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UNDERSTANDING VITILIGO; CAUSES, SYMPTOMS AND PHARMACOLOGICAL TREATMENT OPTION

SWATI, SHRUTI THAKUR, NISHA DEVI, JYOTI GUPTA

IEC University, Kallujhanda, Baddi, Distt: Solan, Himachal Pradesh, India

Email: swati05012003@gmail.com

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ABSTRACT

Vitiligo is a skin condition characterized by the loss of pigment-producing cells, resulting in white patches on the skin. The etiology of vitiligo remains elusive, although it is widely believed to involve a combination of genetic, autoimmune, and environmental factors. Autoimmune destruction of melanocytes, the cells responsible for producing skin pigment, is a key mechanism implicated in vitiligo pathogenesis. Additionally, genetic predisposition and environmental triggers such as stress, trauma, and certain chemicals may contribute to the development of the condition. The impact of vitiligo extends beyond its physical manifestations, often leading to psychological distress and reduced quality of life for affected individuals. Social stigmatization and feelings of self-consciousness associated with visible skin alterations can significantly affect mental health and interpersonal relationships. Several treatment modalities are available for managing vitiligo, although complete repigmentation may not always be achievable. Topical corticosteroids, calcineurin inhibitors, phototherapy, and surgical techniques such as autologous melanocyte transplantation are among the commonly employed treatment options. Clinically, vitiligo presents as well-defined, depigmented macules and patches, most commonly affecting sun-exposed areas, such as the face, hands, and extensor surfaces. The disease course is highly variable, ranging from stable localized involvement to progressive spread and generalized depigmentation, thus necessitating a tailored therapeutic approach guided by disease activity, extent, and patient preferences. Various hypotheses, including autoimmune destruction of melanocytes and defective melanocyte regeneration, have been proposed to elucidate the mechanisms underlying pigment loss. Diagnosis of vitiligo primarily relies on clinical examination, although Dermos copy and Wood's lamp examination can aid in confirming the diagnosis and assessing disease activity. Recent advances in understanding the immunopathogenesis of vitiligo have led to the development of targeted therapies, including topical corticosteroids, calcineurin inhibitors, phototherapy, and emerging biologic agents, such as Janus kinase inhibitors and anti-IL-17 antibodies. Management strategies aim to halt disease progression, induce repigmentation, and improve cosmesis. Combination therapies involving topical agents, phototherapy, and surgical interventions like melanocyte transplantation offer promising outcomes, particularly in stable disease. Additionally, patient education, psychological support, and camouflage techniques play crucial roles in addressing the psychosocial impact of vitiligo. This paper provides an overview of vitiligo, including its causes, effects on individuals, and various treatment approache

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INTRODUCTION

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 no scaly, chalky-white macules. In recent years, considerable progress has been made in our understanding of the pathogenesis of vitiligo understanding of the pathogenesis of vitiligo which is now clearly classified as ab autoimmune disease (1). Vitiligo is often dismissed as a cosmetic problem, although its effect 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 non-segmental Vitiligo. (2). 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 finding, approach to the patient, and some of the therapeutic modalities for this disorder (3). In addition, numerous disorders may be associated with vitiligo. Treatment of the loss of pigment in the skin is prolonged, difficult, and requires a sustained effort by the patient and the physician. Most physician incorrectly advise their patient that is little hope or need to treat the condition. That advice is well-meaning but misguided and discouraging for the patient. The cosmetic disfigurement has a substantial impact on a person's social and professional relationships (4). Some people experience itching before the appearance of a new patch. It affects people of any age or ethnicity, more than half of whom develop it before the age of 20 years. There are two main types: generalised vitiligo, the common symmetrical form, and segmental, affecting only one side of the body. Around 1%of the world's population has vitiligo, a disease-causing white patch on the skin. Several Treatments are available. Some can restore pigment, but none can cure the disease (5). The substantial disfigurement associated with vitiligo can cause serious emotional stress for the patient, which necessitates. Because its pathogenesis is still not understood, there is a plethora of different treatments. Among them, topical steroids and narrowband ultraviolet B monotherapy were the most common as current treatments for localized and generalized vitiligo, respectively. Cosmetic improvement can be achieved by camouflage products and self-tanning dyes. The course of vitiligo is unpredictable, but often progressive. Spontaneous repigmentation may occur in a few people (10-20%), mainly in children, but this tends to be only partial and on sun- exposed areas. In this article, we review vitiligo as a whole, including epidemiology, pathogenesis and etiology, histopathology, clinical manifestations, classification, clinical variants, diagnosis and differential diagnoses, specific investigation, treatment, prognosis, psychosocial view and its association with other disorders (6). The apparently, simple poorly symptomatic presentation pf the disease has been a strong disadvantage to its study, as compared to other common chronic skin disorders such as psoriasis and atopic dermatitis. A good skin- based angle of attack is also lacking because generalized Vitiligo is clearly epitomizing the view of skin diseases as simple targets of a systemic unknown dysregulation

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(diathesis). This view has mostly restricted vitiligo to the manifestation of an auto- immune diathesis and skin events, which are easily detected using skin biopsies in most other situations, have not been precisely in most other situations, have not been precisely recorded, with the argument that a clinical diagnosis was sufficient for the management of the patient with vitiligo. This richly illustrated second edition reflects the constant international gathered about this disorder at the clinical, pathophysiology and therapeutic levels. Its aim being to bridge current knowledge at the clinical and investigative level, to point to the many unsolved issues, and to delineate future priorities for research (7). The patient with moderate to severe anxiety will seek help for a disfiguring loss of pigment. The physician will say, "You have vitiligo. There is no cure and we do not know the cause. Your health in general is fine, so please try to adjust to the presence of white spots on your skin and try not be vain. Use makeup if you wish. "The patient does not respond. The physician, satisfied that the patient understands, believes that it was proper to be direct to be straightforward. The patient departs quietly but with inner turmoil and anger. The physician has tried to shame the patient into believing that no real problem exists (8). Vitiligo is an important skin disease having a major impact on the quality of life of the patient suffering from it. The causes of this conditions are uncertain but seem to be dependent on the interaction of genetic, immune logical and neurological factors. Vitiligo co exists with other autoimmune disorders, Sutton or hale nevus, and malignant melanoma (9). Vitiligo is one of the most common hypomelanoses. Current treatments include ultraviolet, topical corticosteroids, calcineurin inhibitors. Orally administered vitamins, acting as antioxidants and in combination with ultraviolet light have also demonstrated skin re -pigmentation. In our pilot study of seven patients, we infected skin affected with vitiligo intra-dermally with a complex of vitamins and minerals and assessed the outcomes. (10) Seven patients had vitiligo associated with pluriglandular insufficiency. There may be a common autoimmune pathogenesis. VITILIGO may be a readily identifiable and early external manifestation, pointing to a possible multiple glandular insufficiency syndrome. Because of the serious nature of the associated glandular deficiencies and since they appear sequentially, yearly examinations for the associated conditions are probably indicated in the propositus and on blood relatives. (11). As vitiligo can have a major effect on quality of life, treatment can be considered and should preferably begin early when then disease is active. Current treatment modalities are directed towards stopping progression of the disease and achieving repigmentation. Therapies include corticosteroids, topical immunomodulators, photo(chemo)therapy, surgery, combination therapies and de pigmentation of normally pigmented skin. (12). The cause of vitiligo appears to be a combination of genetic effects in both the immune system and the melanocytes itself with a precipitating factor instigating their interaction and resulting in the melanocytes destruction. Headway is being made in understanding the etiologic of vitiligo that should culminate in new and improved therapies. (13). Depigmentation therapy can be considered of vitiligo affects more than 60% to 80% of the body. Complementary therapies such as Polypodium leucotomos with UVB therapy. No causative treatment for vitiligo is currently available. More randomized controlled trials on the treatment of vitiligo are necessary (14). It is essential to increase awareness of these comorbidities in order to improve the disease burden and quality of life of patients

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with vitiligo. Herein, we review the association with the most frequent comorbidities associated with vitiligo (15). Photography was considered, including narrowband ultraviolet B (UVB), psoralen with ultraviolet A (UVB), along with combinations of topical preparations and various forms of UV. Surgical treatment that were assessed include full-thickness and spilt skin grafting, mini (punch) grafts, autologous epidermal cell suspensions, and autologous skin equivalent. The effectiveness of cognitive therapy and psychological treatments was considered. Therapeutic algorithms using grades of recommendation and levels of evidence have been produced for children and for adults with vitiligo (16). Vitiligo triggering also involve a major environmental component; dramatic delay in vitiligo age-of-onset, especially from 1973 to 2004, suggests that exposure or reponse to a key vitiligo environmental trigger diminished during this period. Together, these findings pathogenesis and genetic architecture, suggesting that vitiligo represents a tractable model for investigating complex disease genetic architecture and predictive aspects of personalized medicine. (17) Surgical treatment of vitiligo is considered the final resort of repigmentation is lesions failing to respond for various medical and light therapies. The tissue and cellular graft techniques are used for the successful introduction of melanocytes into the vitiligo is the cornerstone of evalution before surgery. Tissue graft includes various techniques of transferring the healthy pigmented skin as a whole without processing to the vitiliginous skin, while the cellular graft involves further processing of these graft into cellular components which are then applied on the recipient site after dermabrasion either as such or after multiplication in culture media. (18)

Classification

Vitiligo itself has been classified based on clinical grounds into two major forms, namely, segmental vitiligo (SV) and non-segmental vitiligo (NSV), the latter including several variants (generalized vitiligo, acrofacial vitiligo, universal vitiligo). Non-segmental vitiligo typically evolves over time, in both distribution and extension patterns. This is the case with focal vitiligo, which may evolve into SV, into NSV, or may remain unclassifiable based on the NSV/SV classification paradigm. For NSV, the disease may be initially classified as acrofacial but will later progress to be better classified as generalized or universal. (19)

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Table 1: Classification of Vitiligo

TYPES	SUB TYPES
Non-segmental vitiligo	Generalized or common Universal Acrofacial Mucosal (more than one site affected) Mixed (associated with segmental vitiligo) Rare form
Segmental	Multisegmental ,bisegmental or unisegmental
Unclassified or indeterminate	Mucosal (only one site affected) Focal [20].

Non-segmental vitiligo

Includes focal, mucosal (when involving more than one mucosal site), acrofacial, generalized, universal, mixed, and other rare variants of vitiligo. Focal vitiligo, which may be a precursor to generalized vitiligo, refers to one or several macules or patches in one area without a segmental distribution that remain stable over a two-year period (Ezzedine et al., 2012). Mucosal vitiligo refers to more than one depigmented patch involving the oral and/or genital mucosa. Acrofacial vitiligo presents with patches that are mostly limited to the face and the distal extremities. Generalized vitiligo refers to scattered patches of vitiligo with a widespread distribution. The term universal vitiligo is used in cases where depigmentation involves greater than 80% of the body surface area (Ezzedine et al., 2012). Mixed vitiligo specifically refers to a combination of segmental and any other form of non-segmental vitiligo (Ezzedine et al., 2011). A variant termed “lip-tip” vitiligo involves the distal fingers, toes, and facial periorificial skin, and occurs most commonly in Southern Asia (Hann & Lee, 1996; Rodrigues et al., 2017). Additionally, exposure to various chemicals, occupational or otherwise, can result in focal depigmentation of exposed skin followed by the development of additional depigmented patches at non-exposed locations, usually progressing to a widespread distribution of disease that is both clinically and histologically identical to other forms of vitiligo (Alikhan, Felsten, Daly, & Petronic-Rosic, 2011; Ghosh & Mukhopadhyay, 2009; Harris, 2017).(21)

● Generalized vitiligo – Generalized vitiligo is characterized by bilateral, often symmetrical, depigmented macules or patches occurring in a random distribution over multiple areas of the body surface. Generalized vitiligo may begin in childhood or early adulthood and often occurs at sites subjected to pressure, friction, and/or trauma. Depigmented patches are common on the face, trunk, and extremities.

● Acrofacial or acral vitiligo – Acrofacial or acral vitiligo consists of depigmented macules confined to the distal extremities and/or the face. It may later include other body sites, resulting in typical generalized vitiligo. A subcategory of the acrofacial type is the lip-tip variety, in which lesions are confined to the cutaneous lips and distal tips of the digits.

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● Mucosal vitiligo – Mucosal vitiligo typically involves the oral and/or genital mucosa. It may occur in the context of generalized vitiligo or as an isolated manifestation

● Universal vitiligo – Universal vitiligo refers to complete or nearly complete depigmentation of the skin. Some skin areas and hairs may be partially spared. Universal vitiligo usually results from progression of generalized vitiligo. (22)

Segmental vitiligo

- Segmental vitiligo presents with one, or rarely multiple, segments of the body demonstrating a block-like or linear patch that usually does not cross the midline (Figure 1b; Hann & Lee, 1996). Compared to other variants, segmental vitiligo is less common, progresses rapidly over a six-month-to-two-year period, tends to halt spontaneously, is commonly associated with leukotrichia, and is less responsive to treatment than other variants of vitiligo (Hann & Lee, 1996; Rodrigues et al., 2017).This variant is more common in pediatric patients, with less association with autoimmune disease than non-segmental vitiligo (Kanwar & Kumaran, 2012).(23)
- **Multi-Segmental Vitiligo**: Multi-segmental vitiligo involves depigmented patches occurring in multiple non-contiguous segments of the body. It may present challenges in treatment due to its extensive and sometimes unpredictable distribution.
- **Bi-Segmental Vitiligo**: Bi-segmental vitiligo refers to depigmented patches affecting two segments of the body. This subtype shares characteristics with both segmental and generalized vitiligo.
- **Uni-Segmental Vitiligo**: Uni-segmental vitiligo involves depigmentation limited to a single segment of the body. It may occur in isolation or progress to involve additional segments over time. (24)

Unclassified/Indeterminate Vitiligo:

In some instances, vitiligo may present with features that do not fit neatly into existing classification systems. These cases may exhibit characteristics of both segmental and generalized vitiligo or may have atypical clinical presentations.

- **Challenges in Classification**: Unclassified or indeterminate vitiligo poses challenges in diagnosis, treatment planning, and prognostication. Clinicians may need to carefully evaluate clinical features, disease progression, and response to treatment to guide management decisions. (25)
- **Clinical Evaluation**: Differential diagnoses, such as other hypopigmentary disorders or autoimmune conditions, should be considered in cases of unclassified vitiligo. Comprehensive clinical evaluation, including history, physical examination, and possibly histopathological examination, may be necessary to establish a diagnosis.

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- **Management**: Treatment strategies for unclassified vitiligo may vary depending on the extent, distribution, and activity of the disease. Treatment options commonly employed for generalized vitiligo, such as topical corticosteroids, calcineurin inhibitors, phototherapy, and systemic immunomodulatory agents, may be considered (26)

One vitiligo or several vitiligo's?

For most authors, vitiligo is a unique disorder with several clinical presentations but one physiopathology. Indeed, almost all the recent genetic studies have ignored the clinical presentation of patients. However, recent data strongly suggest that there is not one vitiligo but several vitiligo's. A complex segregation analysis was performed on 2247 Chinese patients and their families. For the first time the results were analyzed according to their clinical manifestations (27).

The results show a different age of disease onset depending on the subtypes of vitiligo. More interestingly, a polygenetic additive model was found to be the best model for segmental, localized, acrofacial and generalized vitiligo, whereas the best model for universal vitiligo was an environmental one. In an additional study, Human leukocyte antigen (HLA) class II associations with two subtypes of vitiligo, vitiligo vulgaris and halo nevi associated with vitiligo, were investigated (28). A case-control association study showed a significant positive association of HLA-DR4 and DR53 and a negative association of HLA-DR3 with vitiligovulgaris. The group with halo associated with vitiligo did not show these associations but had asignificant negative association with HLA-DR11. All of these data suggest that hetero geneous pathogeneses underlie different phenotypes of vitiligo.

EPIDEMIOLOGY

Vitiligo is a relatively common skin disorder characterized by the loss of melanocytes, resulting in depigmented patches on the skin. Its prevalence varies across different populations and geographic regions. Here's an overview of the epidemiology of vitiligo along with some references:

- **Prevalence**: The prevalence of vitiligo varies widely across different populations, ranging from 0.5% to 2% worldwide. It affects individuals of all races and ethnicities, although it is more noticeable in individuals with darker skin tones due to the contrast between depigmented patches and surrounding pigmented skin. (29)
- **Age of Onset**: Vitiligo can develop at any age but often manifests before the age of 20. However, it can also occur in adulthood. The age of onset may influence disease progression and response to treatment.
- **Gender Distribution**: Vitiligo affects both males and females, with no significant gender predilection. However, some studies suggest a slightly higher prevalence in females compared to males. (30)

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- **Family History**: A family history of vitiligo is reported in approximately 20% to 30% of affected individuals, suggesting a genetic predisposition to the condition. Certain genetic factors, including polymorphisms in genes associated with immune regulation and melanocyte function, may contribute to the development of vitiligo. (31)
- **Association with Other Autoimmune Diseases**: Vitiligo is frequently associated with other autoimmune diseases, such as autoimmune thyroid disorders (e.g., Hashimoto's thyroiditis, Graves' disease), autoimmune adrenal insufficiency (Addison's disease), type 1 diabetes mellitus, and pernicious anemia. The co-occurrence of multiple autoimmune conditions suggests shared underlying pathogenic mechanisms. (32)

Pathogenesis

Vitiligo is a multifactorial disorder characterized by the loss of functional melanocytes (33). 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 underdebate, 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 (34). NSV (Non Segmental Vitiligo) and SV(Segmental Vitiligo) 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 (35).

However, more recent evidence points towards an overlapping in-flammatory 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. (36). 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 (37). However, the distribution pattern of SV is not entirely similar to any other skin disease, and it is rarely, if ever, dermatomal. (38). 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. (39).

Proposed theories

- **Genetic Factors**: Genetic predisposition plays a significant role in the development of vitiligo. Family studies have shown that individuals with a family history of vitiligo are at higher risk of developing the condition. Genome-wide association studies (GWAS) have identified several

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susceptibility loci associated with vitiligo, including genes involved in immune regulation, melanocyte function, and oxidative stress pathways.

- **Autoimmune Mechanisms**: Vitiligo is considered a multifactorial autoimmune disorder, where the immune system mistakenly targets and destroys melanocytes. Autoimmune reactions against melanocytes are thought to be triggered by various factors, including melanocyte-specific autoantibodies, cytotoxic T lymphocytes, and inflammatory cytokines such as interferon-gamma (IFN-γ) and tumor necrosis factor-alpha (TNF-α).
- **Oxidative Stress**: Increased oxidative stress within the skin microenvironment is believed to contribute to the pathogenesis of vitiligo. Oxidative stress leads to the generation of reactive oxygen species (ROS), which can damage melanocytes and trigger apoptosis (cell death). Melanocytes are particularly vulnerable to oxidative stress due to their high metabolic activity and exposure to UV radiation. (40)
- **Neural Hypothesis**: The neural hypothesis suggests that neurogenic factors, including neuropeptides and neurotransmitters released by nerve endings, may play a role in the destruction of melanocytes in vitiligo. Neurogenic inflammation and neural-mediated immune responses have been implicated in the pathogenesis of vitiligo, although the exact mechanisms remain to be fully elucidated.
- **Environmental Triggers**: Environmental factors such as trauma, sun exposure, chemical exposure, and viral infections have been proposed as triggers for the onset or exacerbation of vitiligo. These factors may induce stress responses in melanocytes or trigger autoimmune reactions in genetically susceptible individuals.
- **Imbalance in Regulatory T Cells (Tregs)**: Dysregulation of regulatory T cells (Tregs), which are crucial for maintaining immune tolerance and preventing autoimmune reactions, has been observed in vitiligo patients. Decreased numbers and impaired function of Tregs may contribute to the breakdown of immune tolerance and the development of autoimmune responses against melanocytes (41)

SIGN & SYMPTOMS

Vitiligo is a skin disorder characterized by the loss of pigment-producing cells (melanocytes), resulting in depigmented patches on the skin. The signs and symptoms of vitiligo can vary widely among individuals and may include:

- **Depigmented Patches:** The most prominent symptom of vitiligo is the presence of well-defined, milky-white patches on the skin. These patches may vary in size and shape, and they commonly appear on sun-exposed areas such as the face, hands, arms, feet, and genitalia.
- **Symmetrical Distribution:** In many cases, vitiligo patches occur symmetrically on both sides of the body. For example, if a patch develops on one elbow, a similar patch may appear on the other elbow. (42)
- **Progressive Spread:** Vitiligo may exhibit a progressive course, with the depigmented patches enlarging over time and new patches developing in previously unaffected areas.

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- **Loss of Pigmentation in Mucous Membranes:** In addition to affecting the skin, vitiligo can also involve mucous membranes, leading to depigmentation of tissues such as the lips, inside the mouth, and the genital area.
- **Premature Graying of Hair:** Individuals with vitiligo may experience premature graying or whitening of hair on the scalp, eyebrows, eyelashes, and other body regions.
- **Koebner Phenomenon:** Some people with vitiligo may notice the appearance of new patches following trauma or injury to the skin. This phenomenon, known as the Koebner phenomenon, is characterized by the development of vitiligo lesions at sites of skin trauma or friction. (43)
- **Nail Changes:** In rare cases, vitiligo may affect the nails, leading to loss of pigment, white spots, or striations (lines) on the nails.
- **Associated Autoimmune Conditions:** Individuals with vitiligo may have an increased risk of developing other autoimmune disorders, such as autoimmune thyroid disease, alopecia areata, rheumatoid arthritis, and type 1 diabetes. (44)

DIAGNOSIS

The diagnosis of vitiligo is primarily clinical, based on the characteristic appearance of depigmented patches on the skin. However, several diagnostic tools and criteria may be used to confirm the diagnosis and rule out other conditions.

Clinical Examination: A thorough examination of the skin is conducted by a dermatologist or healthcare provider. They look for depigmented patches that are typically well-defined, symmetrical, and may vary in size and shape. The affected areas often lack pigment and may have a lighter color than the surrounding skin. (45)

Wood's Lamp Examination: A Wood's lamp emits ultraviolet light, which can help accentuate depigmented patches by making them appear more pronounced compared to the surrounding skin. (46) The Wood's lamp examination, also known as a black light examination, is a diagnostic tool used in dermatology to detect certain skin conditions. It utilizes a Wood's lamp, which emits ultraviolet (UV) light, causing certain substances in the skin to fluoresce. (47)

Medical History: Gathering information about the onset, progression, and family history of vitiligo helps in making an accurate diagnosis and understanding potential risk factors. The medical history for vitiligo typically involves gathering information about the patient's symptoms, medical background, family history, and any potential triggers or associations. Understanding the onset, duration, and progression of vitiligo symptoms is crucial. (48)

Biopsy (Optional): A skin biopsy may be performed in atypical cases to confirm the absence of melanocytes in depigmented areas. (49) Biopsy is sometimes performed in cases of vitiligo, particularly when the diagnosis is uncertain or when other skin conditions need to be ruled out. However, it's important to note that biopsy is not always necessary for diagnosing vitiligo, as it can usually be diagnosed based on clinical presentation alone. (50)

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Blood Tests (Optional): Blood tests may be ordered to check for autoimmune markers or associated conditions, such as thyroid disorders or diabetes. (51) While blood tests are not typically used as a primary method for diagnosing vitiligo, they may be performed in some cases to rule out other underlying conditions or to assess specific factors related to vitiligo, such as autoimmune markers. (52)

Pharmacological Treatment

Pharmacological treatments for skin conditions like vitiligo typically involve the use of topical medications, oral medications, or injectable drugs to manage symptoms, slow disease progression, or promote repigmentation.(53) Pharmacological treatments for vitiligo aim to stimulate repigmentation of depigmented areas of the skin by targeting various mechanisms involved in the pathogenesis of the condition.(54) One common approach is the use of topical corticosteroids, which can help suppress the immune response responsible for attacking melanocytes, the pigment-producing cells. Another option is topical calcineurin inhibitors, which work similarly to corticosteroids but may be preferred for sensitive areas or for long-term use due to their lower risk of side effects. (55) Additionally, phototherapy with narrowband ultraviolet B (NB-UVB) is a widely used treatment that can stimulate repigmentation by promoting melanocyte proliferation and migration. Other emerging pharmacological treatments include Janus kinase (JAK) inhibitors, which target the immune pathways involved in vitiligo pathogenesis, and melanocyte transplantation techniques, where melanocytes are transferred from unaffected areas of the patient's skin to depigmented areas. (56) Overall, the choice of pharmacological treatment depends on various factors including the extent of depigmentation, the patient's medical history, and their preferences regarding treatment duration and potential side effects. It's essential for individuals with vitiligo to work closely with a dermatologist to develop a personalized treatment plan that addresses their specific needs and goals. (57) It has been that no drug will fully stop vitiligo- the loss of pigment cells (melanocytes). However, some medication used alone or with light therapy, will faciliate restore some skin tone to some extent. Here are some common treatment options and their mechanisms of action:

Topical Corticosteroids:

Treatment with topical corticosteroids is the therapy of choice for all types of vitiligo with an affected body surface area of < 3 % (limited vitiligo). This therapy is particularly effective in the face and neck region, in dark skin types, and fresh lesions. Due to its side effects, it is, however, problematic on the face. In a meta-analysis, topical corticosteroids of the classes III and IV had a similar therapeutic effect (75 % repigmentation), amounting to 56 % and 55 %, respectively, in patients with vitiligo and an affected BSA of < 20 % [35]. Comparative studies show that the efficacy of topical corticosteroids of class IV (clobetasol propionate) or class III (mometasone furoate) in the face and neck region is similar to topical calcineurin inhibitors (tacrolimus and pimecrolimus). However, the use of topical corticosteroids poses the risk of skin atrophy; less common side effects are telangiectasias, hypertrichosis, striae, acneiform reactions and perioral dermatitis. Systemic absorption has to be considered when applying high-potency corticosteroids on large areas of the body, in intertriginous areas, and, especially, in children. In general, face and neck respond best to therapy. Topical

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corticosteroids are first-line medications for limited vitiligo and extrafacial involvement. No studies on the optimal application schedule (permanent or interval therapy) exist. Potent corticosteroids (class III) with improved therapeutic index such as mometasone furoate are recommended, for example for a period of three months (once daily) or six months (once daily for 15 days each, followed by an interval of 14 days). This therapy is also suitable for children. Here, systemic resorption has to be considered for large-surface application in intertriginous areas. (58)

Drugs: Clobetasol propionate, betamethasone, mometasone Hydrocortisone

Hydrocortisone: Hydrocortisone is a mild corticosteroid available in various formulations, including creams, ointments, lotions, and sprays. It is often used for the treatment of mild to moderate inflammatory skin conditions, including eczema and contact dermatitis. Hydrocortisone works by reducing inflammation, itching, and redness associated with skin conditions. (59)
Side Effects; Increased risk of infection, Gastrointestinal issues, High blood pressure, Weight gain
ADRs; Increased appetite, Nausea or vomiting , Headache, Dizziness, Insomnia

Betamethasone:
Betamethasone is a potent corticosteroid available in various formulations such as creams, ointments, and lotions. It is often prescribed for the treatment of moderate to severe inflammatory skin conditions, including psoriasis, eczema, and dermatitis. Betamethasone works by suppressing the immune response, reducing inflammation, itching, and redness. (60)

Side Effects; Skin reactions, Adrenal suppression, Glaucoma and cataracts, Osteoporosis
ADRs; Stretch marks (striae), Dry skin, Hypertension

Topical Calcineurin Inhibitors:
Topical calcineurin inhibitors are a class of medications commonly used in dermatology to treat inflammatory skin conditions such as atopic dermatitis (eczema). The two main topical calcineurin inhibitors are tacrolimus and pimecrolimus.
Drugs: Tacrolimus, pimecrolimus.

Tacrolimus:
Tacrolimus is a macrolide immunosuppressant drug. It is available in topical form as Tacrolimus ointment. Tacrolimus inhibits calcineurin, a protein necessary for the activation of T-lymphocytes. By inhibiting calcineurin, tacrolimus suppresses the inflammatory response. Tacrolimus ointment is commonly used for the treatment of atopic dermatitis in adults and children over 2 years old. (61)
Side Effects; Increased Risk of Infections, Renal Dysfunction, Neurological Effects, Dermatological Effects:

ADRs; Muscle weakness or pain, Changes in taste sensation, Abdominal pain or discomfort, Skin rash or itching, Hair loss (alopecia)

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Pimecrolimus:
Pimecrolimus is an immunomodulating agent of the calcineurin inhibitor class. It is available in topical form as Pimecrolimus cream. Similar to tacrolimus, pimecrolimus inhibits calcineurin, thereby modulating the immune response. Pimecrolimus cream is also used for the treatment of atopic dermatitis, particularly in patients who have failed to respond adequately to other treatments or who cannot use other therapies. (62)

Side Effects; Redness or warmth of the skin, Headache, Flu-like symptoms (less common)
ADRs; Burning or stinging sensation, Redness or erythema, Cold-like symptoms, Dry skin

Topical Vitamin D Analogues:

Topical vitamin D analogs are used in dermatology for the treatment of various skin conditions, particularly psoriasis. One commonly used topical vitamin D analogue is calcipotriene (also known as calcipotriol).

Drug: Calcipotriol.

Calcipotriene (Calcipotriol):

Calcipotriene is a synthetic vitamin D analogue that acts as a topical antipsoriatic agent. It is available in various formulations such as ointments, creams, and solutions. Calcipotriene is commonly used as monotherapy or in combination with topical corticosteroids for the treatment of psoriasis vulgaris. This vitamin D analogue works by inhibiting keratinocyte proliferation and promoting keratinocyte differentiation, thus reducing the hyperproliferation and inflammation associated with psoriasis. (63)
Side Effects; Skin irritation, Hypercalcemia, Allergic reactions, Photosensitivity.
ADRs; Skin irritation or burning, Dry skin, Skin rash or dermatitis

Oral Corticosteroids:
Oral corticosteroids are not typically used as a primary treatment for vitiligo, a condition characterized by the loss of skin pigment resulting in white patches. Instead, treatments for vitiligo often focus on repigmentation therapies, such as topical corticosteroids, phototherapy, and other immunomodulatory agents.

While oral corticosteroids may sometimes be prescribed for certain inflammatory skin conditions, their use in vitiligo is limited and generally not recommended due to concerns about side effects and lack of evidence supporting their effectiveness in treating this particular condition. (64)
Drug: Prednisone.

Prednisone
Prednisone is not typically considered a first-line treatment for vitiligo due to its limited efficacy and potential side effects. Certain cases where vitiligo is associated with other autoimmune conditions or where rapid control of inflammation is necessary, prednisone may be used as part of combination

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therapy. There is limited clinical evidence supporting the use of prednisone as a monotherapy for vitiligo. (65)

Side Effects; Fluid retention and swelling (edema), Mood changes, Insomnia, Gastrointestinal effects
ADRs; Adrenal crisis, Severe allergic reactions, Muscle weakness, Osteoporosis

PHOTOTHERAPY

Phototherapy is a treatment method that utilizes specific wavelengths of light to treat various skin conditions, including vitiligo.: Phototherapy involves exposing the skin to ultraviolet (UV) light, which can be either ultraviolet A (UVA) or ultraviolet B (UVB). The type of UV light used, as well as the wavelength and duration of exposure, depends on the specific skin condition being treated and the patient's individual needs. (66)

Types: Narrowband UVB, PUVA (psoralen plus UVA).

PUVA

Photochemotherapy is a therapeutic method that uses psoralen and exposure to ultraviolet (UV) A radiation (PUVA). Psoralens can be applied either topically ("topical PUVA") or orally ("oral PUVA"), followed by exposure to artificial UVA radiation. The most widely used photosensitizers for oral PUVA therapy are 8-methoxypsoralen (8-MOP) and 5-me - tho xypsoralen (5-MOP). 8-MOP (0.6 mg/kg body - weight) should be given two hours and 5-MOP (1.2 mg/kg bodyweight) one hour prior to UVA radiation exposure. 5-MOP is a less phototoxic agent. This reduced phototoxicity is important when treating a disease like vitiligo. The incidence and severity of adverse events, such as nausea, vomiting, pruritus, and erythema, is 2 to 11 times more frequent with 8-MOP than with 5-MOP (11). Both treatments are administered two to three times per week. An initial dose of UVA radiation is approximately 0.5 J/cm2 (2). Alternatively, the initial dose can also be based on minimal phototoxic dose (MPD) and it is about 75% of the MPD. PUVA is the most useful for extensive vitiligo, and the areas that respond most favourably are the face and trunk (67).

Broadband UVA (320–400 nm)

Ultraviolet A has been used in association with fluticasone propionate (FP) in vitiligo patients and compared with UVA alone and FP alone: in this large study on 135 adults, the combination of FP with UVA appeared to be equally effective as FP alone, and both options were more effective than UVA alone. The authors concluded that UVA alone was scarcely effective in vitiligo. Ultraviolet A without psoralen has also been used three times weekly in a controlled, comparative and randomized trial in 20 selected patients: after 48 sessions, spread over 16 weeks with 15 J/cm2 , 4 60% repigmentation was observed in 50% of the patients, suggesting UVA as an alternate therapy for vitiligo. The effectiveness of UVA alone has not been confirmed in other studies and this does not seem to be a popular approach in vitiligo phototherapy.

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Broad-band UVB (BB UVB)

Wavelengths from 290 to 320 nm (BB UVB), were widely used in the past for the treatment of a variety of skin disorders. There is only one report on the efficacy of BB UVB in vitiligo. Fourteen patients were treated, and eight patients (57.1%) achieved 75% repigmentation in 12 months; in this series, the patients showing the best results were those with facial lesions and skin types V and VI. These results have never been confirmed. BB UVB phototherapy is being replaced by NB UVB in other indications and also in vitiligo.

NB UVB

In 1981, Parrish and Jaenicke found that 311 nm wavelength UVB radiation was most effective for the treatment of psoriasis. This finding provided the impetus for developing the Philips TL 01 fluorescent bulb (Royal Philips Electronics, Eindhoven, The Netherlands), the NB UVB light source. Currently, there are several clinical indications for NB UVB phototherapy including psoriasis, atopic dermatitis, desensitization therapy for photo dermatoses and patch-stage cutaneous T cell lymphomas. (68)

Depigmentation Therapies

These therapies are generally recommended for extensive and refractory vitiligo, when >50% of the body surface is affected or if cosmetically sensitive areas are the major component involve . Monobenzyl ether of hydroquinone (MBEH) 10% is applied topically daily the first month, then MBEH 20% is applied daily for 1 month, and after that twice daily. The concentration can be increased to 30-40% if the areas are unresponsive, if tolerated. In general, patients present depigmentation after 3-6 months in areas distal to the application. Other treatment options are 4-methoxyphenol, 88% phenol solution, laser and cryotherapy (69).

Combination Therapies

In numerous studies, attempts have been made to improve the repigmentation effect of phototherapy in vitiligo by combination with external or systemic therapies. The majority of available data is derived from very heterogeneous non-controlled studies with relatively low case numbers and mostly a maximum intervention period of six months. Accordingly, it remains an open question whether an adjuvant therapy is only temporarily accelerating the response to phototherapy or will also result in better therapeutic outcomes in the long term. (70) Combination therapies for vitiligo involve the use of multiple treatment modalities simultaneously or sequentially to achieve better outcomes in terms of repigmentation and disease stabilization.

Types of Combination Therapies:

- **Topical Therapies**: Combining different topical agents such as corticosteroids, calcineurin inhibitors (e.g., tacrolimus), vitamin D analogs, and topical psoralen (for PUVA therapy) can

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enhance their individual effects and broaden the spectrum of treatment. For example, combining a potent corticosteroid with a calcineurin inhibitor may have synergistic immunosuppressive effects and reduce the risk of corticosteroid-induced side effects.

- **Phototherapy with Topical Agents**: Phototherapy, including narrowband UVB (NB-UVB) or PUVA therapy, can be combined with topical treatments to enhance repigmentation. Topical treatments can prepare the skin for phototherapy, improve melanocyte proliferation and migration, and maintain repigmentation achieved with phototherapy.
- **Phototherapy with Oral Agents**: Oral medications such as oral corticosteroids or oral immunosuppressants may be combined with phototherapy for more extensive or recalcitrant vitiligo. This combination can target both the local and systemic aspects of the disease, modulating the immune response and promoting melanocyte function.

Surgical Therapies with Adjunctive Treatments: Surgical interventions such as autologous melanocyte transplantation (e.g., melanocyte-keratinocyte transplantation procedure, MKTP) or suction blister grafting can be combined with adjuvant treatments like phototherapy or topical agents to enhance repigmentation outcomes and improve the longevity of results. (71)

Photochemotherapy

Photosensitizers used in photochemotherapy (psoralen or khellin) increase the sensitivity of the skin or melanocytes, respectively by, for example, activation of melanocytes or melanosomes as well as induction of IL1 synthesis. One study shows topical KUVA and systemic PUVA therapy leading to similar responses. These end responses were achieved by PUVA in a statistically significant shorter treatment period ($t = 15.5$, $p < 0.001$) as topical KUVA therapy. Two randomized placebo-controlled trials showed significantly more rapid and strong repigmentation for combined PUVA and calcipotriol therapy. Side effects were slight irritation, erythema and/or pruritus. A study comparing PUVA with UVB-nb showed UVBnb to be superior after four months; one-fifth more patients showed repigmentation. A retrospective analysis over ten years showed that PUVA resulted in repigmentation over 90 % in only 8 % of patients (usually inhomogeneous and weak repigmentation.(72)

ReCell System in Vitiligo Therapy

ReCell is a robust point-of-care autologous therapy designed to treat skin defects such as small and large thermal burn wounds using a patient's regenerative cells. The ReCell system enables the harvesting of autologous cells, processing them, and delivering them using a spray applicator. Three clinical trials analyzed the results of treating patients with stable vitiligo with ReCell (a cell suspension with keratinocytes, melanocytes, dermal papillary fibroblasts, and Langerhans cells sprayed over the wound). Mulekar et al. compared the efficacy of the ReCell system and melanocyte–keratinocyte transplantation 4 months after the procedure. In both methods, the cell suspension was spread to previously dermabraded areas, and the results of the treatments were comparable.

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Due to efficacy, time, and cost, surfaces that can be covered with cultured melanocytes are larger than those that can be covered with non-cultured cells. Cervelli et al. treated 15 patients, and 12 of them (80%) achieved more than 75% repigmentation. The authors observed an excellent color match in 66% of patients.

In 2010, the same group presented a case report of a 30-year-old man suffering from stable vitiligo on his hands. Before undergoing ReCell therapy, he had vitamin A, C, E, and UVB therapy, none of which were beneficial. Treatment with the ReCell system gave excellent results, both in the extent of repigmentation and the skin color match. The clinical applications of the ReCell system in vitiligo are summarized. (73)

The ReCell® system is a novel technique used in vitiligo therapy that involves autologous cell transplantation. This system allows for the extraction, processing, and application of a patient's own skin cells to promote repigmentation in areas affected by vitiligo.

- **Cell Harvesting**: The first step in the ReCell® system involves the harvesting of a small sample of the patient's own healthy skin. This sample is typically taken from an area of unaffected pigmented skin, such as the thigh or abdomen.
- **Cell Processing**: The harvested skin sample is processed using the ReCell device, which involves enzymatic digestion and mechanical disaggregation to isolate a suspension of individual skin cells, including melanocytes. (74)
- **Cell Application**: Once processed, the suspension of skin cells, including melanocytes, is applied to the areas of depigmented skin affected by vitiligo. The cells are sprayed onto the skin using a specialized spray device, allowing for uniform coverage of the treatment area.
- **Wound Healing and Repigmentation**: The transplanted melanocytes migrate and proliferate within the depigmented skin, leading to repigmentation over time. The surrounding keratinocytes provide a supportive environment for melanocyte survival and function, aiding in the restoration of pigment. (75)

CONCLUSION

vitiligo is a challenging condition characterized by the loss of skin pigmentation, which can significantly impact the physical appearance and psychological well-being of affected individuals. While there is no definitive cure for vitiligo, various treatment options are available to help manage the condition and promote repigmentation of the affected areas. These treatment modalities include topical corticosteroids, calcineurin inhibitors, phototherapy (such as narrowband UVB or PUVA therapy), surgical interventions (such as autologous melanocyte transplantation), and combination therapies. The choice of treatment depends on factors such as the extent and severity of vitiligo, patient preferences, response to previous treatments, and the presence of any associated medical conditions. Combination therapies, which involve the simultaneous or sequential use of multiple treatment modalities, may offer enhanced efficacy and better outcomes compared to monotherapy in certain cases. Additionally, patient

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education, psychological support, and camouflage techniques can play a vital role in improving the quality of life for individuals living with vitiligo. Overall, the management of vitiligo requires a multidisciplinary approach involving dermatologists, psychologists, and other healthcare professionals working collaboratively to address both the physical and emotional aspects of the condition. Continued research into the underlying mechanisms of vitiligo and the development of novel treatment strategies are essential to improve therapeutic outcomes and enhance the quality of life for individuals affected by this condition.

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