Infections and Associated Mortality in VEXAS Syndrome: A Systematic Review and Meta-Analysis

Öykü Zeynep Avarbek[1], Özlem Arıkan[2], Furkan Ak[3], Aysu Tatari[4], Bengisu Gür[5], Sinem Nursel Düzenci[6], Yasin Taha Tuncar[7], Mustafa Sivri[8], Mustafa Ovayolu[9], Miray Kurtca[10]

[1]Bezmialem Vakif University, Faculty of Medicine, Istanbul, Türkiye

[2]Istanbul Aydin University, Faculty of Medicine, Istanbul, Türkiye

[3]Sofia University St. Kliment Ohridski, Faculty of Medicine, Sofia, Bulgaria

[4]Pamukkale University, Faculty of Medicine, Denizli, Türkiye

[5]Istanbul University, Istanbul Faculty of Medicine, Istanbul, Türkiye

[6]Balikesir University, Faculty of Medicine, Balikesir, Türkiye

[7]Akdeniz University, Faculty of Medicine, Antalya, Türkiye

[8]Gazi University, Department of Emergency Medicine, Ankara, Türkiye

[9]Hacettepe University, Faculty of Medicine, Ankara, Türkiye

[10]Richmond University Medical Center, Department of Internal Medicine, New York, USA

Background: Vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic (VEXAS) syndrome is a late-onset, monogenic autoinflammatory disorder driven by somatic mutations in the UBA1 gene of hematopoietic stem cells. Given that the management of VEXAS syndrome often requires long-term treatment with intense immunosuppressive drugs, the overall susceptibility to infections is elevated in VEXAS patients. This systematic review aims to assess the spectrum of reported infectious pathogens and their associated complications in patients with VEXAS syndrome.

Methods: This study followed the PRISMA 2020 Statement, with its protocol prospectively registered in PROSPERO (CRD420250643566). We screened MEDLINE (via PubMed) and EMBASE from the earliest record until March 25, 2025. Cohort studies that reported infections caused by a confirmed pathogen during the follow-up of patients with VEXAS syndrome were eligible for inclusion. We excluded case reports and patients who lacked confirmation of the VEXAS diagnosis or the infectious etiology. The primary outcome was determined as the frequency distribution of reported infectious agents, stratified by pathogen type, including bacterial, viral, and fungal categories. The secondary outcome was the infection-related mortality risk. A pairwise meta-analysis was conducted to calculate the pooled mortality risk among included patients.

Results: Five cohorts with 333 patients were included. At the time of enrollment, 299 (89.8%) of these patients were receiving glucocorticoids (Table 1). Among the included patients, 110 (33%) were reported to have experienced at least one episode of infection with a confirmed etiologic agent, and multiple infections were observed in 10 (3%). A total of 146 infectious episodes were

identified in these patients. Bacterial agents were responsible for 72 (49.3%) of the cases. The most frequently isolated bacterial pathogens were Enterobacteriaceae (22.2%), Legionella pneumophila (19.4%), and non-tuberculous mycobacteria (19.4%). Among viral agents, the highest frequencies were observed for SARS-CoV-2 (41.2%), varicella-zoster virus (21.6%), and herpes simplex virus (15.7%). Pneumocystis jirovecii (73.9%) was the most common cause of fungal infections (Table 2). Most infections were localized to the bronchopulmonary system (64.4%). In the context of glucocorticoid-sparing treatment strategies, 23 (19.3%) infectious episodes occurred during cDMARD therapy, 35 (29.4%) during bDMARD use, 41 (34.4%) during JAK inhibitor treatment, and 20 (16.8%) during azacitidine therapy. According to the meta-analysis outcomes, the overall infection-related mortality risk among included patients was 8% [95% CI (0.04,0.13), Figure 1].

Conclusion: Infections are among the significant causes of morbidity and mortality in patients with VEXAS syndrome. Physicians should closely monitor patients throughout the follow-up period and maintain careful control over immunosuppressive drug dosing. Further studies are needed to evaluate the efficacy of anti-infective prophylaxis in these patients.

Keywords: autoinflammatory diseases, infection, mortality, inflammation

Figures and Tables

Table 1. Characteristics of the included studies

Study label	Country	Design	Number of patients, female (n)	Age (median [range])	Glucocorticoid users (n,%)	Glucocorticoid dosage (*mg/day*, median [range])	Glucocorticoid-sparing medications	Prophylaxis
De Valence 2024	France	Retrospective cohort	124, 4	68 (63-75)[a]	112, 90%	12.5 (10.0–24.8)[a]	cDMARD, bDMARD, JAKi, Azacitdine	Prophylaxis was received by 46% of the infected patients
Johansen 2025	Denmark	Retrospective cohort	16, 0	74 [51-78]	14, 87.5%	0 (n=3) 5-10 (n=7) 25 (n=1) ≥25 (n=4)	bDMARD, Azacitdine	Not reported
Kirino 2024	Japan	Prospective cohort	30, 0	73.5 [55-88]	20, 66.7%	9 [0-40]	cDMARD, bDMARD, JAKi	Not reported
Vitale 2025	Multinational	Retrospective cohort	69, 4	71.8 ± 8[b]	59, 85.5%	Not reported	cDMARD, bDMARD, JAKi	Not reported
Czech 2024	USA	Retrospective cohort	94, 0	64 [40-78]	94, 100%	21 (15–29)[a]	csDMARD, bDMARD, JAKi	PJP: 25% risk reduction VZV: 15% risk reduction HSV: no significant reduction

bDMARD: biological disease-modifying antirheumatic drugs, cDMARD: conventional disease-modifying antirheumatic drugs, HSV: Herpes simplex virus, JAKi: Janus-kinase inhibitors, PJP: Pneumocystis jiroveci pneumonia, VZV: Varicella zoster virus

[a]: Presented in median (IQR)

[b]: Presented in mean ± SD

Table 2. Distribution of identified pathogens in patients with VEXAS Syndrome

Category	Pathogen	n	Frequency Among All Cases (%)	Frequency Within Category (%)
Bacterial (n =72)				
	Enterobacteriaceae	16	10.96%	22.22%
	Legionella pneumophila	14	9.59%	19.44%
	Non-tuberculous mycobacteria	14	9.59%	19.44%
	Pseudomonas aeruginosa	6	4.11%	8.33%
	Staphylococcus aureus	6	4.11%	8.33%
	Streptococcus spp.	1	0.68%	1.39%
	Listeria monocytogenes	1	0.68%	1.39%
	Actinomyces odontolyticus	1	0.68%	1.39%
	Nocardia spp.	1	0.68%	1.39%
	Coagulase-negative Staphylococci	1	0.68%	1.39%
	Francisella philomiragia	1	0.68%	1.39%
	Achromobacter spp.	1	0.68%	1.39%
	Stenotrophomonas maltophilia	1	0.68%	1.39%
	Campylobacter jejuni	1	0.68%	1.39%
	Acinetobacter johnsonii	1	0.68%	1.39%
	Sphingomonas koreensis	1	0.68%	1.39%
	Mycobacterium tuberculosis	1	0.68%	1.39%
	Clostridioides difficile	1	0.68%	1.39%
	Haemophilus species	1	0.68%	1.39%
Viral (n = 51)				
	SARS-CoV-2	21	14.38%	41.18%
	Varicella-zoster virus	11	7.53%	21.57%
	Herpes simplex virus	8	5.48%	15.69%
	Human metapneumovirus	2	1.37%	3.92%
	Influenza virus	2	1.37%	3.92%
	Cytomegalovirus	2	1.37%	3.92%
	Hepatitis E virus	1	0.68%	1.96%
	Toscana virus	1	0.68%	1.96%
	JC virus	1	0.68%	1.96%
	Parainfluenza virus	1	0.68%	1.96%
Fungal (n = 23)				
	Pneumocystis jirovecii	17	11.64%	73.91%
	Nocardia spp.	2	1.37%	8.70%
	Aspergillus spp.	2	1.37%	8.70%
	Candida albicans	1	0.68%	4.35%
	Cryptococcus neoformans	1	0.68%	4.35%

Figure 1. Infection-related mortality in patients with VEXAS syndrome