

VEXAS Syndrome: A Comprehensive Review of Pathogenesis, Clinical Manifestations, and Therapeutic Strategies

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Abstract

Vacuoles, E1 enzyme, X-linked, Autoinflammatory, Somatic (VEXAS) syndrome is a recently characterized, adult-onset systemic hematoinflammatory disease driven by acquired somatic mutations in the *UBA1* gene.¹ This genetic aberration disrupts the cellular ubiquitylation cascade, precipitating profound innate immune hyperactivation and subsequent multiorgan inflammation.²

VEXAS syndrome demonstrates a highly heterogeneous clinical phenotype, predominantly presenting with recurrent fever, treatment-refractory neutrophilic dermatosis, relapsing polychondritis, pulmonary infiltrates, and systemic vasculitis.³ Concurrently, patients exhibit progressive hematologic anomalies, including macrocytic anemia, thrombocytopenia, characteristic myeloid and erythroid cytoplasmic vacuolization, and a substantial predisposition to myelodysplastic syndrome (MDS).⁴

Diagnosis relies on the identification of pathogenic *UBA1* variants, optimized by targeted next-generation sequencing (NGS), integrated with comprehensive bone marrow evaluations.⁵ Due to its complex pathophysiology, disease management requires a multidisciplinary strategy.

Current therapeutic paradigms focus on eradicating *UBA1*-mutated clones utilizing hypomethylating agents (e.g., azacitidine) or allogeneic hematopoietic stem cell transplantation (HSCT), alongside suppressing the autoinflammatory cascade via high-dose glucocorticoids and targeted biologicals, particularly Janus kinase (JAK) inhibitors.⁶ Considering the elevated mortality risk associated with VEXAS syndrome, early recognition, precise genetic screening, and individualized targeted therapies are imperative to optimize clinical outcomes and patient survival.⁷

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Introduction

Vacuoles, E1 enzyme, X-linked, Autoinflammatory, Somatic (VEXAS) syndrome constitutes a severe, adult-onset systemic inflammatory disorder initially characterized in 2020.¹ The pathogenesis is driven by somatic missense mutations in the *UBA1* gene—located on the X chromosome—specifically at the methionine-41 (p.Met41) codon within hematopoietic stem cells and the myeloid lineage.⁸ The *UBA1* gene encodes the ubiquitin-activating enzyme (E1), a critical component of the ubiquitin-proteasome system required for cellular homeostasis, protein degradation, and immune signaling.⁹ The p.Met41 mutation leads to the loss of the cytoplasmic UBA1b isoform and prompts the expression of a catalytically impaired UBA1c isoform.¹ This perturbation compromises cellular ubiquitylation, inducing profound cellular stress and hyperactivation of innate immune pathways. Consequently, patients manifest a complex, life-threatening overlap of systemic autoinflammation and progressive hematologic dyscrasias.

Epidemiology

VEXAS syndrome predominantly affects males older than 50 years of age due to the X-linked nature of the *UBA1* gene. Females are largely protected by the presence of a second, unmutated *UBA1* allele, though rare manifestations occur in individuals with monosomy X.¹⁰ Genomic screening of large clinical cohorts estimates the prevalence of pathogenic *UBA1* variants to be approximately 1 in 13,591 individuals in the general population.⁸ When demographically stratified, the prevalence significantly increases to 1 in 4,000 among men older than 50 years, underscoring that VEXAS is likely an underdiagnosed entity.

Pathogenesis of VEXAS Syndrome

VEXAS syndrome is an acquired, adult-onset systemic autoinflammatory and hematologic disorder. The pathogenesis is fundamentally driven by somatic missense mutations in the *UBA1* gene, located on the X chromosome (Xp11.23). These acquired mutations are strictly lineage-restricted to hematopoietic stem cells and the myeloid compartment, notably sparing lymphocytes and fibroblasts.¹¹

Under normal physiologic conditions, the *UBA1* gene encodes the ubiquitin-activating enzyme (E1), which serves as the initiating catalyst in the ubiquitin-proteasome system (UPS). The cellular ubiquitylation cascade involves a sequential interaction among ubiquitin-activating (E1), ubiquitin-conjugating (E2), and ubiquitin-ligating (E3) enzymes.² This post-translational modification is essential for maintaining cellular homeostasis, regulating the degradation of misfolded proteins, controlling cell cycle progression, and modulating immune signaling pathways. The *UBA1* gene generates two primary isoforms: UBA1a, a long form localized in the nucleus that is initiated at the methionine-1 (p.Met1) codon, and UBA1b, a short form localized in the cytoplasm that is initiated at the methionine-41 (p.Met41) codon. The functional role of the E1 enzyme within the ubiquitylation pathway is illustrated in Figure 1.

In VEXAS syndrome, the canonical genetic aberrations are somatic mutations predominantly occurring at the p.Met41 codon within exon 3 of the *UBA1* gene (most commonly resulting in p.Met41Thr, p.Met41Val, or p.Met41Leu substitutions).¹² This specific mutation severely disrupts the translation of the cytoplasmic UBA1b isoform. Consequently, cells aberrantly express a truncated, catalytically impaired isoform known as UBA1c. The profound loss of functional cytoplasmic E1 enzyme activity halts the normal ubiquitylation cascade, leading to an intracellular accumulation of misfolded proteins and the induction of severe cellular stress.

This ensuing cellular stress acts as a potent trigger for the hyperactivation of innate immune pathways within the affected myeloid cells (e.g., neutrophils and monocytes). The hyperactivated innate

immune system subsequently drives a massive, dysregulated overproduction of pro-inflammatory cytokines, prominently including tumor necrosis factor (TNF), interleukin-6 (IL-6), interleukin-8 (IL-8), and interferon-gamma (IFN- γ).¹³ Ultimately, this profound systemic inflammatory cascade, combined with defective ubiquitylation and cellular apoptosis, manifests clinically as the severe, treatment-refractory multiorgan autoinflammation and progressive bone marrow dysplasia characteristic of VEXAS syndrome

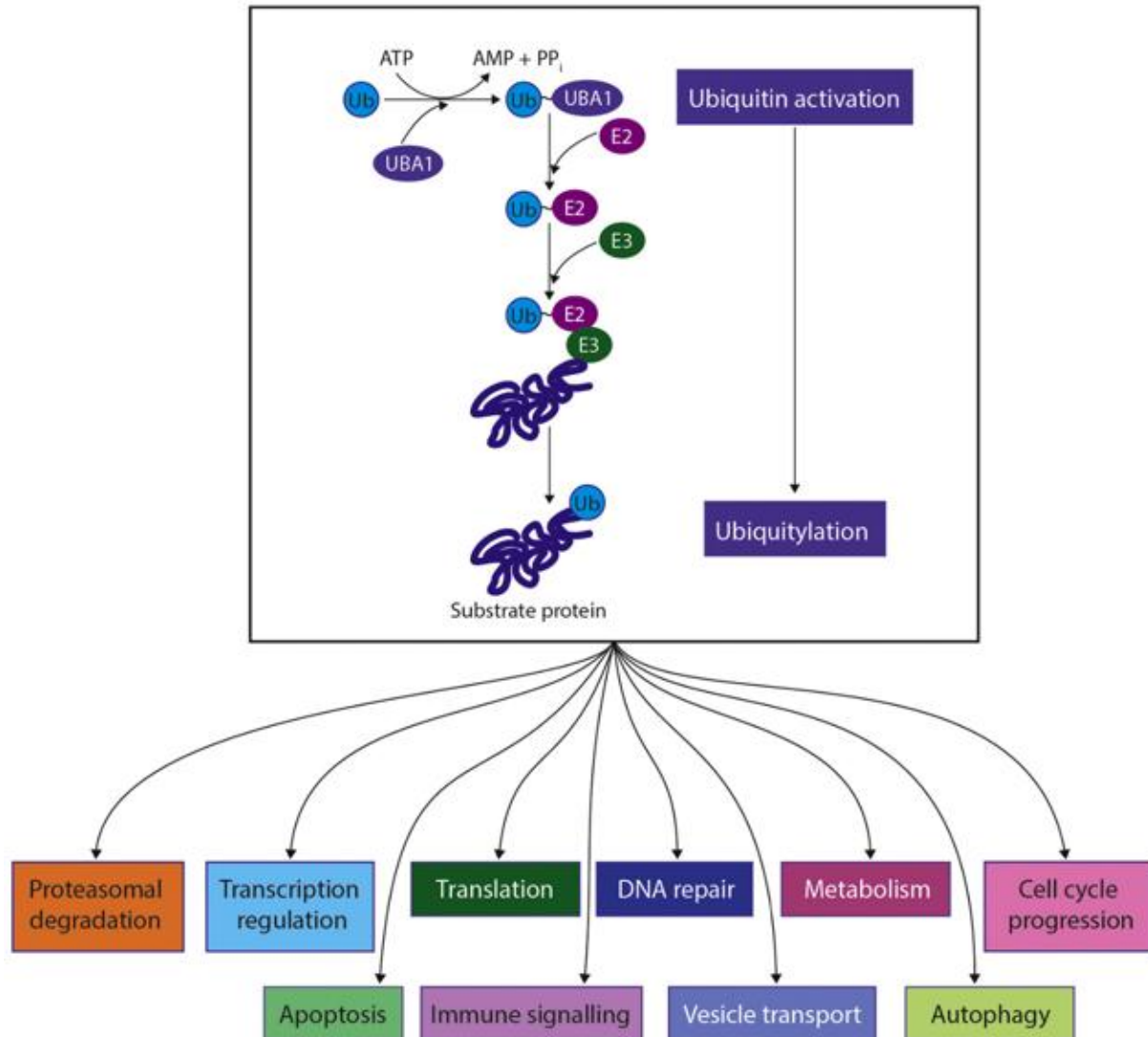


Figure 1. Schematic representation of the E1 ubiquitin-activating function of UBA1, the ubiquitylation pathway and downstream UBA1/ubiquitylation-dependent cellular processes.¹⁴

The ubiquitylation process is an ATP-dependent pathway that involves the sequential interaction among E1 (ubiquitin-activating), E2 (ubiquitin-conjugating), and E3 (ubiquitin-ligase) enzymes. *UBA1* acts as the primary E1 ubiquitin-activating enzyme in mammalian cells. It is essential for regulating various fundamental cellular processes, including the ubiquitin-proteasome system (UPS), transcription regulation, DNA repair pathways, cell cycle progression, translation, metabolism, immune signaling, selective autophagy, vesicle transport, apoptosis, and the degradation of misfolded proteins. ATP, Adenosine

triphosphate; AMP, Adenosine monophosphate; PPI, Pyrophosphate anion; Ub, Ubiquitin; UBA1, Ubiquitin-like modifier activating enzyme 1. (Adapted from Lambert-Smith, Isabella A et al.)

Clinical Manifestations of VEXAS Syndrome

VEXAS syndrome is an adult-onset autoinflammatory disorder defined by diverse rheumatologic, dermatologic, and hematologic manifestations. Given its complex clinical spectrum, which spans multiple subspecialties, diagnosis requires a high index of suspicion. The primary clinical indications for somatic UBA1 variant testing are summarized in Table 1.

Inflammatory Features

Systemic inflammation in VEXAS syndrome is ubiquitous and multiorgan in nature.

- **Constitutional Symptoms:** Recurrent, non-infectious fever is a prominent initial presentation, occurring in 74% to 100% of patients.³ These febrile episodes are frequently accompanied by profound fatigue, anorexia, and significant weight loss.
- **Dermatologic Manifestations:** Cutaneous involvement is highly prevalent, observed in approximately 88% of cases.¹⁵ Neutrophilic dermatosis serves as the hallmark histologic finding. While these lesions may clinically mimic Sweet's syndrome, VEXAS-associated dermatoses are markedly relapsing, treatment-refractory, and often mandate moderate-to-high-dose glucocorticoid therapy.¹⁵ Additional cutaneous findings include small-vessel leukocytoclastic vasculitis, tender pressure plaques, erythema nodosum, and severe injection-site reactions.
- **Otorhinolaryngologic Features:** Auricular and nasal chondritis are highly prevalent, affecting 40% to 60% of patients.³ Notably, over 50% of patients with VEXAS initially meet the diagnostic criteria for relapsing polychondritis (RP).¹⁶ The "VEXAS-RP" variant correlates with higher inflammatory markers, characteristic cytopenias, and an inferior survival rate compared to idiopathic RP.¹⁶
- **Pulmonary Involvement:** Respiratory complications are widespread, with 45% to 95% of patients experiencing pulmonary manifestations.³ These commonly present radiographically and clinically as neutrophilic alveolitis, interstitial infiltrates (predominantly ground-glass opacities), and pleural effusions.
- **Ocular and Vascular Disease:** Ophthalmic manifestations include periorbital edema—frequently misdiagnosed as preseptal cellulitis—uveitis, and scleritis. Furthermore, systemic vasculitis is a recognized complication, primarily affecting small-to-medium-sized vessels.¹

Hematologic Features

Progressive bone marrow failure and hematologic dyscrasias are intrinsic defining components of the disease.

- **Cytopenias:** Macrocytic anemia (mean corpuscular volume > 100 fL) is nearly universal, independent of vitamin B12 or folate deficiency.⁵ This is frequently accompanied by moderate thrombocytopenia and profound monocytopenia, which are highly characteristic of severe autoinflammatory syndromes like VEXAS.
- **Vacuolization and Malignancy:** A critical diagnostic hallmark is the visualization of distinct cytoplasmic vacuoles within early myeloid and erythroid precursor cells upon bone marrow aspiration.¹ While this vacuolization is not exclusively specific to the disorder, its widespread

presence in the context of systemic inflammation is strongly indicative of VEXAS. In addition, patients are at a substantial risk of developing hematologic malignancies, with MDS observed in up to 50% of cases.⁵

- **Thrombosis:** Unprovoked venous and arterial thromboembolic events are major complications, affecting approximately 40% to 50% of patients. These events typically occur within the first two years of inflammatory symptom onset and are likely driven by extensive endothelial disruption, dysregulated ubiquitylation, and profound systemic inflammation.¹⁷

Table 1. When to consider testing for VEXAS.¹⁸

When to consider testing for somatic UBA1 variant	
Pre-test probability is higher for males compared to females, for patients older than 50 years, and when acute phase reactants are elevated	
Typical disease features	
Inflammatory	Hematologic
• Fever of unknown origin • Auricular and/or nasal chondritis • Neutrophilic dermatosis or urticaria-like lesions (Bx) • Leukocytoclastic vasculitis (LCV) or leukocytoclasia (Bx) • Non-infectious periorbital swelling • Recurrent, non-infectious inflammatory eye disease • Non-infectious ground glass or nodular pulmonary infiltrate • Unprovoked or recurrent thromboembolic disease • Steroid dependency	• Vacuoles in myeloid or erythroid precursor cells on marrow aspirate • Macrocytosis or macrocytic anemia • MDS or myelodysplasia • Thrombocytopenia • Monocytopenia • Lymphopenia
Less common disease features	
• Erythema nodosum (Bx) • Recurrent urticaria / urticarial plaque • Injection site reaction to anakinra • Inflammatory arthritis • Vasculitis (any size), relapsing / recurrent or with lack of response to SOC • Pericarditis / Myocarditis	• Exudative pleural or pericardial effusion • Testicular inflammation • Sensorineural hearing loss • Atypical or opportunistic infection including nontuberculous mycobacterial infection • Nephrotic syndrome with renal amyloidosis (Bx) • Interstitial nephritis (Bx)

A list of typical and less common disease features of VEXAS are presented to help guide clinicians regarding when to consider testing for acquired mutations in UBA1. Bx, biopsy confirmation required; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; LCV, leukocytoclastic vasculitis; MCV, mean corpuscular volume; MDS, myelodysplastic syndrome; SOC, standard of care; VEXAS, vacuoles E1 enzyme X-linked autoinflammatory somatic syndrome.

Investigation

Laboratory evaluations typically reveal persistently elevated acute-phase reactants (Erythrocyte Sedimentation Rate [ESR] and C-Reactive Protein [CRP]). A peripheral blood smear conventionally demonstrates macrocytic anemia, monocytopenia, and lymphopenia. Bone marrow aspiration and biopsy

frequently identify hypercellularity, granulocytic hyperplasia with an elevated myeloid-to-erythroid ratio, and the characteristic cytoplasmic vacuolization within precursor cells.¹⁹ Furthermore, flow cytometric analysis routinely indicates an absence of precursor B cells.

VEXAS diagnosis

A collaborative multidisciplinary approach is pivotal for an accurate diagnosis, integrating clinical phenotypes with hematologic indices and subsequent genetic confirmation. The diagnostic workup and recommended indications for somatic *UBA1* genetic testing are summarized in the algorithmic approach presented in Figure 3.¹⁸

- **UBA1 screening modalities consensus statements:** The majority of typical VEXAS presentations are attributed to missense or splice site mutations at exon 3 of the *UBA1* gene.⁴ A variety of sequencing methodologies are clinically validated for diagnosis, contingent upon institutional resources and expertise.
- **Genetic testing for VEXAS:** Definitive diagnosis requires identifying a pathogenic somatic mutation in *UBA1*. Next-generation sequencing (NGS) is the preferred diagnostic modality, providing superior sensitivity for detecting low-level somatic variants (Variant Allele Fraction [VAF] >1%) and comprehensive coverage of all coding or splice site regions.⁴ Targeted exon 3 testing via Sanger sequencing remains a viable alternative but harbors limitations, specifically the potential to miss low VAF mutations or variants localized outside exon 3. DNA is reliably extracted from either peripheral blood or bone marrow aspirates. Active therapeutic interventions, notably hypomethylating agents, may artificially reduce mutational burdens, necessitating clinical caution during interpretation.
- **Diagnosis of MDS in patients with VEXAS consensus statements:** A comprehensive bone marrow examination is strongly recommended in VEXAS patients exhibiting cytopenias to systematically exclude concomitant hematologic neoplasms.¹⁹ Concurrent karyotyping and NGS for co-occurring somatic mutations are highly advised. Interpreting bone marrow dysplasia presents a significant diagnostic challenge; VEXAS routinely induces morphologic atypia (e.g., vacuolization, hypercellularity) without strictly fulfilling the WHO or ICC 2022 diagnostic criteria for myelodysplastic syndrome (MDS).¹⁹ Consensus dictates that an overlapping MDS diagnosis necessitates overt dysplasia beyond vacuolization, elevated blast counts, or definitive MDS-associated cytogenetic abnormalities. The somatic clonal landscape in VEXAS is frequently dominated by coincident *DNMT3A* and *TET2* mutations.²⁰

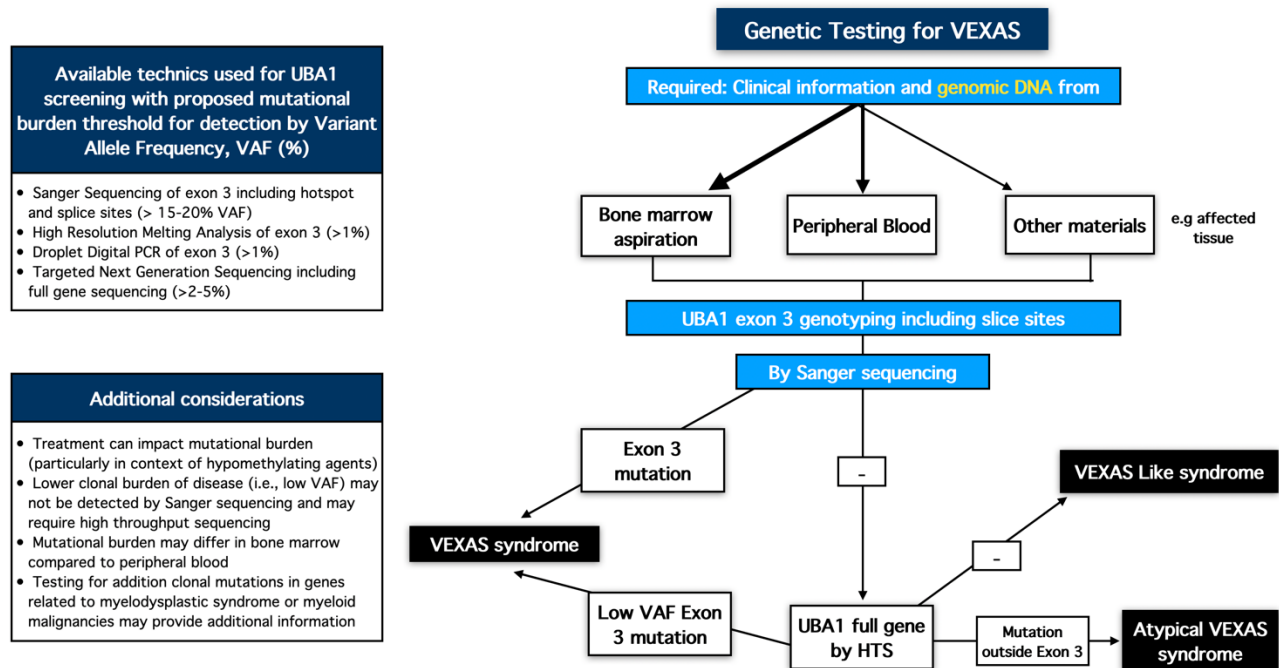


Figure 2. Genetic testing strategies for VEXAS.¹⁸ A practical approach to genetic testing is shown. Testing can be performed on bone marrow aspirate or peripheral blood. In rare instances when a bone marrow or peripheral blood sample is not available, testing could be performed on affected tissue. Different genetic testing strategies have different sensitivities to detect mutational burden of disease. Choice of genetic testing may be guided by access to resources. HTS, high throughput sequencing; PCR, polymerase chain reaction; VEXAS, vacuoles E1 enzyme X-linked autoinflammatory somatic syndrome.

Treatment of VEXAS Syndrome

Currently, there is no universally standardized treatment protocol for VEXAS syndrome. Management necessitates a highly individualized, multidisciplinary approach. Therapeutic strategies fundamentally bifurcate into two distinct paradigms: targeting and eradicating the underlying *UBA1*-mutated clonal cells, and blocking the downstream autoinflammatory cascade. The current therapeutic landscape for VEXAS syndrome, including supportive care, immunosuppressive strategies, and hematopoietic stem cell transplantation, is summarized in the management algorithm in Figure 4.

1. Targeting and Eradicating *UBA1* Mutated Cells

1.1 Hypomethylating agents (e.g., azacitidine and decitabine): Hypomethylating agents (HMAs), predominantly azacitidine, function as DNA methyltransferase inhibitors and exhibit both disease-modifying and immunomodulatory properties.²¹ Clinical evidence indicates that azacitidine effectively reduces the *UBA1* mutational burden, particularly in patients harboring concurrent *DNMT3A* mutations or those with coexisting MDS.²¹ Sustained administration (typically requiring 4 to 6 cycles) facilitates significant clinical responses and substantial glucocorticoid tapering, presenting a viable clone-directed therapy.

1.2 Allogeneic hematopoietic stem cell transplantation (AHSCT): AHSCT remains the sole definitive, curative intervention for VEXAS syndrome, as it completely replaces the aberrant hematopoietic stem cell compartment.⁷ Despite its efficacy in achieving molecular and clinical remission, AHSCT is

associated with substantial procedure-related morbidity and mortality, including severe infections and graft-versus-host disease (GVHD).⁷ Consequently, it is strictly reserved for carefully selected candidates—typically patients younger than 75 years of age—who present with severe, progressive bone marrow failure (e.g., transfusion-dependent cytopenias), MDS transformation, or life-threatening, glucocorticoid-refractory autoinflammation.

2. Targeting and Blocking the Inflammatory Cascade

- 2.1 Glucocorticoids** Glucocorticoids remain the fundamental initial therapy to suppress acute systemic inflammation.²² Moderate to high daily doses (e.g., >15–20 mg/day of prednisone equivalents) are routinely required to establish clinical control. However, VEXAS patients are universally steroid-dependent; tapering below 15 mg/day almost invariably precipitates rapid disease relapse.¹⁸
- 2.2 Traditional disease-modifying anti-rheumatic drugs (DMARDs):** Conventional synthetic DMARDs (e.g., methotrexate, mycophenolate mofetil) demonstrate negligible steroid-sparing efficacy.²² Crucially, **azathioprine must be strictly avoided, as it has been implicated in promoting myeloid clonal transformation and exacerbating hematologic malignancies.**
- 2.3 JAK inhibitors (e.g., ruxolitinib and baricitinib):** JAK inhibitors have emerged as the most efficacious targeted anti-inflammatory agents in VEXAS by broadly suppressing disease-associated pro-inflammatory cytokines.²² Retrospective cohorts demonstrate that ruxolitinib possesses superior clinical efficacy compared to tofacitinib or upadacitinib, significantly resolving cutaneous manifestations, normalizing CRP, and enabling substantial glucocorticoid tapering. Vigilant monitoring for worsening cytopenias, viral infections, and thrombotic events is imperative.¹⁸
- 2.4 Interleukin-6 (IL-6) inhibitors (e.g., tocilizumab):** Tocilizumab, an IL-6 receptor antagonist, provides moderate inflammatory control and steroid-sparing capabilities in a subset of patients.²² However, complete remission rates are low (~20%), and its utilization requires extreme caution due to a heightened risk of severe intestinal perforation, particularly in patients with baseline gastrointestinal manifestations.
- 2.5 Interleukin-1 (IL-1) inhibitors (e.g., anakinra and canakinumab):** The therapeutic efficacy of IL-1 inhibitors is highly inconsistent.²² While transient biochemical responses have been noted, the clinical utility of anakinra is frequently negated by the development of severe, treatment-limiting cutaneous injection-site reactions, often necessitating therapy cessation.
- 2.6 Others** Alternative immunosuppressants, including calcineurin inhibitors (cyclosporine, tacrolimus) and B-cell depleting therapies (rituximab), yield minimal or transient clinical benefits and are not recommended as primary therapies.²²

3. Supportive Treatment¹⁸

Comprehensive supportive care is paramount for mitigating disease morbidity and treatment-related toxicities.

- 3.1 Anemia:** Severe macrocytic anemia and concurrent MDS may necessitate routine packed red blood cell transfusions or the administration of Erythropoiesis-Stimulating Agents (ESA).
- 3.2 Neutropenia:** Granulocyte-colony stimulating factor is indicated for profound neutropenia. Aggressive antimicrobial prophylaxis against *Pneumocystis jirovecii* pneumonia and viral reactivation (e.g., Herpes Zoster) is highly recommended for all patients on substantial immunosuppression.
- 3.3 Thrombocytopenia:** Thrombopoietin receptor agonists, such as eltrombopag, may be cautiously considered to stimulate megakaryopoiesis in profound thrombocytopenia.
- 3.4 Glycemic Monitoring:** Stringent blood glucose monitoring is mandatory to detect and manage glucocorticoid-induced diabetes mellitus.

sequencing.⁴ While high-dose glucocorticoids serve as the initial cornerstone for suppressing acute inflammation, strategic transitions to targeted interventions—such as JAK inhibitors, hypomethylating agents, or AHSCT—are crucial for minimizing systemic toxicity and addressing the underlying clonal expansion.²² Future prospective, randomized clinical trials are urgently required to formulate definitive, evidence-based therapeutic algorithms for this formidable syndrome

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