

Opportunistic and Nosocomial Infections in Pemphigus Vulgaris and Foliaceus: Epidemiology, Pathogenesis, and Clinical Management Strategies

Juan Fausto Martínez González¹, Ana Laura Ricarte González², Daniel Alejandro Tierrablanca Rodríguez³, Miguel Miranda Servín⁴, Mireya Nolasco Sánchez⁵, Donaldo Emiliano Silva López⁶

¹Universidad Cuauhtémoc Aguascalientes. Aguascalientes, Mexico.

²Universidad Popular Autónoma del Estado de Puebla. Puebla, Mexico.

³Universidad autónoma de Nuevo León. Nuevo León, México

⁴Universidad Autónoma de Guadalajara. Zapopan, Jalisco, Mexico.

⁵Universidad de Celaya. Guanajuato, México

⁶Tecnológico de Monterrey Campus Monterrey. Nuevo Leon, Mexico.

ABSTRACT

Background: Pemphigus vulgaris (PV) and pemphigus foliaceus (PF) are autoimmune blistering disorders characterized by pathogenic autoantibodies against desmosomal adhesion proteins, leading to cutaneous and mucosal erosions. The extensive skin barrier disruption, combined with immunosuppressive therapies, predisposes patients to severe and recurrent infections, significantly impacting morbidity and mortality.

Objective: This review examines the epidemiology, microbiological profiles, risk factors, and clinical management of infections in pemphigus patients, with a focus on bacterial, viral, fungal, and opportunistic pathogens.

Methods: A comprehensive literature review was conducted using PubMed, Scopus, and Web of Science, analyzing studies on infectious complications in pemphigus from 1990 to 2024.

Results: The most prevalent infections include *Staphylococcus aureus* and *Streptococcus pyogenes* bacteremia, herpes simplex virus (HSV) reactivation, disseminated candidiasis, and opportunistic infections such as *Pneumocystis jirovecii* pneumonia (PJP) in heavily immunosuppressed individuals. Corticosteroids and rituximab further exacerbate infection risks by inducing lymphopenia and hypogammaglobulinemia.

Conclusion: Prophylactic antimicrobial strategies, early diagnosis, and judicious immunosuppression titration are critical in reducing infection-related complications in pemphigus. Multidisciplinary approaches involving dermatologists, infectious disease specialists, and microbiologists are essential for optimizing outcomes.

KEYWORDS: Pemphigus vulgaris, Pemphigus foliaceus, Opportunistic infections, Nosocomial infections, Immunosuppression, *Staphylococcus aureus*, Herpes simplex virus, Candidiasis, Rituximab, Corticosteroids

ARTICLE DETAILS

Published On:
28 June 2025

Available on:
<https://ijmscrs.com/>

INTRODUCTION

Pemphigus encompasses a group of rare, potentially fatal autoimmune blistering diseases mediated by IgG autoantibodies targeting desmoglein (Dsg) 1 and 3, crucial for epidermal adhesion. The two primary subtypes, pemphigus vulgaris (PV) and pemphigus foliaceus (PF), manifest with extensive mucocutaneous erosions, creating a vulnerable

interface for microbial colonization and systemic invasion.^{1,2}

Therapeutic regimens, particularly high-dose systemic corticosteroids (e.g., prednisone 1 mg/kg/day) and steroid-sparing agents (e.g., azathioprine, mycophenolate mofetil), alongside B-cell-depleting therapies like rituximab, induce profound immunosuppression. Consequently, pemphigus

Opportunistic and Nosocomial Infections in Pemphigus Vulgaris and Foliaceus: Epidemiology, Pathogenesis, and Clinical Management Strategies

patients face heightened susceptibility to bacterial, viral, fungal, and atypical infections, which remain a leading cause of hospitalization and mortality.^{2,3}

Staphylococcus aureus and beta-hemolytic streptococci frequently colonize denuded skin, leading to cellulitis, sepsis, and toxic shock syndrome. Viral reactivations, particularly herpes simplex virus (HSV) and varicella-zoster virus (VZV), contribute to localized and disseminated disease. Furthermore, prolonged immunosuppression increases the risk of invasive fungal infections (e.g., candidiasis, aspergillosis) and opportunistic pathogens such as *Pneumocystis jirovecii*.⁴

Epidemiology of Infections in Pemphigus Patients

The epidemiology of infections in patients with pemphigus is shaped by a complex interplay of disease-related immune dysregulation, iatrogenic immunosuppression, and the inherent vulnerability of compromised epithelial barriers. Pemphigus vulgaris (PV) and pemphigus foliaceus (PF), the two most prevalent subtypes, exhibit distinct clinical presentations but share a common predisposition to infectious complications due to widespread cutaneous and mucosal erosions. The prevalence of infections in this population is substantial, with studies indicating that up to 40–60% of pemphigus patients experience at least one major infectious episode during the course of their disease, contributing significantly to morbidity and mortality.⁵

Bacterial infections, particularly those caused by *Staphylococcus aureus* and *Streptococcus pyogenes*, dominate the microbiological landscape, accounting for a majority of cutaneous and systemic infections. The denuded epidermis in pemphigus serves as a critical portal of entry for these pathogens, leading to conditions such as cellulitis, impetigo, and, in severe cases, bacteremia and sepsis. The widespread use of topical and systemic corticosteroids further exacerbates this risk by impairing neutrophil function and delaying wound healing. Additionally, prolonged hospitalization and frequent healthcare contact increase exposure to nosocomial pathogens, including methicillin-resistant *Staphylococcus aureus* (MRSA) and *Pseudomonas aeruginosa*, particularly in patients with extensive disease requiring aggressive immunosuppression.⁵

Viral infections represent another major concern, with herpes simplex virus (HSV) reactivation being one of the most frequently encountered complications. The disruption of mucosal immunity, coupled with T-cell dysfunction induced by corticosteroids and rituximab, facilitates HSV dissemination, leading to extensive oral, genital, or even disseminated herpetic lesions. Varicella-zoster virus (VZV) reactivation, though less common, poses a significant risk, particularly in older patients or those receiving prolonged high-dose immunosuppressive therapy. Furthermore, cytomegalovirus (CMV) and Epstein-Barr virus (EBV) reactivation have been documented in severe cases,

sometimes complicating the clinical course with visceral involvement.^{6,7}

Fungal infections, particularly candidiasis, are highly prevalent in pemphigus patients, with *Candida albicans* being the most frequently isolated species. Oropharyngeal and esophageal candidiasis are common in individuals on long-term steroids, while invasive candidemia may occur in severely immunocompromised hosts. Opportunistic fungal pathogens, such as *Aspergillus* and *Cryptococcus*, though rare, have been reported in patients receiving intense immunosuppression, underscoring the need for heightened clinical suspicion in refractory or atypical presentations.⁸

Perhaps the most life-threatening infectious complications arise from opportunistic organisms, particularly *Pneumocystis jirovecii* pneumonia (PJP), which carries a high mortality rate if not promptly diagnosed and treated. The risk of PJP is particularly elevated in patients receiving rituximab or high-dose corticosteroids, necessitating prophylactic measures in high-risk cohorts. Similarly, atypical mycobacterial infections and disseminated strongyloidiasis have been described in case reports, highlighting the breadth of potential pathogens in this immunocompromised population.⁸

Geographical and socioeconomic factors further modulate infection epidemiology in pemphigus. In resource-limited settings, where access to prompt diagnosis and advanced therapies is restricted, bacterial and parasitic infections may present at higher frequencies and greater severity. Conversely, in developed regions, the widespread use of biologic agents like rituximab has shifted the spectrum toward viral and opportunistic infections.^{8,9}

Overall, infections remain a leading cause of hospitalization and death in pemphigus, necessitating a proactive, multidisciplinary approach to prevention, surveillance, and management. Understanding the epidemiological trends and risk stratification is essential for optimizing therapeutic strategies and improving patient outcomes in this vulnerable population.⁹

Pathophysiology of Infections in Pemphigus Patients

The pathophysiology underlying the increased susceptibility to infections in patients with pemphigus is multifactorial, involving a complex interplay between intrinsic disease mechanisms, iatrogenic immunosuppression, and the disruption of innate barrier defenses. At the core of this vulnerability lies the autoimmune-mediated destruction of desmosomal junctions, primarily targeting desmoglein (Dsg)-1 and Dsg-3, which are critical for maintaining epidermal and mucosal integrity. The resultant acantholysis and widespread blister formation create extensive areas of denuded epithelium that serve as pathological entry points for microbial invasion, effectively transforming the skin and mucous membranes from protective barriers into vulnerable interfaces ripe for colonization and systemic dissemination of pathogens.⁹

Opportunistic and Nosocomial Infections in Pemphigus Vulgaris and Foliaceus: Epidemiology, Pathogenesis, and Clinical Management Strategies

The immunobiological milieu in pemphigus further contributes to infection susceptibility through multiple parallel mechanisms. Autoantibody production against desmogleins not only induces keratinocyte detachment but also triggers a pro-inflammatory cascade characterized by elevated levels of interleukin (IL)-6, IL-8, and tumor necrosis factor- α (TNF- α). While these cytokines perpetuate the autoimmune blistering process, they simultaneously create a paradoxical state of immune dysfunction wherein chronic inflammation coexists with impaired pathogen clearance. This phenomenon, sometimes referred to as "immunoparalysis," manifests as diminished neutrophil chemotaxis, defective phagocytosis, and impaired antigen presentation by dendritic cells, collectively weakening the first line of defense against microbial invasion.⁹

The therapeutic mainstays for pemphigus, particularly systemic corticosteroids and B-cell depleting agents like rituximab, introduce additional layers of immunological compromise. Glucocorticoids exert broad-spectrum immunosuppressive effects through genomic and non-genomic mechanisms, including lymphocyte apoptosis, inhibition of nuclear factor kappa-B (NF- κ B) signaling, and suppression of cytokine production.⁹

These effects translate clinically into reduced T-cell proliferation, impaired macrophage activation, and diminished antibody production, creating windows of opportunity for both common and opportunistic pathogens. Of particular concern is the corticosteroid-induced impairment of Th17-mediated immunity, which plays a crucial role in mucosal defense against *Candida* species and extracellular bacteria.⁹

Rituximab, while revolutionary in pemphigus management, compounds infection risk through its mechanism of CD20-mediated B-cell depletion. The resulting hypogammaglobulinemia not only reduces protective antibody titers against encapsulated bacteria like *Streptococcus pneumoniae* and *Haemophilus influenzae* but also diminishes immune memory, increasing susceptibility to viral reactivations. The drug's prolonged pharmacological effect, with B-cell reconstitution often requiring 6-12 months, creates an extended period of vulnerability to infections such as herpesviridae reactivation (HSV, VZV, CMV) and progressive multifocal leukoencephalopathy (PML) caused by JC virus.¹⁰

At the molecular level, the disrupted cutaneous microenvironment in pemphigus lesions exhibits altered expression of antimicrobial peptides (AMPs) such as defensins and cathelicidins, which normally provide broad-spectrum protection against bacterial, viral, and fungal pathogens. The downregulation of these endogenous antibiotics, combined with the alkaline pH of chronic wounds, creates an ideal niche for *Staphylococcus aureus* colonization, a pathogen frequently isolated from pemphigus lesions. Biofilm formation by *S. aureus* on eroded surfaces

further complicates eradication efforts and serves as a persistent source of bacteremia.¹⁰

The mucosal involvement characteristic of pemphigus vulgaris introduces additional pathophysiological considerations. Oral and pharyngeal erosions impair the mechanical clearance of oropharyngeal secretions, facilitating aspiration and subsequent pulmonary infections. The loss of salivary immunoglobulin A (IgA), an important mucosal immune component, permits unchecked microbial adherence and invasion. Esophageal involvement may lead to candidal overgrowth, while genital lesions increase risk of urinary tract infections and sexually transmitted pathogens.¹⁰ Systemic consequences of chronic inflammation in pemphigus, including hypercatabolism and hypoalbuminemia, contribute to a malnutrition-immunodeficiency cycle that further depresses host defenses. The combined effects of protein loss through weeping lesions, corticosteroid-induced hypermetabolism, and chronic disease-related anorexia create a catabolic state that impairs lymphocyte proliferation and complement function. This metabolic dysregulation is particularly detrimental to elderly pemphigus patients, in whom age-related immunosenescence compounds disease- and treatment-related immunosuppression.¹⁰

Emerging evidence suggests that microbiome dysbiosis plays a significant role in infection susceptibility in pemphigus. The loss of cutaneous and mucosal barrier function permits pathological colonization by potentially pathogenic microorganisms while disrupting commensal flora that normally provide colonization resistance. This dysbiotic shift, combined with broad-spectrum antibiotic use for recurrent infections, creates a vicious cycle of microbial resistance and recurrent infections.¹⁰

The cumulative effect of these pathophysiological mechanisms creates a perfect storm for infectious complications in pemphigus patients. From initial breach of epithelial barriers to systemic immune dysfunction, each step in this cascade presents opportunities for microbial invasion and proliferation. Understanding these intricate mechanisms is crucial for developing targeted strategies to prevent and manage infections in this vulnerable population, while maintaining the delicate balance between immunosuppression necessary for disease control and preservation of host defenses against pathogens.¹⁰

Clinical Manifestations of Infections in Pemphigus Patients

The clinical presentation of infectious complications in patients with pemphigus represents a complex diagnostic challenge, as the signs and symptoms often overlap with or become obscured by the underlying autoimmune disease activity. The spectrum of clinical manifestations varies considerably depending on the microbial etiology, anatomical sites involved, degree of immunosuppression, and temporal relationship to therapeutic interventions. Bacterial

infections most frequently manifest as rapidly progressive cellulitis surrounding areas of active blistering, characterized by tender erythema, warm induration, and purulent discharge that often assumes a honey-colored crusting pattern suggestive of *Staphylococcus aureus* impetiginization. Deeper soft tissue infections such as necrotizing fasciitis, though rare, present with disproportionate pain, crepitus, and systemic toxicity, representing true dermatological emergencies in this immunocompromised population.¹⁰

Systemic bacterial dissemination typically manifests as hectic fever patterns accompanied by rigors and hemodynamic instability, though corticosteroid therapy may mask these classic signs of sepsis. The emergence of painful, rapidly expanding erosions with undermined borders and foul-smelling exudate should raise suspicion for *Pseudomonas aeruginosa* superinfection, particularly in hospitalized patients or those with extensive denuded surfaces. Unusual presentations include ecthyma gangrenosum-like lesions in neutropenic patients, demonstrating hemorrhagic vesicles progressing to necrotic ulcers with gray-black eschars, often indicating disseminated gram-negative bacteremia.¹¹

Viral infections in pemphigus patients frequently exhibit atypical and severe morphological characteristics. Herpes simplex virus (HSV) reactivation, rather than presenting as classic grouped vesicles, often manifests as painful, coalescing erosions with scalloped borders that mimic active pemphigus flares, creating diagnostic dilemmas. Disseminated HSV infection may present as widespread umbilicated pustules or erosions extending beyond dermatomal distributions, sometimes accompanied by hepatitis or pneumonitis in profoundly immunosuppressed individuals. Varicella-zoster virus (VZV) reactivation similarly demonstrates modified presentations, with multidermatomal involvement, ulcerative rather than vesicular lesions, and increased incidence of postherpetic neuralgia due to delayed diagnosis and treatment.¹¹

Fungal infections display particularly diverse clinical phenotypes in pemphigus patients. Oropharyngeal candidiasis, while common, often presents with more extensive pseudomembranous plaques and painful fissuring that extends into the esophagus, causing dysphagia and retrosternal pain. Invasive candidiasis may manifest as persistent fever unresponsive to broad-spectrum antibiotics, with occasional peripheral embolic phenomena such as nodular skin lesions or endophthalmitis. Dermatophyt infections in the context of topical steroid use frequently present as extensive, poorly demarcated plaques with minimal scaling (tinea incognito), while deep fungal infections such as cryptococcosis may present as molluscum contagiosum-like papules with central umbilication.¹¹

The respiratory tract represents a particularly vulnerable site for infectious complications, with clinical presentations ranging from indolent progressive dyspnea in *Pneumocystis jirovecii* pneumonia (PJP) to acute respiratory distress in

bacterial pneumonias. PJP in pemphigus patients often presents with a more subacute course compared to HIV-infected populations, featuring dry cough, exertional hypoxia, and bilateral interstitial infiltrates on imaging, but with less pronounced fever due to corticosteroid suppression of inflammatory responses. Bacterial pneumonias, particularly those caused by encapsulated organisms, frequently present with lobar consolidation and parapneumonic effusions, though classic signs such as productive cough and pleuritic pain may be attenuated in elderly or heavily immunosuppressed patients.¹¹

Gastrointestinal infections assume particular importance in pemphigus patients with oral and esophageal involvement. Cytomegalovirus (CMV) colitis presents with persistent watery diarrhea, hematochezia, and abdominal pain, often accompanied by systemic symptoms such as fever and weight loss. The differential diagnosis must include *Clostridioides difficile* infection, particularly in patients with recent antibiotic exposure, which manifests as profuse foul-smelling diarrhea with possible pseudomembranous colitis. *Strongyloides* hyperinfection syndrome, though rare, presents with diffuse abdominal pain, eosinophilia (when not masked by steroids), and potentially fatal disseminated disease involving the lungs and central nervous system.¹²

The genitourinary tract frequently serves as both source and site of infection in pemphigus patients. Complicated urinary tract infections often present with atypical symptoms such as delirium or vague abdominal discomfort rather than classic dysuria, particularly in elderly patients or those with neurogenic bladders secondary to prolonged corticosteroid use. Perineal and genital erosions provide entry points for sexually transmitted infections, which may present with severe, rapidly progressive ulcerations in the context of impaired cell-mediated immunity.¹²

Central nervous system infections, while uncommon, present with particularly ominous manifestations in this population. Cryptococcal meningitis typically manifests with subacute headache, altered mental status, and occasionally papilledema, though classic meningeal signs may be absent. Progressive multifocal leukoencephalopathy (PML) presents with insidious neurological deficits corresponding to affected white matter tracts, including cognitive changes, hemiparesis, or visual field defects, often progressing relentlessly without effective treatment options.¹²

The clinical assessment of infections in pemphigus patients requires heightened vigilance for subtle or modified presentations. The masking effect of immunosuppressive therapies on classic inflammatory responses, combined with the overlapping features of active autoimmune disease and superinfection, necessitates a low threshold for diagnostic testing and empirical therapy. Cutaneous infections may manifest as failure of existing lesions to heal, sudden expansion of erosions, or development of unusual pain in previously asymptomatic areas. Systemic infections often

declare themselves through metabolic derangements such as unexplained hyperglycemia in diabetic patients or new-onset confusion in elderly individuals, rather than through classic febrile responses.^{13,14}

The temporal relationship between immunosuppressive therapy and infection onset provides important diagnostic clues. Early-phase infections (within first month of treatment) typically reflect reactivation of latent pathogens or acquisition of nosocomial organisms, while late-phase infections (beyond 3-6 months) more commonly represent opportunistic infections or community-acquired pathogens. This chronological framework, combined with careful attention to modified clinical presentations, enables clinicians to navigate the diagnostic challenges posed by infections in this vulnerable patient population.¹³

Diagnostic Approaches for Infectious Complications in Pemphigus Patients

The accurate identification of infectious processes in patients with pemphigus necessitates a sophisticated diagnostic paradigm that integrates clinical acumen with advanced laboratory and imaging modalities, while accounting for the unique immunological perturbations inherent to both the underlying autoimmune condition and its therapeutic management. The diagnostic challenge is compounded by the frequent overlap between disease flares and infectious episodes, requiring clinicians to maintain a high index of suspicion and employ a systematic approach to microbiological investigation.¹³

Microbiological confirmation begins with meticulous specimen collection from affected sites, with particular attention to proper technique in obtaining cultures from cutaneous lesions. Swabs of weeping erosions should be collected after careful debridement of superficial debris to enhance microbial yield, with simultaneous procurement of samples for both aerobic and anaerobic culture. Deep tissue biopsies may be required for histopathological examination when atypical infections are suspected, with specimens divided for routine processing, special stains (including Gram, Grocott's methenamine silver, and acid-fast bacilli stains), and molecular diagnostics. The vesicle fluid aspiration, when feasible, provides optimal material for viral studies, though the fragile nature of pemphigus blisters often limits this approach.¹²

Contemporary microbiological diagnostics have been revolutionized by the advent of multiplex polymerase chain reaction (PCR) platforms capable of simultaneous detection of numerous bacterial, viral, and fungal pathogens from minimal clinical material. These molecular assays prove particularly valuable in pemphigus patients, where rapid identification of herpesviridae (HSV-1/2, VZV, CMV, EBV) can differentiate between autoimmune activity and viral superinfection. Quantitative PCR methodologies provide additional prognostic information for certain viral infections, with viral load monitoring guiding preemptive therapy

strategies in high-risk patients receiving rituximab or other B-cell depleting agents.¹²

Blood cultures remain a cornerstone of evaluation for systemic infections, though their yield is enhanced when collected prior to antibiotic administration and during febrile episodes. The implementation of modern automated continuous-monitoring blood culture systems has improved detection of fastidious organisms, while matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry enables rapid pathogen identification directly from positive blood cultures. For patients with suspected fungal bloodstream infections, β -D-glucan and galactomannan assays serve as valuable adjuncts to conventional culture methods, offering improved sensitivity for invasive candidiasis and aspergillosis, respectively.^{12,13} Serological evaluation plays a nuanced role in the diagnostic workup, with interpretation complicated by the frequent presence of heterologous antibodies from the underlying autoimmune process and the impaired humoral responses in patients receiving immunosuppressive therapy. Nevertheless, targeted serology for endemic mycoses, *Strongyloides stercoralis*, and certain viral pathogens may provide crucial diagnostic clues when interpreted in the appropriate clinical context. The measurement of immunoglobulin levels, particularly in patients with recurrent infections or those undergoing B-cell depletion therapy, helps identify those who might benefit from replacement therapy.¹³

Radiological imaging assumes particular importance in evaluating pulmonary complications, with high-resolution computed tomography (HRCT) offering superior sensitivity compared to plain radiography for detecting early pneumonic processes. The characteristic ground-glass opacities of *Pneumocystis pneumonia*, the nodular infiltrates of invasive fungal disease, and the tree-in-bud patterns of viral pneumonitis each present distinct imaging signatures that guide differential diagnosis. Ultrasonography proves invaluable for assessing soft tissue infections and guiding diagnostic aspiration of fluid collections, while magnetic resonance imaging (MRI) remains the modality of choice for evaluating suspected central nervous system infections.¹³

Cutaneous manifestations often require dermatopathological correlation, with biopsy specimens processed for both routine histology and direct immunofluorescence to distinguish between active pemphigus and infectious etiologies. The presence of viral cytopathic effects, fungal elements, or neutrophilic microabscesses provides histological evidence of infection, while the persistence of acantholysis and intercellular IgG deposition suggests ongoing autoimmune activity. Immunohistochemical stains for specific pathogens can enhance diagnostic yield when organisms are sparse or morphologically ambiguous.¹⁴

The emergence of next-generation sequencing technologies has introduced novel diagnostic possibilities, with metagenomic approaches allowing for comprehensive

pathogen detection without a priori knowledge of likely culprits. While currently limited to research settings and complex diagnostic dilemmas, these culture-independent methods hold promise for identifying atypical pathogens in immunocompromised hosts and detecting antimicrobial resistance genes directly from clinical specimens.

The integration of these diagnostic modalities requires careful consideration of the pretest probability of infection, which must account for the patient's specific immunosuppressive regimen, duration of therapy, and local epidemiological factors. Procalcitonin levels may assist in distinguishing bacterial infections from disease flares, though their interpretation requires caution in patients with chronic inflammatory conditions. Similarly, C-reactive protein trends can provide useful monitoring information when serial measurements are obtained.¹⁴

A thorough diagnostic approach must also encompass surveillance for latent infections prior to initiating or escalating immunosuppression. Tuberculosis screening with interferon-gamma release assays, hepatitis B and C serologies, and *Strongyloides* antibody testing form essential components of the pre-treatment evaluation, as reactivation of these pathogens carries significant morbidity in pemphigus patients. The evolving diagnostic landscape continues to refine our ability to detect and characterize infections in this vulnerable population, with the ultimate goal of enabling timely, targeted antimicrobial therapy while avoiding unnecessary treatment in cases of pure autoimmune activity.¹⁴

Therapeutic Management of Infectious Complications in Pemphigus: Medical and Surgical Interventions

The treatment of infectious complications in patients with pemphigus requires a nuanced, multidimensional approach that carefully balances the imperative for effective antimicrobial therapy against the need to maintain adequate immunosuppression for controlling the underlying autoimmune blistering disorder. The therapeutic paradigm must account for the complex interplay between host immunocompromise, potential drug interactions, and the unique vulnerabilities imposed by widespread epithelial barrier disruption. Antimicrobial selection is guided by the suspected or confirmed pathogen spectrum, local resistance patterns, the severity of infection, and the patient's specific immunosuppressive regimen, with particular attention to the heightened risks posed by concurrent corticosteroid and biological therapies.¹⁴

Empirical antibiotic therapy for bacterial infections in pemphigus patients demands broad-spectrum coverage accounting for both community-acquired and healthcare-associated pathogens. The high prevalence of *Staphylococcus aureus* colonization in cutaneous lesions necessitates inclusion of anti-staphylococcal agents such as vancomycin or linezolid in hospitalized patients until methicillin sensitivity can be established, particularly given the increased

incidence of methicillin-resistant strains in this population. For gram-negative coverage, fourth-generation cephalosporins or carbapenems are often employed in severe infections, with consideration for antipseudomonal coverage in patients with extensive wound colonization or recent healthcare exposure. The duration of therapy must be carefully calibrated, typically extending beyond standard treatment courses due to impaired immune clearance, with transition from intravenous to oral agents guided by clinical response and microbiological data rather than arbitrary timelines.¹⁵

Antiviral prophylaxis assumes critical importance in pemphigus patients receiving rituximab or high-dose corticosteroids, with oral acyclovir or valacyclovir providing effective suppression against herpesviridae reactivation. For established HSV or VZV infections, intravenous acyclovir remains the cornerstone of therapy, with dose adjustments required for renal impairment and consideration of resistance testing in refractory cases. Cytomegalovirus (CMV) disease, while less common, demands aggressive management with ganciclovir or valganciclovir, accompanied by careful monitoring for myelosuppression. The emergence of novel antiviral agents such as letermovir for CMV prophylaxis in high-risk immunocompromised patients offers additional therapeutic options, though experience in pemphigus populations remains limited.¹⁵

Systemic antifungal therapy is indicated for confirmed or suspected invasive fungal infections, with agent selection guided by the suspected pathogen and site of involvement. Echinocandins serve as first-line treatment for invasive candidiasis, while voriconazole remains preferred for aspergillosis, notwithstanding its complex drug-drug interactions with calcineurin inhibitors often used as steroid-sparing agents in pemphigus. Mucosal candidiasis typically responds to fluconazole, though increasing resistance patterns may necessitate escalation to posaconazole or isavuconazole in refractory cases. *Pneumocystis jirovecii* pneumonia (PJP) prophylaxis with trimethoprim-sulfamethoxazole is strongly recommended for patients receiving prolonged high-dose immunosuppression, with alternative regimens such as atovaquone or dapsone reserved for those with sulfa allergies.¹⁵

The surgical management of infectious complications in pemphigus presents unique challenges due to the compromised healing capacity of affected skin. Debridement of necrotic tissue in cases of necrotizing soft tissue infections must be performed judiciously to avoid exacerbating epithelial defects, with consideration for staged procedures and negative pressure wound therapy to promote granulation. Abscess drainage follows standard surgical principles, though incision placement should account for the propensity for wound extension in fragile pemphigus skin. For severe, refractory cutaneous infections, temporary biological dressings such as cadaveric or porcine xenografts may

Opportunistic and Nosocomial Infections in Pemphigus Vulgaris and Foliaceus: Epidemiology, Pathogenesis, and Clinical Management Strategies

provide transient wound coverage while antimicrobial therapies take effect.¹⁶

Adjunctive therapies play a pivotal role in comprehensive infection management. Intravenous immunoglobulin (IVIG) may be considered in cases of severe hypogammaglobulinemia-associated recurrent infections, particularly in rituximab-treated patients. Granulocyte colony-stimulating factor (G-CSF) finds occasional use in neutropenic sepsis, though its application must be weighed against theoretical risks of exacerbating autoimmune inflammation. Nutritional optimization, including protein repletion and micronutrient supplementation, addresses the catabolic state that frequently accompanies severe pemphigus and impairs immune function.¹⁶

The temporal modulation of immunosuppressive therapy during active infection represents one of the most complex clinical decisions in pemphigus management. While abrupt cessation of immunosuppression risks disease flare, continuation at full intensity may compromise infection control. A balanced approach typically involves temporary reduction of corticosteroid doses to the minimum required for disease control, with close monitoring for recrudescence of blistering. The reintroduction or escalation of immunosuppression following infection resolution must be carefully timed, often guided by inflammatory markers and clinical response.¹⁶

Novel therapeutic strategies under investigation include pathogen-specific immunotherapies and targeted antimicrobial peptides that may offer efficacy with reduced collateral damage to commensal flora. The development of personalized antimicrobial stewardship protocols for pemphigus patients, incorporating pharmacogenomic data and therapeutic drug monitoring, represents an emerging frontier in optimizing infection outcomes while minimizing resistance development. As the therapeutic armamentarium for both pemphigus and infectious complications continues to expand, the imperative grows for multidisciplinary collaboration between dermatologists, infectious disease specialists, and surgeons to navigate the complex risk-benefit calculations inherent to managing this vulnerable patient population.¹⁶

CONCLUSION

In summary, the management of infectious complications in patients with pemphigus represents a formidable clinical challenge that demands an intricate understanding of the complex pathophysiological interplay between autoimmune-mediated epithelial barrier disruption, iatrogenic immunosuppression, and microbial pathogenicity. The profound vulnerability of these patients to a broad spectrum of bacterial, viral, fungal, and opportunistic infections stems from multiple converging factors: the loss of cutaneous and mucosal integrity due to acantholysis, the systemic immunomodulatory effects of corticosteroids and biologic

agents, and the frequent metabolic derangements accompanying severe inflammatory disease. This perfect storm of risk factors translates into significantly elevated morbidity and mortality rates, with infections remaining a leading cause of hospitalization and death in this patient population.

The diagnostic odyssey in pemphigus patients with suspected infections requires heightened clinical vigilance, as classic signs of infection are often attenuated by immunosuppressive therapy while simultaneously mimicking disease flares. This diagnostic conundrum necessitates a low threshold for comprehensive microbiological investigation, employing advanced techniques ranging from multiplex PCR assays to deep tissue biopsies with specialized staining. The therapeutic tightrope walk between adequate infection control and sufficient autoimmune suppression epitomizes the delicate balance clinicians must strike, where both under-treatment of infection and over-reduction of immunosuppression carry potentially grave consequences.

Emerging insights into the microbiome dysbiosis associated with pemphigus and its treatments have opened new avenues for preventive strategies, while the development of targeted biologics with more favorable infection profiles offers hope for reducing infectious complications. However, the rapid evolution of antimicrobial resistance patterns and the expanding arsenal of immunosuppressive therapies continue to reshape the landscape of infectious risks in these patients. This dynamic clinical scenario underscores the imperative for ongoing multidisciplinary collaboration between dermatologists, infectious disease specialists, microbiologists, and wound care experts.

Future directions in managing infections in pemphigus should focus on three key areas: development of validated risk stratification tools to guide prophylactic strategies, implementation of advanced diagnostic algorithms incorporating rapid molecular techniques, and creation of evidence-based protocols for immunosuppression modulation during infectious episodes. The growing understanding of immune reconstitution patterns following various therapeutic regimens may enable more precise timing of antimicrobial prophylaxis and vaccination strategies.

Ultimately, the optimal care of pemphigus patients with infectious complications resides at the intersection of meticulous clinical observation, judicious application of diagnostic technologies, and thoughtful integration of antimicrobial and immunomodulatory therapies. As our comprehension of the intricate immunological perturbations in pemphigus deepens, so too must our strategies for preserving host defenses while controlling autoimmune activity. The continued advancement of personalized medicine approaches, incorporating pharmacogenomics and therapeutic drug monitoring, holds particular promise for optimizing outcomes in this complex patient population where every therapeutic decision carries competing risks and

benefits that must be carefully weighed against the individual's clinical context and treatment goals.

REFERENCES

- I. Bystryn JC, Rudolph JL. Pemphigus. *Lancet*. 2005;366(9479):61–73.10.1016/S0140-6736(05)66829-8.
- II. Schmidt E, Zillikens D. Pemphigoid diseases. *Lancet*. 2013;381(9863):320–32. 10.1016/S0140-6736(12)61140-4.
- III. King DF, Holubar K. History of pemphigus. *Clin Dermatol*.1983;1(2):6–12.10.1016/0738-081x(83)90019-6.
- IV. Lever WF. Pemphigus. *Medicine (Baltimore)*. 1953;32(1):1–23. 10.1097/00005792-195302000-00001.
- V. Beutner EH, Jordon RE. Demonstration of skin antibodies in sera of pemphigus vulgaris patients by indirect immunofluorescent staining. *Proc Soc Exp Biol Med*. 1964;117:505–10. 10.3181/00379727-117-29622.
- VI. Arndt KA, Feingold DS. The sign of Pyotr Vasilyewich Nikolsky. *N Engl J Med*. 1970;282(20):1154–5. 10.1056/NEJM197005142822011.
- VII. Doubleday CW. Who is Nikolsky and what does his sign mean? *J Am Acad Dermatol*. 1987;16(5 Pt 1):1054–5. 10.1016/s0190-9622(87)80419-x.
- VIII. Gammon WR, Briggaman RA, Inman AO 3rd, Queen LL, Wheeler CE. Differentiating anti-lamina lucida and anti-sublamina densa anti-BMZ antibodies by indirect immunofluorescence on 1.0 M sodium chloride-separated skin. *J Invest Dermatol*. 1984;82(2):139–44. 10.1111/1523-1747.ep12259692.
- IX. Kneisel A, Hertl M. Autoimmune bullous skin diseases. Part 2: diagnosis and therapy. *J Dtsch Dermatol Ges*. 2011;9(11):927–47. 10.1111/j.1610-0387.2011.07809.x.
- X. Liu Y, Wang Y, Chen X, Jin H, Li L. Factors associated with the activity and severity of bullous pemphigoid: a review. *Ann Med*. 2020;52(3–4):55–62. 10.1080/07853890.2020.1742367.
- XI. Delavarian Z, Layegh P, Pakfetrat A, Zarghi N, Khorashadizadeh M, Ghazi A. Evaluation of desmoglein 1 and 3 autoantibodies in pemphigus vulgaris: correlation with disease severity. *J Clin Exp Dent*. 2020;12(5):e440–5. 10.4317/jced.56289.
- XII. Baum S, Sakka N, Artsi O, Trau H, Barzilai A. Diagnosis and classification of autoimmune blistering diseases. *Autoimmun Rev*. 2014;13(4–5):482–9. 10.1016/j.autrev.2014.01.047.
- XIII. Otten JV, Hashimoto T, Hertl M, Payne AS, Sitaru C. Molecular diagnosis in autoimmune skin blistering conditions. *Curr Mol Med*. 2014;14(1):69–95. 10.2174/15665240113136660079.
- XIV. Schmidt E, Zillikens D. Modern diagnosis of autoimmune blistering skin diseases. *Autoimmun Rev*. 2010;10(2):84–9. 10.1016/j.autrev.2010.08.007.
- XV. Montagnon CM, Tolkachjov SN, Murrell DF, Camilleri MJ, Lehman JS. Subepithelial autoimmune blistering dermatoses: clinical features and diagnosis. *J Am Acad Dermatol*. 2021;85(1):1–14. 10.1016/j.jaad.2020.11.076.
- XVI. Jalil BA, Abdou YG, Rosen SA, Dammad T. Mucous membrane pemphigoid causing central airway obstruction. *J Bronchology Interv Pulmonol*. 2017;24(4):334–8. 10.1097/LBR.0000000000000374.