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**Review Article**

# Vitiligo: An In-Depth Review of Pathogenesis, Clinical Aspects, and Therapeutic Advances

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## ABSTRACT

Vitiligo is a chronic, acquired pigmentary disorder distinguished by selective destruction of functional melanocytes resulting in depigmented macules and patches on skin and mucosa. Its pathogenesis implies intricate relationships of genetic predisposition, autoimmune reaction, and oxidative stress, and perhaps neural mechanism. Very recently, particularly with respect to immune dysregulation and cytokine signaling, advances have been made using molecular assays for understanding the pathways underlying vitiligo. Over these advances, Janus kinase (JAK) inhibitors have arisen as a significant clinical milestone, facilitating novel therapeutic pathways. This review highlights the advances between 2021 and 2024 on the epidemiology, pathogenesis, manifestations, diagnosis, psychosocial impact and evolving treatment landscape of vitiligo, particularly the emergence of JAK inhibitors as a new class of therapies.

## INTRODUCTION

Vitiligo is among the most common skin diseases associated with loss of pigmentation, estimated to affect 0.5–2% of the world population (Ezzedine et al., 2021). While the disease itself is not a direct danger to physical health, the visible signs of the condition often carry significant psychological and social implications. Vitiligo was historically thought of recalcitrant to treatment, and this perception has changed significantly over the past two decades through a better understanding of immunology, genetics, and ultimately the advent of targeted therapeutics. At the core of these advances has been our evolving insight into the immune mechanisms underlying the loss of melanocytes—particularly the role of interferon-gamma (IFN-γ) signaling and cytotoxic T-cell activity. Consequently, recent research has focused on new therapeutic targets, particularly the Janus kinase (JAK) pathway, which is an essential mediator for conveying inflammatory

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signals thought to be involved in vitiligo pathogenesis. The U.S. Food and Drug Administration's official approval of topical ruxolitinib in 2022 as a JAK inhibitor for the treatment of non-segmental vitiligo signifies a milestone in the therapeutic landscape, potentially heralding more effective and personalized treatments for patients in future (Rodrigues et al., 2023). This review narrates the recent advances in the epidemiology, pathogenesis, clinical features, diagnosis, psychosocial implications, and management strategies of vitiligo with particular emphasis on the coming role of JAK inhibitors and other upcoming therapies in contrast to a general overview.

## 2. Epidemiology [1,2,3]

Vitiligo is one of the most common pigmentary disorders whose global prevalence is generally estimated to range anywhere between 0.5% and 2% of the population (Ezzedine et al., 2021; Rodrigues et al., 2023). However, the actual prevalence could be quite different depending on the different research methods used, ethnic background considered, geographic area studied, and access to the regional medical systems. Epidemiological studies done in the last five years have sharpened our understanding of these patterns, pointing out critical demographic and regional differences.

### 2.1 Global Prevalence

Multiple meta-analyses and broad studies agreed that vitiligo affects around 0.5% to 2% of the global population (Ezzedine et al., 2021). Some examples are as follows:[1] A systematic review by Ezzedine et al. (2021) found pooled prevalence estimates ranging from 0.2% in Western Europe to 2%–3% in parts of India and Africa. Prevalence estimates suggest that as per the Global Burden of Disease Study 2019, there is worldwide a prevalence of about 0.76% cases of vitiligo, showing variation between regions (Rodrigues et al., 2023).

### 2.2 Regional Differences

India and South Asia:
India harbors some of the highest rates of prevalence in the world. Studies give rates to be in the range of 2%-3% with some subpopulation even higher (Chatterjee et al., 2023). The heavy cultural stigma against visible skin conditions leads to either underreporting or extensive delay in medical help seeking. [2]

- ✓ **Africa:**

Prevalence in African populations is estimated to fluctuate between 1% and 2%, although underdiagnosis in these populations may be suspected, given the poor dermatologic services in the rural areas (Rodrigues et al., 2023).

- ✓ **Europe and North America:**

Reports indicated a consistent prevalence ranging from 0.2% to 1.5%. The lower rates may reflect differential skin phototypes, genetic susceptibility, and possibly less stigmatization attached to skin disorders in some societies (Speeckaert et al., 2022).

- ✓ **Middle East and North Africa:**

Although estimates vary, they generally fall between 0.5% and 1.5%. Cultural factors influence reporting rates and healthcare-seeking behavior considerably (Ezzedine et al., 2021).

### 2.3 Gender Differences

While most studies find no marked sexual difference in overall prevalence, some studies suggest a slight female predominance. The reasons behind this discrepancy may include:

1. Greater concern by females about their skin may result in more requests for consultations.
2. Differences in autoimmunity prevalence among the genders.[3]

### 2.4 Racial and Ethnic Differences

The impact of vitiligo is felt by all ethnic groups, although individuals with dark skin are often more conscious of the cosmetic effects when there exists a marked contrast between affected and unaffected skin. This brings about enormous social consequences and reflects on health-seeking behaviour and quality of life assessment among patients.[3] But while there are some regional variations in prevalence, the risk of getting vitiligo appears to be comparably uniform among ethnicities after taking diagnostic and reporting biases into account (Harris, 2022).

## 3. Pathogenesis

### 3.1 Genetic Susceptibility

More than 50 genes have been associated with increased vitiligo susceptibility, including:

1. NLRP1 (inflammatory signaling)
2. PTPN22 (immune regulation)
3. TYR (tyrosinase, melanin synthesis)

### 3.2 Autoimmune Mechanisms

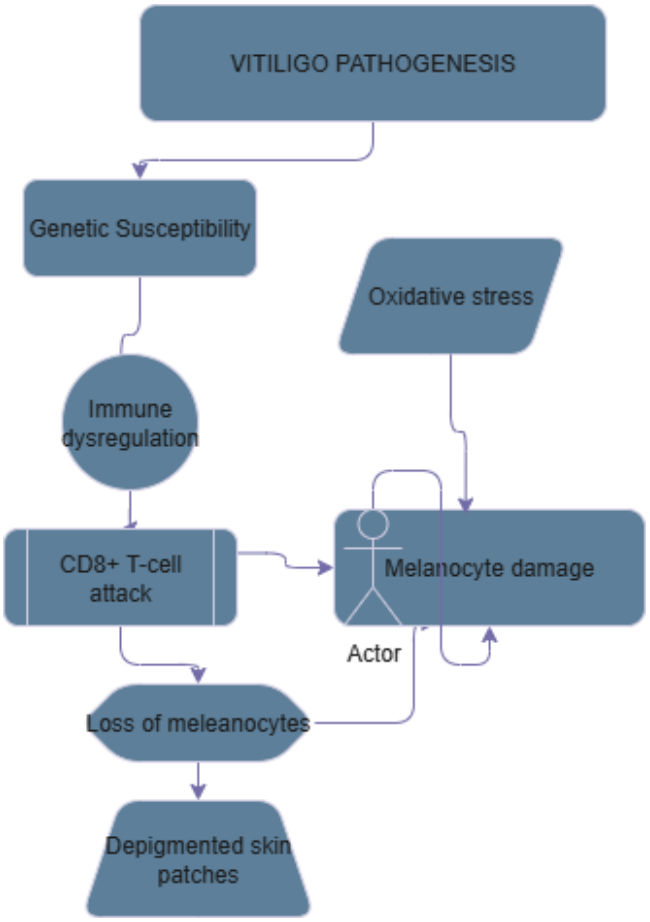
**Autoimmunity is considered central to vitiligo's pathogenesis:**

1. Cytotoxic **CD8+ T lymphocytes** infiltrate perilesional skin and destroy melanocytes.
2. **IFN-γ** and **CXCL10** are key cytokines driving melanocyte destruction.
3. Studies from 2021–2023 have demonstrated the involvement of immune checkpoints, such as the **PD-1/PD-L1 axis**, indicating potential targets for therapy (Rodrigues et al., 2023).

### 3.3 Oxidative Stress

**Oxidative stress plays a crucial role:**

1. Excess reactive oxygen species (ROS) damage melanocytes directly.
2. Mitochondrial dysfunction has been observed in affected skin.
3. Lower levels of antioxidants, such as catalase and superoxide dismutase, have been documented in patients (Ezzedine et al., 2021).




## 4. Clinical Features

Vitiligo presents with sharply defined, milky-white patches. Common sites include:

1. Face
2. Neck
3. Hands
4. Periorificial areas (mouth, eyes, genitals)

### 4.1 Types of Vitiligo

1. **Non-segmental vitiligo (NSV):** Symmetrical, progressive, most common form.
2. **Segmental vitiligo (SV):** Unilateral, often stabilizes after initial spread.
3. **Mixed vitiligo:** Features of both types.

## 5. Associated Disorders

Vitiligo frequently coexists with other autoimmune conditions, including:

1. Autoimmune thyroid disease
2. Type 1 diabetes mellitus
3. Alopecia areata
4. Pernicious anemia

## 6. Diagnostic Workup [456}

Vitiligo is predicated mostly on clinical diagnosis, but modern practice increasingly utilizes other tools to confirm diagnosis and assess disease activity, exclude differential entities, and individualize management strategies. Dermatologic imaging, histopathology, immunoassays, and newer molecular techniques have all advanced in the last five years to improve the diagnostic workup of vitiligo .A systematic evaluation yields proper definition, management, and teaching to the patients regarding differential diagnosis, considerably in discriminating between vitiligo and other hypopigmentary disorders.[4]

### 6.1 Clinical Evaluation

The cornerstone of diagnosis is a careful clinical examination:

- **History-taking should cover:**

1. Age at onset
2. Progression speed
3. Family history of vitiligo or other autoimmune diseases
4. Triggers (stress, trauma, sunburn, chemical exposures)
5. Symptoms of associated autoimmune conditions (e.g., thyroid dysfunction)

- **Physical examination focuses on:**

1. Distribution and pattern of lesions (segmental vs non-segmental)
2. Signs of activity (Koebner phenomenon)
3. Presence of leukotrichia (white hair within lesions)
4. Mucosal involvement

### 6.2 Laboratory Testing

1. Thyroid function tests (T3, T4, TSH)
2. Antithyroid antibodies (e.g., anti-TPO, anti-thyroglobulin)
3. Blood glucose or HbA1c (screening for diabetes)
4. Vitamin B12 levels (especially if other autoimmune diseases are suspected) [5]

### 6.3 Disease Activity Scoring

- **Vitiligo Disease Activity Score (VIDA):**

**A patient-reported scale assessing activity over the past 6–12 months:**

1. VIDA +4 = activity in past 6 weeks
2. VIDA 0 = stable disease for 1 year

- **Vitiligo Area Scoring Index (VASI):**

1. Estimates body surface area involved and degree of depigmentation
2. Increasingly used in clinical trials

- **Vitiligo Extent Score (VES):**

Simplified alternative for clinical practice and research [6]

## 7. Treatment

### 7.1 Topical Therapies

1. Corticosteroids: Effective but may cause skin atrophy.
2. Calcineurin inhibitors (e.g., tacrolimus): Useful for facial lesions and sensitive areas.

### 7.2 Phototherapy

1. Narrowband UVB (NB-UVB): The current gold standard for widespread vitiligo.
2. Excimer laser: Useful for localized lesions.
Long-term phototherapy is often required, and repigmentation varies.

### 7.3 Systemic Therapies

1. Short-term oral corticosteroids help halt rapid progression.
2. Other systemic immunosuppressants are reserved for severe cases.

### 7.4 JAK Inhibitors

**One of the most significant breakthroughs:**

1. Ruxolitinib cream received FDA approval in 2022 for non-segmental vitiligo (Rodrigues et al., 2023).
2. Oral JAK inhibitors (e.g. tofacitinib, baricitinib) are under investigation.
3. They block cytokine signaling pathways (e.g. IFN-γ) critical in vitiligo pathogenesis.
Clinical trials report promising results, with significant repigmentation in many patients.

### 7.5 Surgical Techniques

1. For stable, treatment-resistant vitiligo:
2. Mini-punch grafting
3. Suction blister grafting
4. Cellular grafting (e.g. melanocyte-keratinocyte transplantation)

### 7.6 Camouflage and Depigmentation

1. Cosmetic camouflage improves appearance and self-esteem.
2. Depigmentation therapy (e.g. monobenzone) is considered for extensive disease.

## 8. Recent Advances and Future Directions [7891011]

Some advances in understanding vitiligo and even its treatment have been very significant in recent years, and the condition has emerged from being poorly understood into a condition that now serves as a model for targeted dermatologic therapeutic regimens. These advances are in the areas of molecular immunology, targeted pharmacotherapy, regenerative medicine, and artificial intelligence (AI). Here, we summarize the most promising developments and ongoing research that may define the future of vitiligo management.[7]

### 8.1 Janus Kinase (JAK) Inhibitors

The paradigm in vitiligo therapy is the clinical application of JAK inhibitors that inhibit the IFN-γ–CXCL10 axis, which is an important pathway for melanocyte destruction. In 2022, after promising results from the TRuE-V1 and TRuE-V2 trials, showing significant facial and total body repigmentation (Rosmarin et al., 2022), ruxolitinib cream 1.5% became the first FDA-approved topical medication for non-segmental vitiligo.[8] Systemic JAK inhibitors such as tofacitinib and baricitinib are still being studied and preliminary trials show results, mainly in conjunction with phototherapy (Harris, 2022).

### 8.2 Targeted Cytokine Blockade and Immune Modulation

Besides inhibiting JAK, researchers investigate specific immune interventions to target specific mediating molecules in the cascade of vitiligo:[9] CXCL10 is an upregulated chemokine by IFN-γ that induces elevation in lesional skin and serum. Blocking this chemokine or its receptor CXCR3 appears to be therapeutically promising in preclinical models (Zhang et al., 2022).[10] Immune checkpoint proteins such as PD-1/PD-L1 are viewed as contributions to pathogenesis and potential therapeutic targets.

### 8.3 Regenerative and Cell-Based Therapies

NCES and MKTP have undergone improvements whereby studies reported landscapes of repigmentation from 60% to 80% in stable lesions. Tissue Engineering innovations are incorporated into the scaffold biomaterials/stem cells so that graft survival and pigmentation quality can be enhanced.[11]

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