

American College of Rheumatology Guidance Statement for Diagnosis and Management of VEXAS Developed by the International VEXAS Working Group Expert Panel

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Objective. Vacuoles E1 enzyme X-linked autoinflammatory somatic syndrome (VEXAS) is a recently identified rare genetic disorder associated with somatic mutations in the *UBA1* gene. VEXAS presents with a combination of inflammatory and hematologic manifestations, leading to increased morbidity and mortality.

Methods. Given the variability in disease presentation and the limited number of studies to date, no clinical documents currently exist to provide guidance to health care providers about the management of VEXAS. To address this gap, we formed an international multidisciplinary panel of VEXAS experts.

Results. Through formalized meetings and a voting process, the group developed consensus clinical guidance considerations for the management of VEXAS. These considerations offer practical advice on several key topics: (1) clinical features of VEXAS, (2) *UBA1* screening methods, (3) the diagnosis of myelodysplastic syndromes (MDSs) in patients with VEXAS, and (4) prognosis and management. The aim is to provide expert guidance on which patients to test, how to test for VEXAS, how to approach MDS in the context of VEXAS, and considerations for management.

Conclusion. This work marks the first formal international consensus guidance for VEXAS and is intended to be used as a resource for clinicians seeking to understand the disease and its management.

INTRODUCTION

Vacuoles E1 X-linked autoinflammatory somatic syndrome (VEXAS) is a newly recognized rare disease associated with

pathogenic, somatic mutations in the *UBA1* gene, resulting in a combination of inflammatory and hematologic manifestations.¹ Since its first description in 2020, more than 450 cases have been documented, with clinical profiling showing heterogeneous manifestations.

[Correction added on 11 March 2026, after first online publication: The last name of Mael Heiblig was initially misspelled and has been corrected in this version.]

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The prevalence of VEXAS is estimated to be nearly one million individuals worldwide, and *UBA1* pathogenic variants are present in 1 in 13,591 individuals, although comprehensive global data are still lacking.² VEXAS presents a significant diagnostic challenge, as its clinical and laboratory features often mimic those of other established rheumatologic and hematologic diseases. Genetic identification of patients with VEXAS is crucial to guide appropriate management and promote optimal outcomes. Because of the broad spectrum of nonspecific symptoms and limited awareness of the disease, it is likely that many patients remain undiagnosed or misdiagnosed.

This guidance summary was developed by a multidisciplinary panel of experts, including rheumatologists, hematologists, dermatologists, internists, immunologists, pathologists, geneticists, and infectious disease specialists, selected for their experience with VEXAS. The primary purpose of this document is to assist health care providers in identifying the clinical manifestations of VEXAS, promote early confirmatory molecular diagnosis, and provide

evidence-based management recommendations. The ultimate goal is to reduce morbidity and mortality associated with this disease. Given the recent identification of VEXAS and the lack of extensive prospective and randomized studies, each statement is primarily based on expert consensus and currently available literature.

The guidance summary presented here was developed using systematic voting and iterative modifications and by including a diverse group of clinicians. The goal is to provide succinct guidance for physicians treating patients with suspected or confirmed VEXAS and support this guidance with available evidence.

METHODS

Composition of the panel and item generation

Consensus guidance was developed by a multidisciplinary expert panel composed of 57 internationally recognized members

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Author disclosures are available at <https://onlinelibrary.wiley.com/doi/10.1002/art.43287>.

[Correction added on 21 October 2025, after first online publication: the names of Arsene Mekinian and Sophie Georgin-Lavaille have been corrected.]

[Correction added on 27 August 2025, after first online publication: Affiliation number 41 was added to Francesco Muratore and Carlo Salvarani.]

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Submitted for publication December 13, 2024; accepted in revised form April 25, 2025.

from 18 countries including Armenia, Australia, Belgium, Canada, Czech Republic, France, Germany, Italy, Japan, The Netherlands, Poland, Portugal, Romania, Spain, Switzerland, Tunisia, the United Kingdom, and the United States. Each panelist was selected based on clinical expertise in the treatment of patients with VEXAS, with representation from dermatology, genetics, hematology, immunology, internal medicine, rheumatology, infectious diseases, critical care, and pathology specialists. Patient representatives were not included in these efforts.

To ensure comprehensive coverage of the topic, the panel conducted a series of structured virtual meetings. During these discussions, the panel identified and prioritized the critical topics that needed to be addressed. The identified items were organized into four major groups, each reflecting a core aspect of VEXAS.

- Group 1: Clinical and laboratory features of VEXAS. This category focused on identifying the clinical and laboratory features that should prompt consideration of genetic testing for VEXAS.
- Group 2: *UBA1* screening. This section addressed the modalities and best practices for screening *UBA1* mutations, which are pivotal for the diagnosis of VEXAS.
- Group 3: Diagnosis of myelodysplastic syndrome (MDS) in patients with VEXAS. This group explored the intersection of VEXAS with MDS, providing guidance for accurate diagnosis and differentiation.
- Group 4: Outcome, prognostic factors, and management. This category covered the management strategies for VEXAS, including prognostic factors influencing patient outcomes.

Each category was assigned to a subgroup of experts who were responsible for conducting a detailed review of the relevant literature and generating a draft document (please see Appendix A for members of each group). The subgroups worked independently, holding multiple virtual meetings to discuss their findings, synthesize data, and formulate initial statements. A comprehensive virtual and in-person meeting was convened, bringing together all panel members to discuss the proposed items from each group. The panel engaged in an in-depth review and debate of each item, followed by an electronic voting process to determine whether the item should be included in the final statements. This rigorous process ensured that the statements were built on a foundation of consensus and expert validation, resulting in the generation of the actual initial guidance document.

Literature review and level of evidence

The foundation of the statements was an extensive review of the current literature related to VEXAS from January 2020 to August 2024. Each subgroup undertook a thorough literature search using PubMed and Medline, focusing on articles published in English and abstracts from leading international rheumatology

and hematology conferences. Given that VEXAS is a newly discovered disease with limited evidence, a formal systematic review was not performed by each subgroup. For cases in which prospective data were unavailable, the statements were based on the best available evidence and expert opinion. All statements are conditional, due in part to a lack of randomized controlled trials in VEXAS. Additionally, the Grading of Recommendations Assessment, Development, and Evaluation methodology was used to rate the quality of evidence supporting each statement.^{3,4}

Supportive references are provided for each consensus statement but are nonexhaustive and meant to highlight studies with more participants to provide stronger evidence.

Final item generation and voting

The process of finalizing the statements took place at an international, two-day VEXAS workshop held in Paris in May 2024, where the majority of the panel gathered to review, discuss, and refine the proposed items. This workshop provided a critical opportunity for face-to-face deliberation, allowing the panelists to address any outstanding issues, reconcile differing opinions, and achieve a stronger consensus. Following the workshop, an electronic tool was used to conduct a final consensus vote on all items. This tool allowed panel members to provide their feedback anonymously, ensuring that the final statements reflected the true consensus of the group. There was a single round of voting in which participants were asked to vote “yes” or “no” on their agreement to each statement and to provide reasoning in cases of disagreement. Consensus for item inclusion in the statements was defined by a threshold of 80% agreement among the panelists. All proposed statements achieved consensus, and all final voting results are included with each statement (Table 1). Consensus statements are bulleted within the text with expert panel voting results in parentheses, followed by an explanation and supporting data.

RESULTS/RECOMMENDATIONS

The following results summarize the agreed-upon clinical indicators, diagnostic strategies, and therapeutic recommendations developed through structured expert review and formal consensus statements for the four key domains.

Clinical features of VEXAS consensus statements (Figure 1)

VEXAS is a hematoinflammatory disease characterized by a spectrum of rheumatologic, dermatologic, and hematologic features.

Persistently elevated markers of inflammation with a combination of skin, ocular, lung, or cartilage manifestations and/or cytopenia are suggestive of VEXAS.

Table 1. Statements and level of agreements of different guidance statements of groups 1 through 4*

Statements	Agree, n (%)	Disagree, n (%)	Total, n (%)
Group 1: clinical and laboratory features			
VEXAS is a hematoinflammatory disease characterized by a spectrum of rheumatologic, dermatologic, and hematologic features	52 (98)	1 (2)	53 (100)
Persistently elevated markers of inflammation with a combination of skin, ocular, lung, or cartilage manifestations and/or cytopenia are suggestive of VEXAS	50 (94)	3 (6)	53 (100)
Macrocytic anemia is a common hematologic abnormality in VEXAS but may not always be present	52 (98)	1 (2)	53 (100)
Vacuoles present in early erythroid or myeloid precursors from bone marrow aspirates are suggestive of, but not diagnostic for, VEXAS	53 (100)	0 (0)	53 (100)
VEXAS is not a heritable disease	53 (100)	0 (0)	53 (100)
Most cases of VEXAS have been reported in men older than 50 years	52 (98)	1 (2)	53 (100)
Group 2: <i>UBA1</i> mutation screening			
The majority of patients with typical VEXAS have missense or splice site mutations at exon 3 of <i>UBA1</i>	52 (100)	0 (0)	52 (98)
A variety of sequencing methods can be used to diagnose VEXAS depending on resources and expertise	51 (98)	1 (2)	52 (98)
NGS has increased sensitivity to detect low-level somatic variants with coverage of all coding or splice site regions	50 (96)	2 (4)	52 (98)
Targeted testing for exon 3 variants can be used as an alternative to NGS with the understanding that such modalities may miss somatic variants with low VAF (Sanger sequencing) or variants outside of exon 3 (Sanger sequencing and ddPCR)	50 (96)	2 (4)	52 (98)
Active treatment may affect the accuracy of genetic testing by decreasing mutation level	45 (87)	7 (13)	52 (98)
Somatic mutations defining VEXAS are detected in peripheral blood or bone marrow-derived DNA	51 (98)	1 (2)	52 (98)
If clinical suspicion is high and genetic testing for mutations in <i>UBA1</i> at exon 3 is negative on the peripheral blood, clinicians should ensure that testing covers the complete gene and consider testing a bone marrow sample	47 (90)	5 (10)	52 (98)
Group 3: diagnosis of MDS in patients with VEXAS			
Bone marrow examination is recommended in patients with VEXAS with associated cytopenia to exclude an associated hematologic neoplasm	51 (98)	1 (2)	52 (98)
Karyotype and NGS for coexisting somatic mutations should be performed with bone marrow examination	50 (96)	2 (4)	52 (98)
Interpretation of bone marrow is challenging in VEXAS due to the frequent presence of signs of dysplasia, without meeting existing criteria for myelodysplastic syndrome diagnosis based on the WHO and ICC 2022 classifications	50 (96)	2 (4)	52 (98)
The somatic clonal landscape in VEXAS is dominated by mutations in <i>DNMT3A</i> and <i>TET2</i> , generally without other driver mutations	49 (94)	3 (6)	52 (98)
Group 4: outcomes, prognostic factors, and management			
Patients with VEXAS should be managed by a multidisciplinary team with consideration of referral to an expert center when available evidence	52 (100)	0 (0)	52 (98)
Disease activity is defined by inflammation or worsening bone marrow failure	48 (92)	4 (8)	52 (98)
The goals of treatment include controlling inflammation; preventing and treating bone marrow failure; preventing and treating secondary medical complications arising from implemented treatments; and improving quality of life	50 (96)	2 (4)	52 (98)
Infections, thromboembolic disease, and treatment-related comorbidities are common in VEXAS and can mimic disease activity	49 (94)	3 (6)	52 (98)
Flare of disease can be defined as recurrence of clinical or laboratory signs or symptoms of VEXAS	47 (90)	5 (10)	52 (98)
Glucocorticoids are usually needed to control inflammation in patients with VEXAS and should be tapered slowly to achieve the minimal dose required to control disease activity	52 (100)	0 (0)	52 (98)
Medications that target inflammatory pathways (eg, JAK inhibitors, IL-6 inhibitors) are more effective than conventional DMARDs (eg, methotrexate, azathioprine) or B cell-directed therapies (eg, rituximab)	48 (92)	4 (8)	52 (98)
Medications that reduce or eliminate the clonal burden of disease (eg, azacytidine) can be an effective treatment in some patients with VEXAS syndrome	51 (98)	1 (2)	52 (98)
Allogeneic hematopoietic stem cell transplantation may be a curative treatment but should be reserved for select patients with VEXAS after a careful hematologic evaluation	50 (96)	2 (4)	52 (98)
Prophylaxis against opportunistic infections, prevention of thromboembolic disease, and minimization of side effects related to chronic glucocorticoid therapy should be considered in all patients with VEXAS	51 (98)	1 (2)	52 (98)
Future clinical trials will be needed to identify the best treatment for patients with VEXAS	52 (100)	0 (0)	52 (98)

* ddPCR, digital droplet polymerase chain reaction; DMARD, disease-modifying antirheumatic drug; ICC, International Consensus Classification; IL-6, interleukin-6; MDS, myelodysplastic syndrome; NGS, next-generation sequencing; WHO, World Health Organization; VAF, variant allele fraction; VEXAS, vacuoles E1 enzyme X-linked autoinflammatory somatic syndrome.

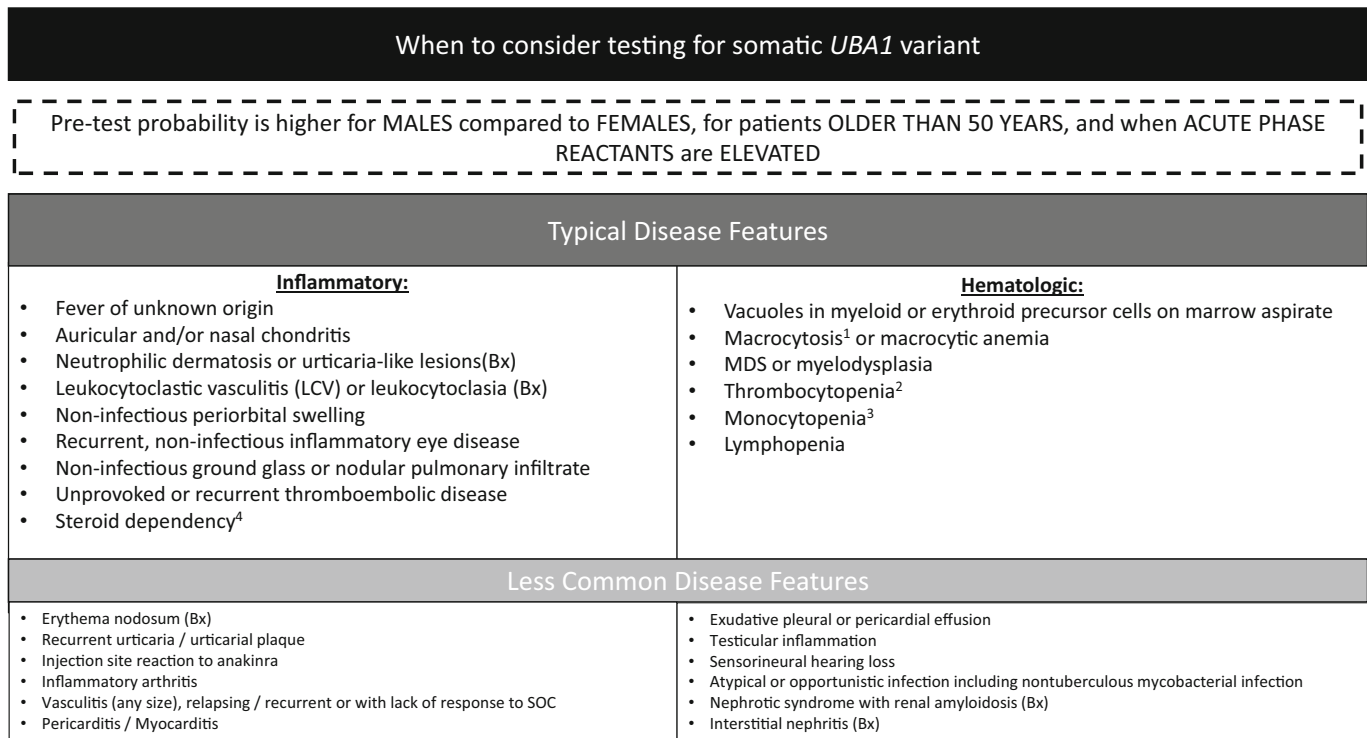


Figure 1. When to consider testing for VEXAS. A list of typical and less common disease features of VEXAS are presented to help guide clinicians regarding when to consider testing for acquired mutations in *UBA1*. Bx, biopsy confirmation required; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; LCV, leukocytoclastic vasculitis; MCV, mean corpuscular volume; MDS, myelodysplastic syndrome; SOC, standard of care; VEXAS, vacuoles E1 enzyme X-linked autoinflammatory somatic syndrome.

Inflammatory features. Inflammatory manifestations are ubiquitous in patients with VEXAS, and elevated acute phase reactants are present at some point in the majority of patients.^{1,5} The spectrum of clinical features of VEXAS is wide and highly variable and overlaps several domains and organ systems. Although rare, mild disease forms can occur with minimal to no inflammation (sometimes detectable only in laboratory results).

It is crucial for clinicians and other health providers to be familiar with the most common features present in confirmed patients with VEXAS, including recurrent noninfectious fever (75–100%); various skin involvements (erythema nodosum, maculopapular lesions, panniculitis, urticarial, and possibly others; 85%); lung involvement (interstitial infiltrates, pleuropericarditis; 55–95%); auricular, nasal, and tracheal chondritis (14–64%); venous thrombosis (50%); and various inflammatory ocular involvements (20–50%). Less common organ involvement could also be present, such as peripheral nervous system, heart, and kidneys impairments. A multidisciplinary approach is crucial for both diagnosis and treatment, as patients can require treatment by various medical specialists.

Erythrocyte sedimentation rate (ESR), ferritin, and C-reactive protein (CRP) are increased in most untreated patients and can

trend with acute episodes of inflammation. Patients often carry specific rheumatologic diagnoses, but in most cases, their clinical course and initial manifestations are atypical for these diseases with respect to disease severity, pattern of organ system involvement, and response to treatment. For example, a patient with VEXAS may be initially diagnosed with polymyalgia rheumatica or seronegative rheumatoid arthritis, but over time they may develop treatment-refractory systemic inflammation, progressive bone marrow failure, and additional clinical symptoms that phenocopy other rare diseases, such as Sweet syndrome or urticarial vasculitis. Inflammation can occur in various tissues, most commonly affecting the skin, lungs, cartilage, and eyes.^{1,5–7} Histologic characteristics are mainly available from skin biopsies, showing the presence of inflammatory infiltrates consisting of immature **myeloid cells** and variable proportions of mature **neutrophils**, lymphocytes, and **histiocytes**.

Most cases of VEXAS have been reported in men older than 50 years

Demographics. In a large cohort of VEXAS comprising 116 patients, the median age at symptom onset was 71 years, and the lower limit of the interquartile range was 66 years.⁵ Similar

age at onset has been shown in other cohorts, although the age range extended below 50 years of age in multiple reports.^{8–10} Additionally, there is a single case report of a patient presenting with VEXAS-like symptoms at age 23, with a confirmed pathogenic *UBA1* mutation.¹¹ Many factors likely influence the reported age at disease onset, including heterogeneity of patient and physician reporting, inconsistent recognition of mild symptoms caused by the disease, and disease-related variability such as sex, variant allele fraction (VAF) levels, and mutation type, each of which is currently being studied. Future research on younger populations will help clarify the natural history of this disease, including the timing of somatic mutation emergence and the development of clinical and hematologic manifestations. Testing for VEXAS can be considered in individuals under 50 years of age when clinical suspicion is high; however, most cases to date involve disease onset after age 60. The vast majority of patients identified are male, due to *UBA1* being an X-chromosomal gene, although VEXAS has been reported in women, particularly those with monosomy X.¹²

Macrocytic anemia is a common hematologic abnormality in VEXAS but may not always be present

Hematologic features. Macrocytosis and macrocytic anemia are the most common peripheral blood findings in patients with VEXAS,^{13,14} and macrocytosis should be recognized early because it could be initially an isolated presenting feature. Additionally, patients may present with lymphopenia, thrombocytopenia, and monocytopenia. The degree and instances of cytopenia often increase as the disease progresses and may not be evident in early presentations. The bone marrow is typically hypercellular with an increased myeloid-to-erythroid ratio.^{13,14} Concurrent conditions such as thalassemia or iron deficiency may obscure red cell macrocytosis by causing pseudonormalization of the mean corpuscular volume. MDS is present at diagnosis in one-third to one-half of patients with VEXAS, although diagnosing MDS in the setting of VEXAS can be challenging^{1,5,13,14} (see group 3). Association with plasma cell dyscrasias is found in up to one-quarter of patients, and macrophage activation syndrome associated with VEXAS has also been reported.¹

Vacuoles present in early erythroid–myeloid precursors from bone marrow aspirates are suggestive of but not diagnostic for VEXAS

Histopathology. Vacuoles in bone marrow histopathology are neither specific nor sensitive for VEXAS; in fact, they may also be found in individuals with nutritional deficiencies (especially copper) and chemotherapy recipients.^{13,15,16} Although vacuoles in isolation are not specific to VEXAS, vacuoles in combination with

relevant clinical symptoms have provided an 87.5% positive predictive value for pathogenic *UBA1* mutations.¹⁷ Genetic testing for pathogenic *UBA1* variants remains necessary to diagnose VEXAS, regardless of vacuole presence. Absence of vacuoles should not prevent consideration of *UBA1* testing if clinical suspicion remains high.¹⁸

VEXAS is not a heritable disease

Genetics. To date, all reported cases of VEXAS have been attributed to somatic or acquired mutations in *UBA1*, with no evidence of heritable VEXAS. There has yet to be a documented case of a *UBA1* mutation being transmitted to offspring or inherited, consistent with the mutation being restricted to the blood lineage.¹ However, no standardized assessment of children has been performed, and there are reports of pathogenic *UBA1* mutations being found outside of the blood, in both skin and nail samples.^{19–21} In both of these nonhematologic tissues, the *UBA1* mutation may be present due to peripheral blood contamination because the culturing of patient fibroblasts did not reveal any pathogenic mutations.¹

VEXAS diagnosis: *UBA1* screening modalities consensus statements (Figure 2)

The majority of patients with typical VEXAS have missense or splice site mutations at exon 3 of *UBA1*.

A variety of sequencing methods can be used to diagnose VEXAS depending on resources and expertise.

Next-generation sequencing (NGS) has increased sensitivity to detect low-level somatic variants with coverage of all coding or splice site regions.

Targeted testing for exon 3 variants can be used as an alternative to NGS with the understanding that such modalities may miss somatic variants with low VAF (Sanger sequencing) or variants outside of exon 3 (Sanger sequencing and digital droplet polymerase chain reaction [ddPCR]).

Active treatment may affect the accuracy of genetic testing by decreasing mutation level.

The diagnosis of VEXAS requires detection of pathogenic somatic mutations in the *UBA1* gene, which typically result in loss of the *UBA1b* isoform expression or reduction of E1 enzymatic activity.²² The choice of genetic testing modality depends on availability and cost, with the goal of sequencing all genomic regions where pathogenic mutations have been identified in *UBA1*, ensuring sufficient depth to detect lower VAF somatic mutations. As an initial diagnostic approach, low-cost genetic testing, such as exon 3 analysis of the *UBA1* gene by Sanger sequencing, can be used. This method targets the canonical mutations responsible for VEXAS, which involve p. Met41 (eg, p. Met41Thr, p. Met41Val, p. Met41Leu), and surrounding splice site mutations^{1,5,8,20} (eg, c.118-1G>C). Sanger sequencing of

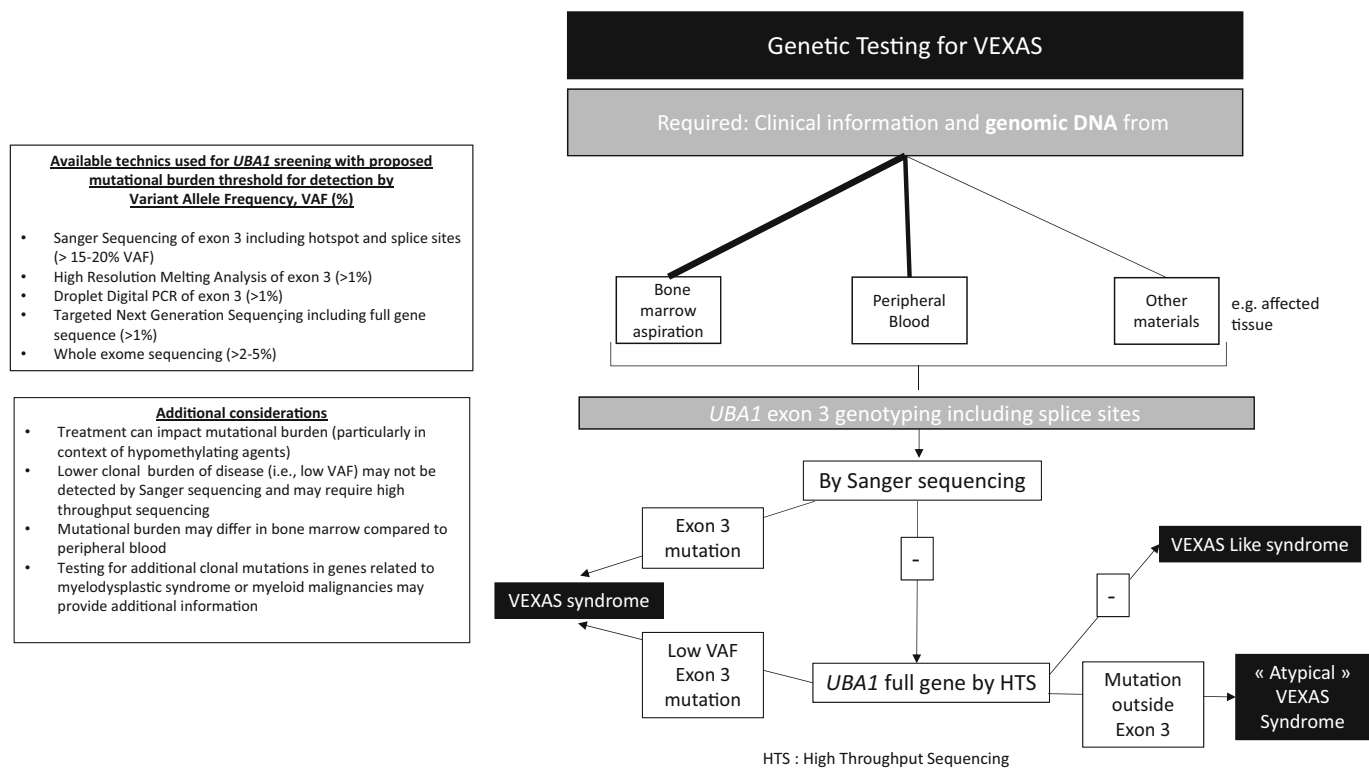


Figure 2. Genetic testing strategies for VEXAS. A practical approach to genetic testing is shown. Testing can be performed on bone marrow aspirate or peripheral blood. In rare instances when a bone marrow or peripheral blood sample is not available, testing could be performed on affected tissue. Different 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 throughout sequencing; PCR, polymerase chain reaction; VEXAS, vacuoles E1 enzyme X-linked autoinflammatory somatic syndrome.

exon 3 also covers the residue p. Ser56; mutations at this position cause reduced E1 enzyme function and are associated with a milder inflammatory phenotype of VEXAS.^{23,24} Sanger sequencing can identify mutations with VAFs roughly above 20% but lacks the sensitivity to detect lower mutational burden. Although most *UBA1* mutations can be detected by Sanger at diagnosis, a subset of patients has lower VAFs that may cause clinically significant VEXAS.

More sensitive methods for genetic testing, including targeted NGS are required to detect low-level pathogenic mutations in *UBA1*. The choice of targeted NGS or Sanger sequencing will depend on factors such as test availability, costs, and clinical need for additional testing. Because VEXAS frequently overlaps with MDS and clonal hematopoiesis of uncertain significance, many patients may already be undergoing a myeloid malignancy-targeted NGS panel, which should ideally include *UBA1* along with standard myeloid malignancy genes.

Many variants of uncertain significance throughout the *UBA1* gene have recently been reported by diagnostic centers, which now routinely include *UBA1* as part of their genetic panel for investigation of hematologic malignancies.²⁵ The functional relevance of these variants for the pathogenesis of VEXAS and other hematologic disorders remains to be fully elucidated. Recently, mutations located outside of exon 3 have been reported to modify

the catalytic function of E1 enzyme and lead to a “VEXAS-like” clinical presentation, suggesting that they might play a role in the disease pathogenesis.^{15,22} The diagnosis of VEXAS will depend on identifying pathogenic or likely pathogenic mutations in *UBA1*, as determined by ACMGG/AMP American College of Medical Genetics and Genomics / Association of Molecular Pathology, which may require functional biochemical validation of such suspected mutations^{26,27} in *UBA1*.

DNA source and screening methods

Somatic mutations defining VEXAS are detected in peripheral blood or bone marrow-derived DNA.

If clinical suspicion is high and genetic testing for mutations in *UBA1* at exon 3 is negative in the peripheral blood, clinicians should ensure that testing covers the complete gene and consider testing a bone marrow sample.

Typically, DNA for genetic testing for VEXAS is obtained from peripheral blood or bone marrow aspirates. *UBA1* mutations originate in the bone marrow progenitors and become lineage restricted to myeloid lineages and are primarily absent in lymphocytes. Occasionally, DNA from affected skin or lymph nodes may be used, although mutation levels tend to be lower due to the

smaller number of myeloid cells infiltrating tissue. The detection of *UBA1* mutations in the blood may be compromised by use of certain treatments, particularly hypomethylating agents, such as azacitidine. Although the mutation is usually identified in the peripheral blood and mutation levels are concordant with mutation burden in the bone marrow, there are isolated cases in which mutations are detected at much higher VAFs in the bone marrow. Thus, the testing site, detection method, and previous treatments should be considered when evaluating results. If clinical suspicion for VEXAS remains high despite negative testing in peripheral blood or skin biopsy, we suggest targeted NGS of bone marrow–derived samples to ensure testing tissue most likely to be enriched with pathogenic mutations, using the most sensitive sequencing approach for low VAF mutations.

In addition to Sanger sequencing, additional methods can be used to detect mutations on exon 3 with very low VAFs. These methods include high-resolution melting analysis, ddPCR, which can target specific mutations, targeted NGS, and whole-exome sequencing to analyze the complete coding sequence of the *UBA1* gene. Additionally, in conjunction with genetic testing, flow cytometry from bone marrow samples can help to identify characteristic vacuolated myeloid cells associated with VEXAS.²⁸

Diagnosis of MDS in patients with VEXAS consensus statements (Figure 3)

We recommend bone marrow examination in patients with VEXAS with associated cytopenia to exclude an associated hematologic neoplasm.

Karyotype and NGS for coexisting somatic mutations should be performed with bone marrow examination.

Although most patients with VEXAS predominantly exhibit inflammatory manifestations, a subset, especially later in the disease course, develop progressive bone marrow failure. Assessment by a hematologist is recommended to diagnose and manage various hematologic conditions including bone marrow failure, MDS, monoclonal gammopathies, and thrombosis.

Cytopenia, particularly macrocytic anemia, is a common finding in VEXAS, even in the absence of associated MDS. The need for bone marrow examination in a patient with a molecularly confirmed VEXAS diagnosis is debated due to lack of data, especially in patients without cytopenia. Macrocytosis is the most common peripheral blood finding in patients with VEXAS, followed by anemia, absolute lymphopenia (80%), moderate thrombocytopenia (30–50%), and monocytopenia (30–50%), whereas neutrophils are often within normal values. We recommend a baseline bone marrow examination in all patients with cytopenic VEXAS, especially before initiating disease-modifying treatments. When a bone marrow examination is performed, cytogenetic analysis should be included to identify additional cytogenetic abnormalities consistent with MDS, and loss of an X chromosome, which can predict

VEXAS in women.¹² An NGS panel targeting somatic mutations for myeloid malignancy, including *UBA1*, is strongly recommended. As with the diagnosis of VEXAS, Sanger sequencing can be used but has limitations in detecting low VAF mutations. If a pathogenic *UBA1* mutation is identified via Sanger sequencing or targeted *UBA1* testing, patients should still undergo NGS myeloid malignancy genetic testing. This testing can be performed from bone marrow or peripheral blood, regardless of clinical phenotype, to assess for coexisting mutations. VEXAS is a chronic and progressive disease. Cytopenia may worsen over time and periodic re-evaluation with bone marrow examination may be needed to assess disease progression or treatment-related toxicity.^{14,29} We recommend that patients with blood count abnormalities are followed closely by a hematologist.

Interpretation of bone marrow is challenging in VEXAS due to the frequent presence of signs of dysplasia, without meeting existing criteria for myelodysplastic syndrome diagnosis based on the World Health Organization (WHO) and International Consensus Classification (ICC) 2022 classifications.

Many patients with undiagnosed VEXAS before the discovery of the disease underwent bone marrow examinations due to varying degree of cytopenia, predominantly macrocytic anemia. Several of these patients were diagnosed with MDS due to presence of dysplasia. However, with a better understanding of the histologic findings in VEXAS, it is important to consider the diagnosis of VEXAS in the differential diagnosis of MDS when reviewing bone marrow for dysplasia.^{14,30} Atypia in one or more lineages, in addition to cytoplasmic vacuolation in erythroid and myeloid precursor cells, is often found in bone marrow examinations of patients with VEXAS, even when they do not meet the diagnostic criteria for MDS.¹⁶ Cellularity is typically high with an increased myeloid-to-erythroid ratio. Marrow flow cytometry analysis commonly shows absence of precursor B cells. In patients with a molecularly confirmed VEXAS diagnosis or with high suspicion, assessment of dysplasia should require morphologic evidence other than the presence of vacuolization alone, given this disease feature's ubiquitous presence in VEXAS.^{13,14} Albeit rare, the presence of increased blasts (5–20%) or MDS-defining cytogenetic abnormalities would also indicate MDS. Importantly, marrow morphologic findings need to be evaluated in the clinical context, including the presence of cytopenia's due to other causes such as nutritional deficiencies, infections, medications, or uncontrolled inflammation. Given these diagnostic complexities, authors of a recent article employed a more stringent approach to diagnosing MDS. They required the presence of significant and persistent cytopenia, defined as transfusion-dependent anemia, and thrombocytopenia (<100K per microliter) along with morphologic or genetic (cytogenetic or molecular) findings consistent with MDS. Using this approach, the incidence of MDS in

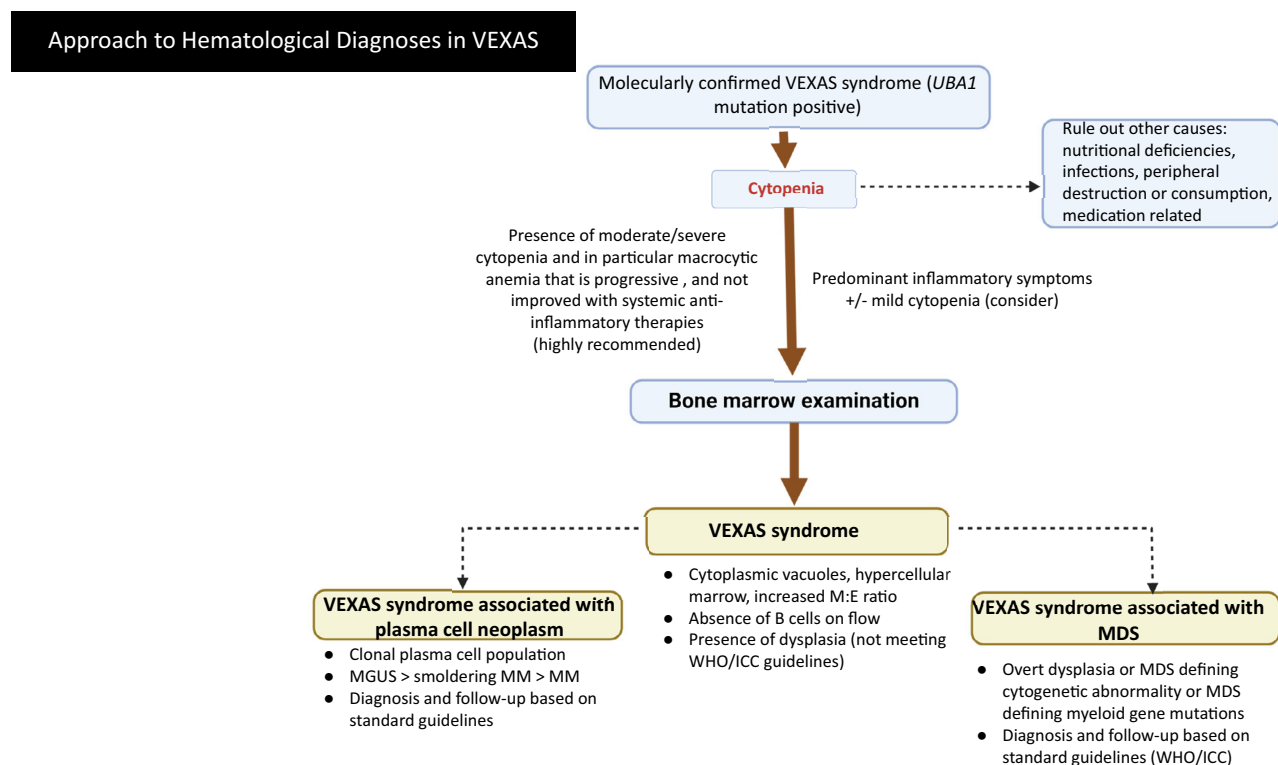


Figure 3. Approach to hematological diagnoses in VEXAS. A flow diagram is provided regarding a practical approach to hematologic evaluation of patients with a genetically confirmed diagnosis of VEXAS. ICC, International Consensus Classification; MDS, myelodysplastic syndrome; M:E, myeloid-to-erythroid; MGUS, Monoclonal Gammopathy of Undetermined Significance; MM, multiple Myeloma; WHO, World Health Organization; VEXAS, vacuoles E1 enzyme X-linked autoinflammatory somatic syndrome.

VEXAS was 18%, lower than reported in earlier literature.²⁹ The importance of diagnosing MDS in a patient with an established diagnosis of VEXAS is crucial because it helps better stratify the risk of progression to acute myeloid leukemia and can inform decisions about when to consider more aggressive treatment strategies.

The somatic clonal landscape in VEXAS is dominated by mutations in DNMT3A and TET2, generally without other driver mutations, but is to date difficult to discriminate from usual age-related to more VEXAS-specific signature.

Most reported cases of MDS in VEXAS are categorized as lower risk according to International Prognostic Scoring System categorization, with a low incidence of progression to acute myeloid leukemia.^{29,31–34} The karyotype is normal in more than 50% of cases. Somatic mutations in myeloid driver genes are present in nearly 60% of patients with VEXAS irrespective of a diagnosis of MDS and likely reflect the underlying inflammatory environment with predominance of *DNMT3A* and *TET2* mutations.^{29,35} Most patients with VEXAS also have additional mutations of clonal hematopoiesis in conjunction with *UBA1* mutations (with *DNMT3A* and *TET2* being most frequent).²⁹ Splicing factor mutations have also

been identified in cases with VEXAS, but their clinical significance is yet to be determined. For the previously mentioned reasons, prognostic tools generally used in MDS such as the International Prognostic Scoring System-Molecular have identified mostly lower-risk cases in the MDS-VEXAS overlap.³⁶ Other myeloid neoplasms such as MDS–myeloproliferative neoplasm overlap syndromes including chronic myelomonocytic leukemia, have also been reported in the literature.³⁷ We recommend that final diagnostic categorization for myeloid neoplasms in patients with VEXAS should follow WHO 2022 ICC guidelines.^{38,39} Similarly, plasma cell neoplasms should be categorized and assessed using the 2014 International Myeloma Working Group diagnostic criteria and treated per standard therapeutic interventions.⁴⁰

Do patients with vacuoles and no other WHO-defined dysplastic features, normal karyotype, and no other somatic mutations have MDS? For these patients, the expert consensus is not to consider these patients as having an MDS diagnosis, as the dysplastic findings may represent inherent VEXAS, but to recommend closer follow-up in case of further evolution. Based on the available data, in many cases, cytopenia appears to be related to bone marrow failure and ineffective hematopoiesis in VEXAS, distinct from MDS.

Outcome, prognosis, and management consensus statements (Figure 4)

Patients with VEXAS should be treated by a multidisciplinary team with consideration of referral to an expert center when available.

Disease activity is defined by inflammation or worsening bone marrow failure.

The goals of treatment include controlling inflammation; preventing, and treating bone marrow failure; preventing and treating secondary medical complications arising from implemented treatments; and improving quality of life.

VEXAS is a complex and potentially life-threatening disease characterized by multisystem organ involvement.^{5,41} The median survival from symptom onset is approximately 10 years.⁸ All patients diagnosed with VEXAS should be evaluated by a hematologist to determine the extent of hematologic involvement and manage the sequelae of progressive bone marrow failure. Rheumatologists, clinical immunologists, or internists play a key role in treating the inflammatory aspects of the disease and mitigating complications arising from immunosuppressive therapies. Dermatologists, pulmonologists, cardiologists, infectious disease specialists, and other health care providers are often needed to

address organ-specific and infectious complications. Given the clinical heterogeneity and death risk associated with VEXAS, referral to an expert center or consultation with a provider who has experience treating these patients is advisable whenever possible.

Infections, thromboembolic embolic disease, and treatment-related comorbidities are common in VEXAS and can mimic disease activity.

Disease-associated and treatment-related complications contribute to the increased morbidity and mortality risk in patients with VEXAS. A wide differential diagnosis should be considered when assessing new or recurrent clinical symptoms in patients with VEXAS, as not all complaints may be directly related to disease activity. Factors such as cytopenia, advanced age, use of immunosuppressive therapy, defects in ubiquitylation, and organ-related damage to skin and mucosal barriers increase susceptibility to typical, atypical, and opportunistic infections, including *Staphylococcus aureus*, *Streptococcus pyogenes*, *Legionella species*, nontuberculous *Mycobacterium*, *Pneumocystis jirovecii* pneumonia, and *alphaherpesviruses*.^{42,43} Inflammation and infection can co-occur in the same patient, often in the skin and lungs. Thromboembolic disease, primarily venous but also arterial, is prevalent in approximately 50% of patients with

Treatment Algorithm For VEXAS Syndrome (confirmed genetic diagnosis)

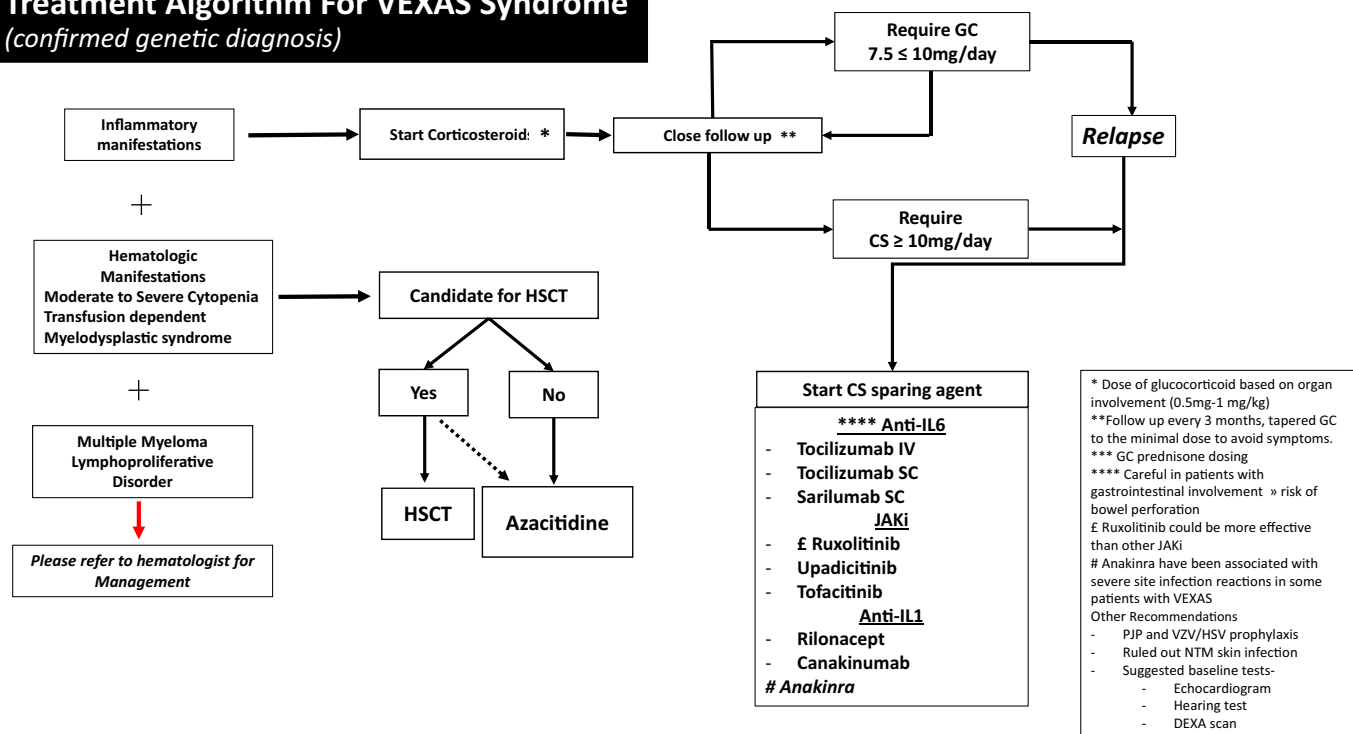


Figure 4. Treatment of VEXAS. A practical treatment algorithm is provided for clinical management of VEXAS syndrome based on current available evidence. Treatment decisions should be customized to each individual patient. CS, corticosteroid; DEXA, dual-energy x-ray absorptiometry; GC, glucocorticoid; HSCT, hematopoietic stem cell transplantation; HSV, Virus Herpes Simplex; IL-1, interleukin-1; IV, intravenous; JAKi, JAK inhibitor; NTM, nontuberculous mycobacteria; PJP, *Pneumocystis jirovecii* pneumonia; VEXAS, vacuoles E1 enzyme X-linked autoinflammatory somatic syndrome; VZV, varicella-zoster virus. Color figure can be viewed in the online issue, which is available at <http://onlinelibrary.wiley.com/doi/10.1002/art.43287/abstract>.

VEXAS, typically in association with ongoing disease activity.⁴⁴ Complications from chronic immunosuppressive treatments, particularly glucocorticoids, can be related to both dose and duration of therapy.

Flare of disease can be defined as recurrence of clinical or laboratory signs or symptoms of VEXAS.

Standardized definitions of disease states and disease activity are essential for clinical and research purposes. In VEXAS, disease activity is related to inflammation and bone marrow failure. Systemic inflammation can affect nearly every organ system, with a predilection for the skin, eyes, cartilage, lungs, and blood vessels. Limited prospective data are currently available regarding the nature and frequency of flares; however, clinical manifestations tend to reoccur during flare episodes. Elevated acute phase reactants are detectable in most patients with VEXAS and can serve as potential biomarkers of disease activity. CRP may be a more reliable marker of inflammation compared to ESR in VEXAS because hematologic abnormalities can elevate ESR independent of inflammation. Progressive bone marrow failure typically manifests as cytopenia, including macrocytic anemia, thrombocytopenia, lymphopenia, and monocytopenia.¹⁴ A subset of patients become transfusion-dependent, a factor associated with increased death.⁸ Hematologic and inflammatory manifestations are often correlated but can worsen independently.

Glucocorticoids are usually needed to control inflammation in patients with VEXAS and should be tapered slowly to achieve the minimal dose required to control disease activity.

Glucocorticoids are highly effective to treat patients with VEXAS, mostly dosed orally. Moderate to high doses of daily glucocorticoids (eg, prednisone 10–25 mg/day or higher) are often needed to control inflammation. Patients may experience flares of disease when glucocorticoids are tapered below specific daily thresholds. Unlike many rheumatologic diseases, glucocorticoid-free remission is unusual in VEXAS, even with the concomitant use of steroid-sparing therapies. Caution should be exercised when tapering glucocorticoids, as small reductions in dosage can precipitate recurrence of inflammation. The goal of steroid therapy is to find the minimal glucocorticoid dose required to control disease activity while minimizing the complications of long-term therapy.

Medications that target inflammatory pathways (eg, JAK inhibitors, interleukin-6 [IL-6] inhibitors) are more effective than conventional disease-modifying antirheumatic drugs (DMARDs) (eg, methotrexate, azathioprine) or B cell-directed therapies (eg, rituximab).

Mutations in VEXAS are lineage restricted to myeloid cells (eg, monocytes, neutrophils) and produce a state of hyperinflammation involving the activation of a myriad of inflammatory pathways. Therapies that target pathways of innate immunity are

more effective than medications targeted against the adaptive immune system.^{1,45} Specific anticytokine therapies may be effective but are often insufficient to control inflammation. Of these, IL-6 inhibitors are the most widely used. IL-1 inhibitors can be considered, but severe injection site reactions have been reported from anakinra,⁷ and few data highlighted the benefit of canakinumab. JAK inhibitors are useful to target a broader spectrum of disease-relevant cytokines (eg, IL-6, type 1 and 2 interferons). Of the various JAK inhibitors, ruxolitinib may be preferred and can be titrated across a greater dose range as needed, typically dosed at 10 mg twice a day to 20 mg twice a day.⁴⁶ Worsening cytopenia related to use of JAK inhibitors should be closely monitored and managed. Given the association of JAK inhibitors and increased risk for viral infections, thromboembolic disease, and cardiovascular events, careful selection of patients to receive this type of therapy is advisable and prophylaxis for alpha herpesviruses should be considered. Conventional DMARDs may have limited efficacy for some patients, potentially related to activation of nonmutant lymphocytes. B cell-depleting therapies are contraindicated because they are not efficacious in VEXAS and can worsen disease-associated B cell lymphopenia. Prospective clinical trials to assess comparative effectiveness and dosing among existing treatment options are needed, and the initial choice of treatment should be individualized to each patient.

Medications that reduce or eliminate the clonal burden of disease (eg, azacitidine) can be an effective treatment in some patients with VEXAS.

The elimination of clonal burden of disease is an aspirational goal for future medical therapies in VEXAS. Preliminary data on the use of azacitidine, a hypomethylating agent commonly used to treat MDS, has demonstrated reduction or elimination of *UBA1* mutation burden in peripheral blood or bone marrow in some patients with VEXAS in conjunction with improvement in inflammation.^{32,33,47} Successful therapy cessation with sustained remission has been reported in small case reports, but long-term data and prospective comparisons are lacking.^{47,48} Identification of specific patients with VEXAS who are most likely to benefit from medical therapies that are cytotoxic to cells harboring *UBA1* mutations remains to be determined. For example, it is currently unknown whether patients with VEXAS and concomitant MDS should be the most appropriate candidates for treatment with hypomethylating agents or whether these therapies may benefit a broader spectrum of patients.

Allogeneic hematopoietic stem cell transplantation may be a curative treatment but should be reserved for select patients with VEXAS after a careful hematologic evaluation.

Because VEXAS is associated with a genetic mutation restricted to the hematopoietic compartment, allogeneic hematopoietic stem cell transplantation is a curative option for this disease.⁴⁹ Benefits of this procedure should be weighed against the morbidity

and mortality associated risks for the procedure, especially infectious complications, and graft-versus-host disease.⁵⁰ Patients with VEXAS who have progressive and severe bone marrow failure (eg, transfusion-dependent) or treatment-refractory inflammation are candidates for allogeneic stem cell transplantation. The timing of bone marrow transplantation and identification of patients who are acceptable candidates is the most challenging because of older patient age, comorbidities, and often suboptimal performance status because of disease and treatment, particularly glucocorticoids.⁵¹ So far, 33 patients have been reported to have undergone allogeneic hematopoietic cell transplantation, with 27 individuals (81.8%) alive and 11 individuals with posttransplant molecular data showing a complete eradication of *UBA1* mutation mostly over a less-than-12-month follow-up period.⁵²

Prophylaxis against opportunistic infections, prevention of thromboembolic disease, and minimization of side effects related to chronic glucocorticoid therapy should be considered in all patients with VEXAS.

Strategies to mitigate disease-associated and treatment-related factors that contribute to morbidity and mortality are essential in the clinical management of patients with VEXAS. Prophylaxis against infectious complications of disease (eg, *Pneumocystis jirovecii* pneumonia or *alpha*herpesviruses) should be considered in all patients, with particular consideration for older patients and any patient with severe cytopenia who are receiving immunosuppressive therapies.^{42,43} For skin lesions that do not respond to treatment, a skin biopsy should be considered to rule out nontuberculous *Mycobacterium* infections before increasing immunosuppression. Given the high risk of thromboembolic disease, patients with VEXAS should receive thromboprophylaxis in high-risk settings (eg, hospitalization) unless contraindicated.⁴⁴ In patients who develop thromboembolic complications of disease, duration and choice of anticoagulation therapy has not been defined. Given the substantial exposure to glucocorticoids experienced by most patients with VEXAS, active management of steroid-related complications, with particular focus on strategies to promote bone health and prevent cardiovascular risk, is critical.

We need future clinical trials to identify the best treatment for patients with VEXAS.

Several recent reports have detailed clinical response to various treatments for VEXAS. Most of these studies provide case report- or case series-level data. Data from prospective observational cohort studies are lacking, and randomized controlled trials have not been performed to date. The quality of data to support treatment considerations in VEXAS is therefore low primarily due to selection bias, insufficient follow-up time and precision in the diagnosis of associated MDS, and a lack of standardized definitions of treatment response. Efficacy of any medication beyond glucocorticoids has not been definitively established. Furthermore, because VEXAS is typically a progressive clonal disease of the bone marrow, the timing of therapy initiation, in addition to the specific therapeutic strategy,

may have an important impact on clinical response and will need to be considered in future therapeutic trials.

VEXAS is a newly recognized disease, and these clinical guidance statements are intended to help clinicians better manage this condition. The statements are based on expert opinion, serving as a guide for current clinical practice and highlighting areas of ongoing investigation. Prospective studies are necessary to validate the different strategies outlined. As evidence accumulates related to the management of VEXAS, future efforts to provide evidence-based clinical guidelines, with input from patient partners, will be important to improve clinical care and promote further research to better define the disease.

ACKNOWLEDGMENTS

We would like to thank FAI2R for their support of the 1st international VEXAS workshop. We would like to thank patients and family members for participating in research. Biorender was used for figure design. This guidance has been endorsed by ISSAID society. HM: VEXAS research supported by: Ministry of Health of the Czech Republic, Agency for Health Research ČR (AZV) grant Nr. NU23-10-00160. [Correction added on 27 August 2025, after first online publication: Grant support “HM: VEXAS research supported by: Ministry of Health of the Czech Republic, Agency for Health Research ČR (AZV) grant Nr. NU23-10-00160” was added to the Acknowledgments section.]

AUTHOR CONTRIBUTIONS

All authors contributed to at least one of the following manuscript preparation roles: conceptualization AND/OR methodology, software, investigation, formal analysis, data curation, visualization, and validation AND drafting or reviewing/editing the final draft. As corresponding authors, Drs Mekinian and Beck confirm that all authors have provided the final approval of the version to be published and take responsibility for the affirmations regarding article submission (eg, not under consideration by another journal), the integrity of the data presented, and the statements regarding compliance with institutional review board/Declaration of Helsinki requirements.

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APPENDIX A: MEMBERS OF VEXAS WORKING GROUPS

The members of the VEXAS working groups are as follows: group 1: Heřman Mann, Benjamin Terrier, François Chasset, Sophie Georgin Laviaille, Alessandro Tomelleri, Campochiaro Corrado, Carlo Salvarani, Francesca Crisafulli, Franco Franceschini, Micol Frassi, Yohei Kirino, Ewa Więsik-Szewczyk, Marcin Milchert, Raquel Faria, Ciprian Jurcut, Joerg Seebach, Sinisa Savic, David Beck, Lauren Madigan, Matthew Koster, Patnaik Mrinal; group 2: Olivier Kosmider, Pierre Sujobert, Juan I. Arostegui, Nakajima, Catherine Cargo, David Viswanatha; group 3: Yervand Hagopian, Mael Heiblig, Pierre Fenaux, Thibault Comont, Bruno Alessandro, Chiara Cattaneo, Elisa Diral, Sara Morais, Austin Kulasekarara, Emma Groarke, Katherine Calvo, Patel Bhavisha; group 4: Anthony Sammel, Arsene Mekinian, Benjamin Terrier, Marie Robin, Sophie Georgin Laviaille, Katja Sockel, Yvan Jamilloux, Carmelo Gurnari, Henrique Coelho, Romana Vieira, Rim Bourguiba, Marcela Ferrada, Peter Grayson.