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Generalized Pustular Psoriasis: A Contemporary Review of Diagnosis, Pathophysiology, and IL-36 Pathway–Directed Management

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ABSTRACT

Importance: Generalized pustular psoriasis (GPP) is a rare, severe, and potentially life-threatening autoinflammatory skin disease characterized by episodic flares of widespread sterile pustulation and systemic autoinflammation. Historically, management strategies for GPP were extrapolated from plaque psoriasis, despite fundamental differences in disease biology, clinical course, and outcomes.

Observations: Emerging epidemiologic, clinical, and real-world data establish GPP as a distinct disease entity associated with high rates of hospitalization, multisystem involvement, and increased mortality. Accurate diagnosis requires recognition of characteristic cutaneous findings together with laboratory and clinical evidence of systemic involvement, and exclusion of key mimickers such as acute generalized exanthematous pustulosis, as well as recognition of patient-reported systemic symptoms such as fever, malaise, and joint pain. Advances in pathophysiologic understanding have identified dysregulated innate immune signaling centered on the interleukin-36 (IL-36) pathway as the primary driver of neutrophilic inflammation and pustule formation. Randomized clinical trials, real-world evidence, and meta-analyses consistently demonstrate that IL-36 receptor blockade achieves rapid and reliable control of acute GPP flares and provides a rational strategy for flare prevention. In contrast, off-label biologic therapies targeting IL-17, IL-23, or tumor necrosis factor–α show more variable and often delayed efficacy, particularly for acute disease control.

Conclusions and Relevance: Contemporary evidence supports a paradigm shift toward disease-specific, pathway-directed management of GPP, with IL-36 pathway inhibition positioned as the cornerstone of modern therapy.

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INTRODUCTION

Generalized pustular psoriasis (GPP) is a rare, chronic, severe autoinflammatory dermatosis distinguished by abrupt flares of sterile pustulation, systemic inflammation, and substantial morbidity and mortality.[1-4] Once viewed as a variant of plaque psoriasis, accumulating epidemiologic, clinical, and mechanistic evidence now establishes GPP as a distinct disease entity with unique diagnostic challenges, extracutaneous manifestations, and therapeutic priorities. Patients may require hospitalization during flares, exhibit marked laboratory evidence of systemic inflammation, and experience recurrent disease associated with significant health care utilization and excess morbidity and mortality.[4-8] In addition, GPP is associated with substantial economic burden, with average annual direct healthcare costs of approximately USD 23,675 per patient, driven primarily by inpatient care, and with all-cause hospitalization rates ranging from 12.6% to 44%, underscoring the high healthcare utilization associated with GPP.[9] Advances in disease biology have identified dysregulated innate immune signaling, centered on the interleukin-36 pathway, as the principal driver of neutrophilic inflammation and pustule formation, reshaping contemporary treatment paradigms.[10-12] This review synthesizes consensus guidance, real-world evidence, randomized clinical trials, and meta-analyses to define the clinical spectrum of GPP, clarify diagnostic and management frameworks, and highlight IL-36 pathway inhibition as the cornerstone of modern, disease-specific therapy.[6,13-16]

Generalized Pustular Psoriasis Epidemiology and Cutaneous Manifestations

Epidemiology

GPP is rare compared with plaque psoriasis, with population-based prevalence estimates ranging from approximately 1 to 180 cases per million, depending on geographic region and case definition.[2] By contrast, psoriasis overall affects approximately 2–4% of the population in many Western countries (equivalent to 20,000–40,000 cases per million).[17,18] Marked geographic variability has been reported in GPP, including higher prevalence estimates in US (~90 per million), South Korea (88–124 per million), and China (~140 per million), intermediate estimates in Sweden (15.3 per million) and Japan (7.46 per million), and lower estimates in France (1.76 per million), suggesting contributions from genetic background, environmental factors, and diagnostic practices.[1,2] Several epidemiologic studies also suggest that GPP occurs more frequently in females than in males, although the magnitude of this difference varies across populations.[3] National data further highlight methodological heterogeneity; for example, in Spain, the 5-year prevalence and incidence of GPP have been estimated at ~13 and ~7 per million, respectively, whereas hospitalization-based analyses report an incidence of ~3.18 per million/year, reflecting capture of more severe disease.[4]

Cutaneous and Histologic Manifestations

GPP is a chronic disease with intermittent episodes of acute, recurrent episodes of widespread sterile pustulation arising on a background of erythematous and edematous skin and frequently accompanied by systemic manifestations of inflammation. Cutaneous symptoms during flares are typically abrupt in onset and may evolve rapidly over hours to days, reflecting the fulminant nature of disease activity.[2,5,6] Consensus frameworks describe flares as rapidly progressive erythema with generalized, non-follicular sterile pustules occurring with or without systemic inflammation and with or without concomitant plaque psoriasis.[2,7,8]

The hallmark cutaneous feature is the eruption of numerous superficial pustules that may coalesce into "lakes of pus" on diffusely erythematous skin, most commonly involving the trunk and proximal extremities.[2,8,9] Lesions are often painful or tender and may be preceded by burning or dysesthesia; fever, malaise, fatigue, leukocytosis, and elevated autoinflammatory markers are common during severe flares.[2,10] As pustules resolve, they characteristically desquamate, leaving sheets of scale and residual erythema.[2,8,9] Classic clinicopathologic series similarly describe recurrent cycles of pustulation and desquamation and emphasize the potential for systemic toxicity during uncontrolled disease.[11-14]

Cutaneous involvement in GPP is frequently dynamic, with cycles of pustulation, desquamation, and partial clearance that may recur over days to weeks if disease control is incomplete.[6,9,10]

GPP may occur in the absence of plaque psoriasis or develop on a background of chronic plaque disease, with concomitant plaque psoriasis reported in approximately 31–67% of patients across different populations.[15-17] Contemporary consensus guidance emphasizes that GPP represents a distinct clinicopathologic entity rather than a severe variant of plaque psoriasis, given differences in clinical course, systemic involvement, and therapeutic priorities.[2,7,8]

Nail involvement can be a manifestation of GPP. Reported changes include onycholysis, subungual pustulation, nail plate dystrophy, Beau lines, and, in severe cases, partial or complete nail shedding (onychomadesis).[2,6,10,18] Nail disease may be painful, functionally limiting, and slow to recover, often persisting beyond the resolution of cutaneous pustulation. In global consensus work incorporating patient representatives, avoidance of hair and nail loss emerged as a prioritized treatment goal for a subset of patients, highlighting these manifestations as high-impact outcomes.[2]

Scalp involvement is common and may present with diffuse erythema, pustulation, erosions, and scaling.[7] Alopecia may occur during severe flares, most often as telogen effluvium related to systemic inflammation and fever, although autoinflammatory alopecia secondary to extensive scalp involvement has also been described.[6] While hair regrowth typically follows disease control, persistent or scarring alopecia has been reported in the context of severe or recurrent flares, reinforcing the importance of early and effective intervention.[2]

Histopathologic findings in GPP reflect intense neutrophilic inflammation. The defining feature is the presence of Kogoj spongiform pustules, consisting of intraepidermal collections of neutrophils within areas of spongiosis.[10,18] Additional findings include parakeratosis, acanthosis, epidermal edema, and dilated dermal capillaries with a predominantly neutrophilic dermal infiltrate. Clinicopathologic series emphasize that histologic findings must be interpreted in a clinical context, particularly when distinguishing GPP from other acute pustular eruptions.[11,12,18]

Differential Diagnoses

Accurate distinction of GPP from other pustular dermatoses is critical, given its potential for rapid systemic deterioration.[2,7,10] The principal diagnostic consideration is acute generalized exanthematous pustulosis (AGEP), a drug-induced eruption characterized by sudden-onset sterile pustules with fever and neutrophilia. Clinical manifestations usually develop within 1–3 days of drug exposure, though latency may extend to 1–2 weeks for certain agents, particularly antibiotics.[19,20] The most commonly implicated drugs include β-lactam antibiotics, macrolides, quinolones, antifungals (eg, terbinafine), calcium channel blockers (notably diltiazem), antimalarials (eg, hydroxychloroquine), and nonsteroidal anti-inflammatory drugs. AGEP typically resolves rapidly after drug withdrawal, in contrast to the relapsing course of GPP.1[9,20]

Histologically, AGEP more often demonstrates papillary dermal edema, necrotic keratinocytes, and prominent eosinophils, whereas GPP shows neutrophil-predominant inflammation with Kogoj spongiform pustules.[20] GPP must also be distinguished from localized pustular psoriasis variants, including palmoplantar pustulosis and acrodermatitis continua of Hallopeau, which are anatomically restricted and typically lack severe systemic inflammation.[7,21] Other entities in the differential diagnosis include subcorneal pustular dermatosis and IgA pemphigus, which are usually identifiable by chronicity, distribution, and immunopathologic findings.[18] Consensus guidance emphasizes that diagnosis of GPP should rely on integration of clinical presentation, disease course, laboratory findings, and histopathology rather than histology alone.[2,7,18] Recent consensus affirms, however, that skin biopsy is not required to make the diagnosis, and treatment should be started without waiting for skin biopsy results.[17]

Comorbidities and Extracutaneous Manifestations of Generalized Pustular Psoriasis

GPP is increasingly recognized as a systemic autoinflammatory disease associated with a broad spectrum of medical and psychosocial comorbidities that extend well beyond cutaneous involvement. These comorbidities substantially contribute to disease burden, health care utilization, and long-term morbidity, underscoring the need for comprehensive, multidisciplinary management strategies.

Cardiometabolic comorbidities are frequently observed in patients with GPP. Observational cohort studies and registry-based analyses demonstrate elevated prevalence of hypertension, dyslipidemia, diabetes mellitus, obesity, and established cardiovascular disease, reflecting shared autoinflammatory pathways and the cumulative effects of recurrent systemic inflammation.[2,5,6] In the SCRIPTOR study (an international, non-interventional retrospective chart review), a substantial portion of patients exhibited multiple cardiometabolic risk factors, many of which were present prior to GPP diagnosis, suggesting both baseline susceptibility and inflammation-driven risk amplification.[5] These findings are consistent with real-world claims analyses demonstrating higher rates of cardiovascular disease and related complications in GPP compared with plaque psoriasis and matched controls.[22]

Psychiatric comorbidities represent a major and often underrecognized component of GPP disease burden. Anxiety, depression, sleep disturbance, and psychological distress are highly prevalent, driven by the unpredictable, relapsing nature of GPP, frequent hospitalization, and fear of sudden, life-threatening flares.[5] Expert opinion emphasizes that psychological morbidity is frequently overshadowed during acute flare management despite its strong association with impaired quality of life, functional limitation, and reduced treatment adherence.[10] Importantly, patient representatives participating in recent consensus initiatives highlighted that the psychological impact of disease unpredictability, emergency care utilization, and loss of perceived control may equal or exceed the burden of cutaneous symptoms, supporting routine screening and integration of psychosocial support into both acute and longitudinal care pathways.[2]

Systemic organ involvement and laboratory abnormalities are common during acute GPP flares and contribute meaningfully to morbidity. Hospitalized patients frequently exhibit electrolyte imbalance, leukocytosis, elevated autoinflammatory markers, and evidence of end-organ stress, including renal impairment and hepatic involvement.[2,10] Transient elevations in liver enzymes (ALT and AST) have been reported during severe flares and are thought to reflect systemic autoinflammatory stress, multiorgan involvement, or concomitant complications such as infection or dehydration.[6,10] Consensus and expert guidance emphasize that abnormal liver function tests should be interpreted as markers of disease severity or systemic involvement rather than predictors of impending flares, particularly given potential confounding from metabolic liver disease and hepatotoxic therapies.[10] Claims-based analyses further demonstrate higher rates of inpatient admission, intensive care utilization, and complication-related hospitalizations among patients with GPP compared with plaque psoriasis, highlighting the systemic vulnerability associated with active disease.[22]

These systemic comorbidities translate into a significantly increased risk of mortality in GPP. In a large US-based claims analysis, Gottlieb et al. demonstrated that patients with GPP had a markedly higher all-cause mortality risk compared with both plaque psoriasis and the general population.[23] At one year following diagnosis, mortality risk was more than fourfold higher than the general population and over twofold higher than plaque psoriasis, with excess risk persisting over longer follow-up. Although claims-based data do not reliably capture cause-specific mortality, converging evidence from observational studies and expert reviews indicates that deaths in GPP are most commonly related to severe systemic complications during acute flares, including sepsis, acute respiratory distress syndrome, cardiovascular events, and multiorgan dysfunction.[7] Mortality risk appears highest within the first year after diagnosis, reinforcing the concept that fatal outcomes are closely linked to uncontrolled flare-related systemic inflammation rather than chronic background risk alone.[23] These findings support consensus recommendations that GPP should be managed as a dermatologic emergency, requiring early recognition, aggressive systemic therapy, and vigilant monitoring for infectious, cardiovascular, renal, and hepatic complications, while also being approached as a chronic disease with the goal of reducing and delaying the probability of future flares.

Musculoskeletal comorbidities, including psoriatic arthritis, may coexist with GPP, although reported prevalence appears lower than in plaque psoriasis populations.[6] When present, consensus guidance emphasizes that therapeutic decision-making should prioritize control of GPP over other psoriatic manifestations due to the acute systemic risks associated with active disease.[2] Furthermore, the neutrophil-driven autoinflammatory milieu characteristic of GPP may contribute to a spectrum of systemic comorbidities beyond musculoskeletal disease, including hepatobiliary involvement such as cholestasis, while neutrophil-associated conditions such as chronic obstructive pulmonary disease (COPD) have been reported in approximately 10% of patients.[5]

Collectively, these data highlight that comorbidities in GPP are common, multifactorial, and clinically consequential. Effective management, therefore, requires not only rapid control of cutaneous inflammation but also long-term disease control, along with proactive identification, monitoring, and treatment of associated systemic and psychiatric conditions. Recognition of the full comorbidity burden of GPP is essential to reducing long-term morbidity, preventing life-threatening complications, and improving overall quality of life for affected patients.

Generalized Pustular Psoriasis Triggers

Generalized pustular psoriasis flares may occur de novo or be provoked by specific triggers, with the pattern of triggers varying based on whether patients have associated plaque psoriasis.[3]

Common triggers across all GPP patients include withdrawal of systemic corticosteroids, infections, stress, pregnancy, and menstruation.[3] In patients with GPP without associated plaque psoriasis, the most frequent triggers are infections, pregnancy, menstruation, and stress, whereas in patients with GPP who also have plaque psoriasis, withdrawal of therapy—particularly systemic corticosteroids—is the most common precipitating factor.[15] The severity of flares varies widely both between patients and between individual flares in the same patient, with most flares lasting 2–5 weeks and approximately 50% requiring hospitalization.[3] Patients may experience multiple flares per year or a flare every few years, and flares occur more frequently in patients without associated plaque psoriasis compared to those with plaque psoriasis (mean 1.35 vs 1.25 flares per patient per year).[15]

Pathophysiology

GPP is characterized by acute innate immune dysregulation with rapid amplification of autoinflammatory signaling that drives episodic, systemic neutrophil-mediated inflammation, resulting in widespread sterile pustulation and, in severe cases, multiorgan involvement. Unlike plaque psoriasis, which is dominated by chronic adaptive immune activation, GPP is marked by abrupt flares with systemic toxicity and laboratory evidence of inflammation, including marked leukocytosis with neutrophilia, elevated C-reactive protein and erythrocyte sedimentation rate, increased ferritin, hypoalbuminemia, and, in severe cases, abnormalities in liver enzymes and electrolyte disturbances.[2,5,10,23,24] These laboratory abnormalities often parallel clinical severity and improve with effective control of acute autoinflammatory activity.

Excessive activation of the interleukin-36 (IL-36) signaling axis, a key driver of neutrophilic inflammation in the skin, is central to the pathophysiology of GPP. IL-36 cytokines (IL-36α, IL-36β, and IL-36γ) are produced primarily by keratinocytes and signal through the IL-36 receptor to induce potent downstream autoinflammatory cascades.[8,13,25] Under physiologic conditions, IL-36 activity is tightly regulated by the endogenous IL-36 receptor antagonist; dysregulation of this checkpoint results in unchecked signaling and robust production of neutrophil-recruiting chemokines and proinflammatory cytokines.[8,13,25]

IL-36 signaling promotes keratinocyte activation and amplification of innate immune responses, resulting in increased expression of CXCL1, CXCL2, CXCL8 (IL-8), and granulocyte colony-stimulating factor, which together drive rapid neutrophil recruitment and pustule formation within the epidermis.[8,13,14] This feed-forward loop between keratinocytes and infiltrating neutrophils contributes to the explosive onset and recurrent nature of GPP flares. Histopathologic features such as Kogoj spongiform pustules directly reflect this intense neutrophilic influx and epidermal inflammation.[4]

Downstream to IL-36, the IL-17 cytokine family plays an important role in sustaining cutaneous inflammation during GPP flares. IL-17A, IL-17F, and related cytokines act on keratinocytes to reinforce neutrophil recruitment, enhance antimicrobial peptide production, and perpetuate epidermal hyperplasia.[2,7,10] In GPP, IL-17 activity is thought to be driven in part by innate immune cells, including γδ T cells and other innate-like lymphocytes, rather than exclusively by classical adaptive Th17 responses.[3,7,10] This distinction helps explain the rapid onset of disease flares and the limited relevance of adaptive immune priming in acute episodes.

Although plaque psoriasis and GPP may coexist in the same patient, accumulating evidence supports the concept that GPP represents a distinct autoinflammatory disease entity rather than a simple exacerbation of plaque psoriasis. Across observational cohorts and consensus reviews, approximately 30–50% of patients with GPP have concomitant plaque psoriasis, while the remainder present with GPP in the absence of chronic plaque disease.[2-4,7,10] Differences in cytokine hierarchy, immune cell involvement, disease kinetics, and therapeutic response patterns reinforce this distinction and underscore the need for management strategies that prioritize rapid suppression of the

acute autoinflammatory cascade driving GPP flares rather than approaches designed primarily for chronic plaque psoriasis.[2,4,8]

Overall, the pathophysiology of GPP is best understood as a disorder of dysregulated innate immune signaling centered on IL-36–mediated keratinocyte activation, downstream neutrophil recruitment, and amplification through IL-17-dependent autoinflammatory circuits. Recognition of these mechanisms has directly informed the development of targeted therapies aimed at interrupting the core drivers of disease activity and preventing the severe systemic consequences of uncontrolled flares.[2,8,25]

Consensus and Expert Guidance on the Management of Generalized Pustular Psoriasis

Standardized treatment goals and management frameworks have historically been lacking for GPP. Recently, international and national consensus initiatives, complemented by expert opinion–based guidance, have sought to harmonize clinical decision-making, therapeutic targets, and outcome assessment in GPP, reflecting advances in disease biology and the emergence of targeted therapies.

The most comprehensive effort to date is the international modified Delphi consensus led by Barker et al, which established consensus-based treatment goals spanning both acute flare management and long-term disease control.[2] Notably, this study represents the first global GPP consensus initiative to formally include patient representatives alongside clinician experts, an approach that was intentionally designed to ensure that treatment goals reflected both clinical priorities and patient-experienced disease burden. This panel emphasized that GPP represents a dermatologic emergency, requiring rapid diagnosis, prompt initiation of effective systemic therapy, and close clinical monitoring to prevent life-threatening complications such as sepsis, electrolyte imbalance, and multiorgan dysfunction. Overarching principles highlighted individualized, patient-centered care, shared decision-making, and frequent reassessment with early treatment modification when response is inadequate.

Short-term treatment goals defined by the Delphi panel prioritized rapid suppression of autoinflammatory activity, with pustular clearance identified as the primary indicator of therapeutic success. Key benchmarks included prevention of new pustule formation within 2–3 days of treatment initiation, achievement of complete pustular clearance within 7 days, resolution of fever within 72 hours, and early evaluation of treatment effectiveness within the first week.[2] However, areas of meaningful discordance emerged between clinician and patient panelists.

Clinicians tended to prioritize physician-assessed cutaneous endpoints, particularly pustule clearance, erythema resolution, and normalization of autoinflammatory biomarkers, as the primary determinants of treatment success. In contrast, while patient representatives valued rapid pustule and erythema clearance, they placed greater emphasis on rapid relief of pain, burning, fatigue, and systemic malaise, restoration of sleep and physical function, and the emotional distress associated with acute flares. Patients emphasized that partial skin improvement without meaningful symptom relief did not constitute true recovery, highlighting a disconnect between traditional clinician-defined response measures and patient-perceived benefit.

Importantly, patients identified avoidance of hair loss and nail involvement as explicit short-term treatment goals, reflecting concern for functional impairment, cosmetic disfigurement, and long-term-term quality-of-life impact associated with these manifestations. In patients with concomitant plaque psoriasis or other psoriatic disease, the consensus further emphasized that treatment decisions should prioritize control of GPP over plaque psoriasis, given the acute systemic risk and potential for rapid clinical deterioration associated with active GPP.

Long-term goals articulated by Barker et al. focused on sustained disease control, defined as continuous, clear, or nearly clear skin, prevention of recurrent flares, prolongation of remission intervals, and durable improvement in quality of life and functional outcomes.[2] Here again, divergence was observed: clinicians largely emphasized maintenance of skin clearance and flare frequency reduction, whereas patients prioritized predictability of disease control, avoidance of hospitalization, treatment durability, and freedom from anxiety related to sudden flare

recurrence. Patient representatives underscored the psychological burden imposed by disease unpredictability, frequent emergency care, and fear of treatment interruption, domains that had been historically underrepresented in clinician-driven outcome frameworks. The panel further emphasized the importance of managing comorbid conditions and educating patients regarding the risk of flare recurrence associated with treatment interruption or tapering.

These global recommendations are reinforced by the Spanish Academy of Dermatology and Venereology consensus and systematic review led by Puig et al.[4] This national consensus underscored that GPP is a distinct clinicopathologic entity rather than a variant of plaque psoriasis and advocated for structured severity stratification incorporating extent of pustulation (agreed to be a minimum of 5% body surface area), systemic inflammation, and laboratory abnormalities. The authors highlighted the central role of innate immune dysregulation, particularly IL-36 pathway activation, in disease pathogenesis, building upon prior European and Japanese consensus statements on pustular psoriasis phenotypes and management.[7,8] Therapeutically, the Spanish consensus discouraged reliance on topical therapy alone and supported early initiation of systemic treatment, with increasing preference for targeted biologic agents given their rapid onset and favorable benefit–risk profiles.

Complementing formal consensus efforts, Marzano et al provided expert opinion–based guidance integrating real-world clinical experience and mechanistic insights.[10] This framework emphasized early aggressive intervention, recognition of prodromal symptoms preceding flares, and the importance of comprehensive supportive care alongside disease-targeted therapy. The authors also highlighted the substantial psychological and quality-of-life burden of recurrent GPP flares and advocated routine screening for psychiatric comorbidities.

Collectively, these consensus and expert guidance documents establish a unified, clinically actionable framework for GPP management that prioritizes rapid flare control, prevention of systemic complications, and durable remission. The explicit inclusion of patient representatives, and the recognition of clinician–patient discordance, represents a critical advance in aligning therapeutic targets with real-world disease impact, providing a foundation for standardized care, harmonized clinical trial endpoints, and improved outcomes for patients with this severe and historically underrecognized disease. Importantly, these frameworks also highlight the need for continued evolution of consensus guidance to emphasize that GPP should be managed as a chronic autoinflammatory disease rather than solely as an episodic flare condition. Failure to adopt a chronic disease management approach may expose patients to frequent, unpredictable flares of varying severity and persistent systemic inflammation, which can contribute to worsening comorbidities and ultimately have detrimental effects on overall patient health.

Treatment Approaches

The management of GPP has historically relied on therapies applied from plaque psoriasis or other autoinflammatory dermatoses, despite fundamental differences in underlying disease biology. Conventional systemic agents, including retinoids, cyclosporine, methotrexate, and systemic corticosteroids, have been widely used for acute flares but are limited by variable efficacy, delayed onset of action, toxicity, and high relapse

rates. Notably, systemic corticosteroids represent a clinical paradox in GPP management: despite being commonly prescribed in real-world practice, including use in approximately 40% of patients in observational cohorts, they are recognized as a potential trigger for disease exacerbation, particularly during dose reduction or withdrawal.[24] Real-world data and expert guidance increasingly emphasize that these approaches do not adequately address the rapid, IL-36–driven autoinflammatory cascade underlying GPP flares and may fail to prevent recurrent disease activity.[2,4,10]

Biologic therapies targeting off-label autoinflammatory pathways, particularly IL-17 and IL-23, have demonstrated efficacy in subsets of patients with GPP, especially those with concomitant plaque psoriasis. IL-17 inhibitors, including secukinumab, ixekizumab, and brodalumab, have been associated with improvement in pustulation and erythema in case series and small observational cohorts, whereas IL-23 inhibitors such as guselkumab, risankizumab, and tildrakizumab appear more effective for chronic plaque psoriasis disease control than for acute pustular flares.[4,6,10] While IL-17 and IL-23 inhibitors have been explored in patients with GPP globally, the available evidence is largely derived from small case series, registry reports, and limited observational cohorts, making it difficult to establish statistically robust conclusions regarding their efficacy specifically for GPP. IL-12/23 blockade with ustekinumab and tumor necrosis factor–α inhibitors (infliximab, adalimumab, etanercept) have also been used off-label with variable success. However, real-world claims analyses indicate that treatment persistence and flare prevention remain suboptimal with these agents, and switching between biologic classes is common, reflecting incomplete disease control.[24] Importantly, these therapies target downstream autoinflammatory mediators rather than the upstream drivers of neutrophilic inflammation central to GPP pathogenesis.

The emergence of therapies targeting the IL-36 pathway represents a paradigm shift in the treatment of GPP. Spesolimab, a monoclonal antibody targeting the IL-36 receptor, is the first and only approved therapy developed specifically to interrupt the core autoinflammatory mechanism driving GPP flares.

In the pivotal EFFISAYIL-1 randomized, double-blind, placebo-controlled trial, intravenous spesolimab demonstrated rapid and clinically meaningful efficacy, with significantly higher rates of complete pustular clearance compared with placebo as early as week 1, establishing IL-36 receptor blockade as an effective strategy for acute flare control in a disease characterized by abrupt onset and systemic toxicity.[26]

The Effisayil-2 trial was designed to evaluate spesolimab for flare prevention, addressing an unmet need in patients with recurrent disease and reinforcing the concept that sustained IL-36 pathway inhibition may modify the natural history of GPP rather than merely treating episodic flares.[27] This distinction is clinically important, as recurrent flares are associated with cumulative morbidity, repeated hospitalizations, and increased mortality risk.

Meta-analytic evidence further supports the superiority of IL-36 pathway blockade in GPP. A broad systematic review and single-arm meta-analysis evaluating biologic therapies for GPP included agents targeting IL-17 (secukinumab, ixekizumab, brodalumab), IL-23 (guselkumab, risankizumab, tildrakizumab), IL-12/23 (ustekinumab), and tumor necrosis factor–α (infliximab, adalimumab, etanercept).[28] Across pooled analyses, IL-36 receptor blockade with spesolimab demonstrated the highest rates of rapid and complete pustular clearance, particularly during acute flares, whereas other more downstream acting biologics showed more variable and often delayed responses, with efficacy frequently influenced by the presence of concomitant plaque psoriasis.

More importantly, a spesolimab-specific systematic review and meta-analysis focusing exclusively on patients with active GPP flares confirmed robust efficacy and a favorable safety profile, with pooled estimates demonstrating markedly increased odds of complete pustular resolution and rapid symptom improvement following IL-36 receptor blockade.[29] Together, these analyses reinforce that targeting the upstream IL-36 axis yields more consistent and rapid clinical benefit than inhibition of downstream cytokines involved in chronic psoriatic inflammation.

Real-world evidence complements these findings. Early compassionate-use case series report rapid resolution of pustulation, systemic symptoms, and laboratory markers of inflammation following spesolimab administration, even in patients with refractory disease and prior biologic exposure.[30] Although limited by small sample size, these observations align closely with Effisayil-1 trial outcomes and meta-analytic data, supporting the external validity of IL-36–targeted therapy in routine clinical practice. In contrast, real-world claims data demonstrate frequent treatment cycling and persistent health care utilization among patients managed with non–IL-36–targeted approaches.[24]

Collectively, available evidence supports a treatment framework in which IL-36 pathway blockade, anchored by Effisayil-1 for acute flares and Effisayil-2 for flare prevention, is prioritized for patients with GPP, whereas downstream biologic therapies may play a supportive role in selected patients, particularly those with prominent concomitant plaque psoriasis. This approach aligns mechanistic understanding with clinical outcomes and reflects a shift away from empiric immunosuppression toward disease-specific, pathway-directed therapy.

DISCUSSION

GPP is a rare, chronic, severe, and potentially life-threatening autoinflammatory dermatosis whose clinical behavior, systemic burden, and therapeutic priorities differ fundamentally from plaque psoriasis. Epidemiologic studies, real-world data, and mortality analyses consistently demonstrate that GPP is associated with high rates of hospitalization, multisystem involvement, and excess all-cause mortality, underscoring the need for early recognition and prompt intervention. The integration of consensus guidance, observational studies, randomized clinical trials, and meta-analyses now supports a unified framework in which diagnostic vigilance and upstream autoinflammatory blockade are central to improving patient outcomes.

Accurate diagnosis of GPP relies on clinical recognition of the acute onset of widespread sterile pustules arising on erythematous skin, often accompanied by systemic symptoms such as fever or malaise. Careful physical examination should include assessment for nail involvement, alopecia during severe flares, and extracutaneous manifestations involving the mucosae and eyes, which may include cheilitis, geographic tongue, conjunctivitis, or uveitis. Laboratory evaluation typically demonstrates marked systemic inflammation, including leukocytosis with neutrophilia, elevated C-reactive protein and erythrocyte sedimentation rate, increased ferritin, hypoalbuminemia, and, in severe cases, abnormalities in liver enzymes. Histopathologic confirmation with identification of spongiform pustules of Kogoj can support the diagnosis but should not delay treatment initiation in patients with severe or rapidly progressive disease.

Differentiation from clinical mimickers, particularly acute generalized exanthematous pustulosis, remains essential and is based on clinical context, laboratory features such as eosinophilia, and disease course. A practical diagnostic framework integrating these elements is summarized in Figure 1.

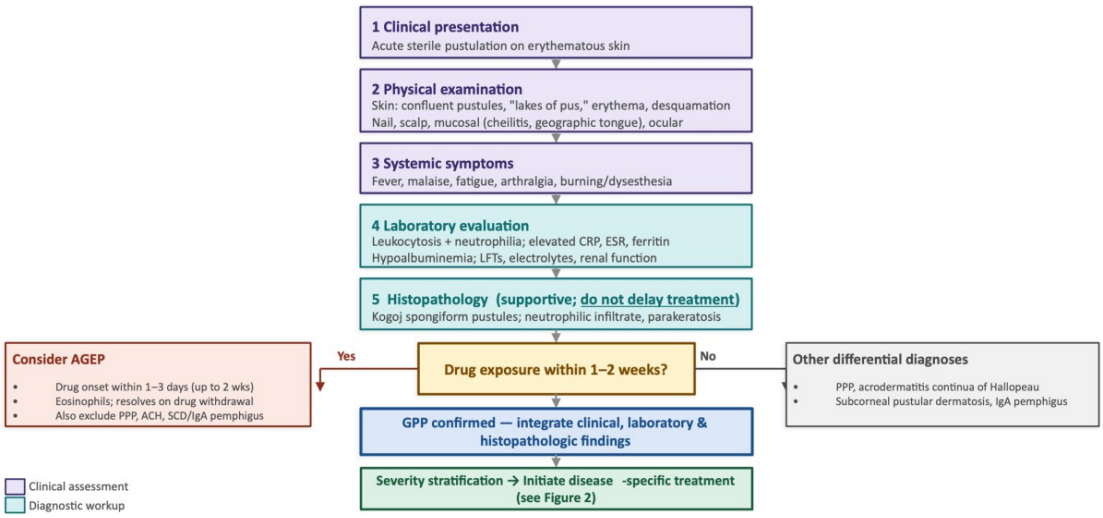
Advances in the understanding of GPP pathophysiology have fundamentally reshaped treatment paradigms. GPP is driven by dysregulated innate immune signaling centered on excessive activation of the interleukin-36 pathway, leading to rapid amplification of neutrophil-mediated inflammation and pustule formation. This mechanistic insight has enabled the development of disease-specific therapies targeting the upstream drivers of inflammation rather than downstream cytokine pathways. In randomized clinical trials, IL-

36 receptor blockade with spesolimab has demonstrated rapid and clinically meaningful efficacy, achieving complete pustular clearance within days during acute flares. Meta-analyses and real-world studies further confirm the superiority of IL-36 pathway inhibition for acute disease control compared with biologic therapies targeting IL-17, IL-23, IL-12/23, or tumor necrosis factor–α.

Beyond acute flare management, prevention of recurrent disease represents a critical unmet need in GPP. Recurrent flares contribute to cumulative morbidity, repeated hospitalizations, and increased mortality risk. Preventive treatment strategies based on sustained IL-36 pathway inhibition, supported by dedicated clinical trial designs, offer a rational approach to modifying the disease course. Off-label biologic therapies may retain a role in selected patients, particularly those with prominent concomitant plaque psoriasis, but available evidence indicates less consistent and slower control of acute pustular inflammation. Accordingly, these agents are best positioned as adjunctive or secondary options rather than primary therapies for active GPP.

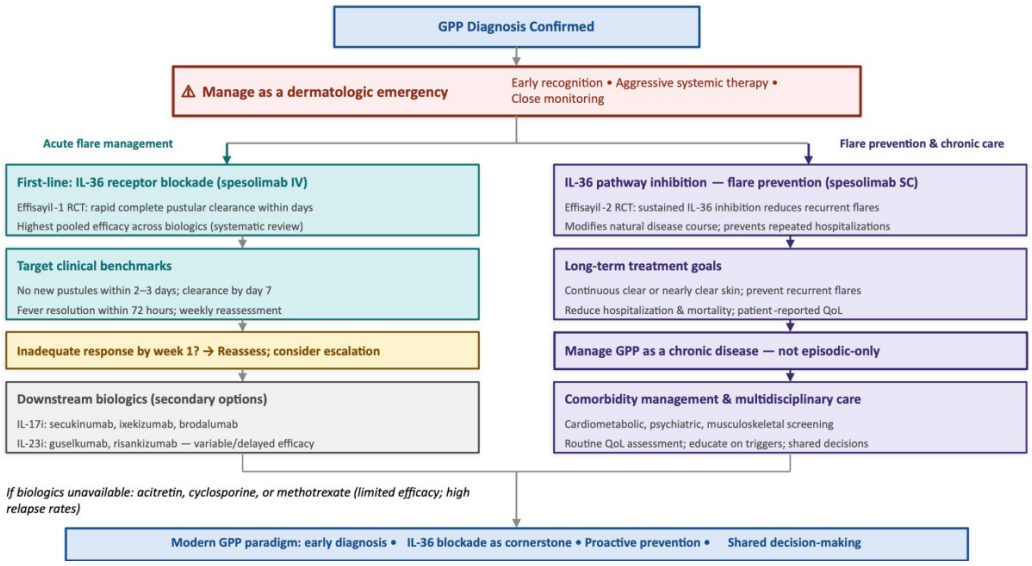
Together, these data support a modern, mechanism-driven approach to GPP management that prioritizes early diagnosis, rapid initiation of IL-36–targeted therapy, and proactive flare prevention. The proposed evidence-based treatment framework is illustrated in Figure 2.

FIGURE 1. Diagnostic Framework for Generalized Pustular Psoriasis.



AGEP, acute generalized exanthematous pustulosis; PPP, palmoplantar pustulosis; ACH, acrodermatitis continua of Hallopeau; SCD, subcorneal pustular dermatosis.

FIGURE 2. Evidence-Based Treatment Framework for Generalized Pustular Psoriasis.



IV, intravenous; SC, subcutaneous; RCT, randomized clinical trial; IL, interleukin; QoL, quality of life.

Adoption of this paradigm has the potential to substantially reduce disease burden, health care utilization, and mortality in this high-risk population.

CONCLUSION

GPP is a distinct, severe autoinflammatory disease characterized by abrupt flares, systemic complications, and increased mortality. Epidemiologic and real-world data highlight the substantial burden borne by affected patients, including recurrent disease activity, frequent hospitalization, and significant healthcare utilization. Advances in clinical characterization and diagnostic frameworks have improved recognition of GPP and clarified its distinction from plaque psoriasis and other pustular dermatoses. Importantly, growing mechanistic understanding of dysregulated innate immune signaling centered on the IL-36 pathway has transformed therapeutic strategies by enabling development of disease-specific targeted therBecause GPP is a chronic disease marked by recurrent flares, effective management requires both rapid control of acute episodes and sustained treatment strategies aimed at preventing future disease activity. Randomized clinical trials, supported by real-world evidence and meta-analyses, demonstrate that IL-36 receptor blockade provides rapid flare control and represents a rational pathway-directed approach for long-term disease management in patients with GPP.

DISCLOSURES

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