCS or topical immune modulators combined with NB-UVB or targeted excimer lamp or laser. Oral steroid minipulse therapy is another option if the lesion is still in its active phase. In contrast, if these medical therapies fail, or at a later stage of the disease, surgery should be offered. Overall, stable SV is a good indication for surgical grafting, especially as the presence of leukotrichia in SV makes it more resistant to standard medical therapies.

*Emerging Therapies*
Afamelanotide, a potent and longer-lasting synthetic analog of α-melanocyte-stimulating hormone, has been shown to be synergistic with NB-UVB in promoting repigmentation [201, 202]. Prostaglandin $E_2$ controls the proliferation of melanocytes by means of stimulant and immunomodulatory effects. In one study of 56 consecutive patients with stable and limited vitiligo, repigmentation, treatment with prostaglandin $E_2$ 0.25 mg/g gel twice daily for 6 months led to repigmentation in 40 patients; the response was excellent in 22 patients, and the repigmentation was complete in 8 [203]. Bimatoprost, a synthetic analog of prostaglandin $F_{2\alpha}$ approved for the topical treatment of glaucoma and hypotrichosis of the eyelashes, was shown in an RCT to provide greater repigmentation than treatment with mometasone [204].

Besides, JAK inhibitors have shown promise in the treatment of vitiligo [116, 205]. Ruxolitinib is a JAK1 and JAK2 inhibitor. In a phase 2, proof-of-concept trial, topical ruxolitinib 1.5% cream was applied twice daily to 11 adult patients with vitiligo involving at least 1% of the body surface area for 20 weeks [206]. Eight of 11 patients achieved a response with a mean improvement of the Vitiligo Area Scoring Index of 23%. The best response was observed in patients with facial vitiligo. Five patients who completed the trial were then followed up at 6 months after treatment discontinuation, and all of them maintained response, with a maximum duration of >40 weeks [205].

*Alternative Treatment Options*
There are limited data regarding the use of systemic immunosuppressants other than corticosteroids in the treatment of vitiligo. A randomized comparative study performed on 52 patients with vitiligo showed that methotrexate is equally effective as oral minipulse therapy with betamethasone or dexamethasone in controlling the disease activity, suggesting that methotrexate could be used in patients with active vitiligo if corticosteroids are contraindicated [207]. Twice daily oral cyclophosphamide (50 mg) was shown to cause repigmentation in 29 patients, including the difficult-to-treat areas such as acral sites; however, significant side effects were reported [208]. Although some authors have suggested that anti-tumor necrosis factor-α can stabilize the disease in progressive vitiligo [209], many studies have demonstrated that these agents do not improve the disorder, and that they may even cause initiation and worsening of the disease [210–214].

Platelet-rich plasma (PRP) is an autologous preparation of platelets in concentrated plasma which contains various growth factors. It is hypothesized that these growth factors promote melanocyte stimulation [215]. Earlier studies showed conflicting results. Lim et al. [216] reported that PRP alone is not effective in treating vitiligo. However, Ibrahim et al. [217] carried out a trial comparing the combination of PRP with NB-UVB and found better results than treatment with NB-UVB alone. Seventy-five percent of patients in the NB-UVB and PRP group had more than 50% repigmentation compared to none of the patients in the NB-UVB group. More recently, a prospective, open-label, randomized trial has shown that combining fractional $CO_2$ laser with PRP injection led to at least 50% repigmentation in all of the patients, whereas

groups receiving PRP alone and fractional $CO_2$ laser alone showed minimal response [218]. Finally, a single-blinded comparative clinical study showed that the combination of excimer laser with PRP injection led to a good response in 50% of patients and an excellent response in 35% of patients, whereas the group receiving excimer laser treatment alone had no response in 65% of patients and only a good response in 35% of patients [219].

Altogether, these studies indicate that PRP, when used adjunctively in combination, can produce better outcomes in treating vitiligo. However, clinicians should be cautious when interpreting the results of these studies which used the combination of a superior mode of therapy with a minor intervention [220]. Furthermore, repeated injections at short intervals are a painful procedure and can induce koebnerization [221]. Further larger RCTs with longer follow-up are required to confirm these findings.

Given the role of oxidative stress in the pathogenesis of vitiligo, several products with antioxidant enzymes (e.g., superoxide dismutase, catalase) have been used for the treatment of vitiligo. Although the rationale for using topical antioxidants in vitiligo is strong, studies have shown conflicting results, probably owing to the difficulty of delivering active antioxidants directly into the skin. Some studies have looked into the use of topical antioxidants as monotherapy; however, in most cases topical antioxidants have been used in combination with phototherapy. One randomized, matched-paired, double-blind trial compared the effect of topical 0.05% betamethasone versus topical catalase/dismutase superoxide [222]. After 10 months of treatment, there was no statistical difference between the two groups. Other studies have shown oral antioxidants to have significant effects on repigmentation, although the level of evidence is limited [223]. Vitamin E [224, 225], *Polypodium leucotomos* [226, 227] and *Ginkgo biloba* [228, 229] seem to be useful, particularly when combined with phototherapy. Further double-blind controlled trials are necessary to further investigate the role of antioxidants in the management of vitiligo.

Fluorouracil (5-FU) has an antimitotic activity with selective cytotoxicity against rapidly proliferating keratinocytes which has been used in the treatment of nonmelanoma skin cancers. One of its side effects is hyperpigmentation [230]. Back in 1985, Tsuji and Hamada [231] found, while 5-FU alone had no effect, applying it following epidermal abrasion resulted in repigmentation in the majority of patients. Since then, several studies have shown the efficacy of 5-FU in the treatment of vitiligo using different methods of application, such as after skin ablation by laser combined with phototherapy [232], after dermabrasion [233] and by combining it with microneedling [234, 235]. A more recent trial demonstrated that in localized NSV, intradermal 5-FU showed better overall improvement compared with intradermal triamcinolone [236]. Its effects were maintained for 6 months, whereas that of triamcinolone stopped at 1 month after the last injection.

## Quality of Life

The psychosocial effect of vitiligo is important and well recognized [1, 8, 160]. The skin plays an important role in our interaction with the world, and visible skin disorders can limit healthy psychosocial development owing to the stigma these disorders create. Historically, there has been a stigma attached to diseases of the skin and the people they affect [237, 238]. There is an important amount of literature witnessing that with vitiligo since ancient times and in different cultural and religious settings. Hippocrates (460–355 BC) did not discriminate between vitiligo and leprosy. Sadly, this confusion with leprosy persists in many communities in the world up until today, where people with vitiligo suffer from social stigma, similarly to the same age-old way as people with leprosy [8]. Old Buddhist literature (624–544 BC) stated that people with vitiligo were not eligible for ordainment [160]. Since ancient times, men and women with vitiligo were often disqualified from marriage, and the emergence of vitiligo has been considered as a defect in marriage, providing a solid reason for divorce [8, 160]. The degree of stigmatization varies among cultures, leading to variations in the Dermatology Quality of Life Index (DLQI) [239].

Quality of life and burden of vitiligo may be measured by generic assessment tools such as Short Form-12 [240] and DLQI or by more specific tools such as the Vitiligo Impact Scale [241], the Vitiligo-Specific Health-Related Quality of Life Instrument [162] or the Vitiligo Impact Patient scale [242]. Although generic instruments such as the DLQI or Short Form-12 may provide a general picture of impaired quality of life, they generally do not detect nuances in how patients deal with the overall vitiligo burden [3, 243, 244]. Porter et al. [245] first described the major impact of vitiligo on patients' quality of life back in the late 1970s. Since then, a growing body of evidence has confirmed that vitiligo has a major effect on the quality of life of patients [3, 160, 161, 169, 243, 246–248]. A recent meta-analysis which included 1,799 people with vitiligo confirmed the quality of life impairment in patients with

vitiligo compared with healthy controls [249]. Patients with vitiligo often have several psychological problems, such as depression, anxiety and shame which can result in low self-esteem and social isolation [161, 245]. One recent meta-analysis found that a range of psychological outcomes are common in people with vitiligo including depression and anxiety [244], and two other meta-analyses confirmed that the prevalence of depression is high in patients with vitiligo [250, 251]. These patients experience significant disease-related burden and self-perceived stress, regardless of phototype [3]. Vitiligo has negative impacts on sexual life [246, 252]. Vitiligo patients report not receiving enough support from their physicians, friends and family [245, 246, 252, 253]. Patients with vitiligo experience discrimination as many people are scared or uncomfortable with others who have vitiligo.

The onset of vitiligo in adolescence is a risk factor for impaired quality of life [246, 254]. Vitiligo occurring during childhood can have a long-lasting impact on the individual's self-esteem and can be associated with substantial psychological trauma [254]. Children with vitiligo have been observed to limit their physical activities, to avoid wearing clothes that expose their vitiligo lesions and skip more school days than children without vitiligo [254]. Vitiligo causes more embarrassment and self-consciousness as these children grow older: 95% of teenagers (15–17 years old) were bothered by their vitiligo compared with 50% of children (6–14 years old) [254].

Compared with patients with other skin diseases, such as psoriasis and atopic dermatitis, patients with vitiligo have a lower overall impact on quality of life [246, 249]. The extent of lesions involving the face, arms, legs and hands correlates with a lower DLQI [246]. However, the presence of visible lesions seems not to affect the global pattern, which implies that impaired quality of life is more related to the activity of the disease rather than to the involvement of exposed areas and that patients experience discomfort secondary to the uncontrolled progression of their disease rather than the presence of lesions in exposed areas [1, 255].

This psychosocial stress and these psychiatric comorbidities should be taken into consideration in vitiligo management, as stress can be a precipitating factor [1]. Indeed, treatment of vitiligo should not be limited to the clinical disease severity but should also address the patient's quality of life [256]. Social anxiety caused by vitiligo can be improved by self-help cognitive behavioral therapy [257]. Papadopoulos et al. [258] had provided preliminary evidence that cognitive behavioral therapy may have a positive effect on the progression of the condition itself.

## Conclusion

Vitiligo is a common multifactorial skin disorder with a very complex pathogenesis. Although considerable progress has recently been made in our understanding of vitiligo, the cause and pathogenesis of vitiligo remain unclear. Uncertainties remain about what ultimately causes the destruction of melanocytes, and further studies are needed to completely elucidate vitiligo pathogenesis. Uncovering the biological mediators and the molecular mechanisms that lead to metabolic defects and therefore melanocyte degeneration and autoimmunity is important in order to identify new therapeutic targets and drugs that could prevent, stop disease progression or even cure vitiligo. Experience with systemic biological therapies that target cytokines such as in psoriasis suggests that a similar approach might be successfully used in vitiligo. As such targeting the IFN-γ-chemokine axis with existing or developing drugs is tempting and promising.

Furthermore, another important issue in vitiligo is improving the relevance of future vitiligo clinical trials and the ability to compare them. There is a significant heterogeneity of outcome measures used in RCTs for vitiligo. Indeed, Eleftheriadou et al. [259] reported that 48 different outcome measurement instruments have been used to measure repigmentation in 54 controlled trials. There are 11 outcome measurement instruments for measuring aspects of vitiligo [260, 261]. Following the above, two international e-Delphi consensus on a core outcome set for vitiligo were conducted [262, 263]. They defined the successful percentage of repigmentation as being ≥80% [262, 263]. Finally, three workshops with patients with vitiligo have recently been conducted following the guidance from the Cochrane Skin Group Core Outcome Set Initiative and the Vitiligo Global Issues Consensus Group [264]. The authors recommended the use of percentage of repigmentation quartiles (0–25, 26–50, 51–79, 80–100%) and the Vitiligo Noticeability Scale [265–267]. This ongoing effort to produce a core outcome set will improve the ability to use trial findings for meta-analyses and will ultimately lead to greater confidence in decisions regarding the proper management of patients with vitiligo [264–267].

## Key Message

Vitiligo is the most common depigmenting skin disorder with a very complex pathogenesis, and its treatment is still one of the most difficult dermatological challenges.

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## Author Contributions

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