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REVIEW

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Literature review and expert opinion on diagnosis and current management of generalized pustular psoriasis

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ABSTRACT

Introduction: Generalized pustular psoriasis (GPP) is a rare, chronic, systemic, autoinflammatory disease characterized by the eruption of sterile pustules, often accompanied by more general symptoms, such as fever, fatigue, and a burning sensation in the skin. GPP can be potentially life-threatening, if untreated, as it can lead to complications, such as sepsis and heart failure.

Areas covered: In this literature review and expert opinion article, we provide an overview of the epidemiology, pathogenesis, clinical presentation, diagnosis, and treatment of GPP. Eleven dermatologists representing seven different Italian regions considered relevant evidence in the literature to discuss the current diagnosis and treatment of GPP. The expert panel of dermatologists identified several weaknesses in the current clinical management of GPP.

Expert opinion: There is an inconsistent definition and classification of the disease across the literature, which can lead to misdiagnosis and delay in disease treatment. Furthermore, there are no international and standardized clinical guidelines on disease management, especially in Europe. There is a profound need for the development of novel therapeutic agents with sustained efficacy to decrease the impact of the comorbidities and mortality associated with GPP, prevent the onset of complications, and support the unmet needs of these patients.

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GPP; generalized pustular psoriasis; inflammatory skin disease; rare disease; IL-36 pathway; biologic therapy

1. Introduction

1.1. Generalized pustular psoriasis

The term psoriasis defines a heterogeneous group of inflammatory skin diseases encompassing plaque psoriasis (also called psoriasis vulgaris, PV) and all its clinical variants, and pustular psoriasis (PP), defined by the presence of sterile, subcorneal neutrophilic pustules [1]. The classification of PP distinguishes localized variants (palmoplantar PP and acrodermatitis continua of Hallopeau), and generalized variants (generalized PP, PP of pregnancy – also known as impetigo herpetiformis -, annular and circinate, and infantile/juvenile PP) [2–4].

The European Rare and Severe Psoriasis Expert Network (ERASPEN) defines generalized pustular psoriasis (GPP) as a disease characterized by primary, sterile, macroscopically visible pustules on non-acral skin (excluding cases where pustulation is restricted to psoriatic plaques) that can occur with or without systemic inflammation, and with or without plaque psoriasis, and can be either relapsing or persistent (more than three months [5,6] (Figure 1). In contrast, the Japanese guidelines state that GPP is a systemic inflammatory condition with fever, malaise, fatigue, and abnormal laboratory findings [7]. Importantly, GPP has been classified within neutrophilic dermatoses as the paradigm of the superficial clinicopathological setting [8].

Systemic complications and comorbidities related to GPP may arise for a variety of reasons, including secondary bacterial infections, hypoalbuminemia, hypocalcemia, renal tubular necrosis (secondary to oligemia), liver damage (secondary to oligemia and neutrophilic cholangitis), and malnutrition. If untreated, these complications may progress into life-

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Article highlights

- GPP is a chronic, heterogeneous disease that requires early and timely diagnosis and treatment to prevent the onset of severe complications.
- There is an urgent need for internationally recognized guidelines for the diagnosis and treatment of GPP to support physicians with management of the disease.
- There is the need to develop improved treatments for GPP with sustained efficacy.
- The needs of patients with GPP remain currently unmet.

threatening conditions, such as sepsis, congestive heart failure, renal failure, or shock [9–14]. Moreover, patients with GPP often experience anxiety and depression, further impacting their quality of life [15,16].

The characteristics and outcomes of GPP flares have been described using the medical history of patients enrolled in the Effisayil™ 1 trial [17]. The authors collected all data on overall historical flares and categorized them as typical, most severe, and longest flares based on systemic symptoms, flare duration, treatment, hospitalization, and time to clearance of skin lesions. The assignment of flares to each category was based on investigator interpretation, and no standard definition was given to these three types of flares [18]. In this cohort, patients experienced a mean of 3.4 flares per year. Flares were painful, associated with systemic symptoms, and often triggered by stress, infections, or treatment withdrawal. The study revealed that flares were resolved within a three-week period in 57.1%, 71.0%, and 85.7% of cases categorized as typical, most severe, and longest flares, respectively. Furthermore, these flares resulted in hospitalization for 35.1%, 74.2%, and 64.3% of patients, respectively.

In the majority of patients, pustules required up to two weeks to resolve during a typical flare, while for the most severe cases, it took even longer, ranging from three to eight weeks. Due to the heterogeneity and complexity of this disease, it has taken more than a century to achieve a more comprehensive understanding of the underlying pathogenic mechanisms involved despite the first GPP patient being described in 1910 by Leopold von Zumbusch [19]. Since more than 65% of individuals with GPP present with an existing/history of plaque psoriasis [12,20], it has historically been categorized as a variant of plaque psoriasis. However, recent clinical, histological, and genetic data suggest that it is a distinct clinical entity that requires different diagnostic and therapeutic approaches [5,7,21–24].

2. Methods

On 28 March 2023, 11 expert dermatologists in the field, representing seven different regions of Italy (Abruzzo, Campania, Lazio, Lombardy, Sicily, Tuscany, and Veneto) participated in a virtual meeting to discuss the diagnosis and treatment of GPP. All participants were key opinion leaders working in GPP referral centers. The session was recorded and analyzed to capture the experts' opinions and to write this article. Relevant literature in the field was selected by searching PubMed for publications published in the 10 years prior to 28 March 2023, and using the terms: 'generalized pustular psoriasis' AND 'diagnosis' OR 'epidemiology' OR 'treatment' OR 'spesolimab' OR 'imsidolimab' OR 'IL 36 inhibitors.' The search was updated in July 2023 and June 2024 to include literature relevant to these topics.

3. Epidemiology

The prevalence of GPP varies considerably in the general population [25], with high variability among different countries, and racial backgrounds (Table 1). The geographic distribution of cases may vary also within the same country, suggesting the possible etiopathological contribution of genetic and environmental factors [26]. A high rate has been found in Korea, where between 88 and 124 patients per million people might be affected by GPP [27]; in Sweden 15.3 per million persons are affected by this disease [28,29]; in Brazil, the prevalence of GPP varies between 7 and 9 patients per million [30], similarly to Japan, with 7.46 cases per million persons. The lowest known prevalence has been estimated in France, with 1.76 cases per million people [14]. Recent data showed a GPP prevalence of 198 per million persons in Johor Bahru, a multiethnic district in Malaysia [31], and in China, 140 GPP cases per million people were estimated [32].

GPP can present at any age, from childhood to old age, but the median age reported at diagnosis is around 50 years [12]. The clinical course of GPP is heterogeneous and population-based studies using electronic health databases reported evidence of a higher occurrence of several comorbidities, such as

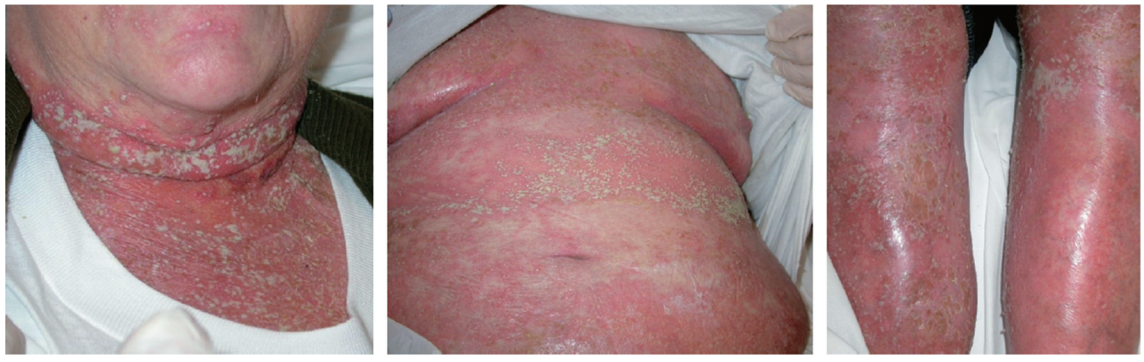

Figure 1. Generalized pustular psoriasis. Sterile pustules on an erythematous base on the neck (a) Trunk (b) and lower limbs (c) Reproduced with permission from [6], © 2022 EDIZIONI MINERVA MEDICA.

Table 1. Prevalence and mortality rates of GPP worldwide.

Country	Prevalence (per 1,000,000 persons)	Mortality rate (%)	Reference
Korea	88–124	6.06	[27]
Sweden	15.3	–	[29]
Brazil	7–9	5.3*	[30]
Japan	7.46	4.2	[36]
France	1.76	2	[14]
Malaysia	198	6.86	[12,31]
China	140	–	[32]

*This percentage refers to a cohort of inpatients, during hospitalization.

diabetes or vascular diseases, in patients with GPP than in the general population or patients with PV, thus highlighting a higher burden of disease for these patients [33,34]. The global mortality rate data for GPP is relatively limited and confined to geographically localized studies. Data suggested that patients with GPP have a higher mortality rate than the general population and patients with PV, with a higher risk of mortality across different age groups [35]. Although with a high data variability across countries, it is estimated to be between 2% and 16% worldwide. Malaysian, Korean, Japanese, and French studies found mortality rates of 6.86%, 6.06%, 4.2%, and 2%, respectively [6,12,14,36].

4. Diagnosis

The European consensus diagnostic criteria define GPP as a skin inflammation disease characterized by primary, sterile, macroscopically visible pustules not limited to the palms and soles [5]. Clinical symptoms and their reported frequencies are heterogeneous. High fever has been recorded in 24–96% of patients during a GPP flare, and approximately 30–70% presented leukocytosis with neutrophilia. Some comorbidities have been associated with the onset of GPP as previous plaque psoriasis (31–78%), arthritis (31–34%), and malaise/fatigue (100%) [12].

Diagnosis can be difficult because of the heterogeneity of the signs, and symptoms, and the small number of patients affected (Table 2). A skin biopsy may be necessary in certain cases, particularly when differentiating GPP from AGEP. Histopathology reveals epidermal hyperplasia with parakeratosis and acanthosis, elongation of rete ridges, and a reduced thickness of stratum granulosum. A dermal infiltrate mainly of neutrophils, which migrate into the epidermis from the papillary capillaries, to form the characteristic intraepidermal pustular infiltrate [6,37,38].

A careful clinical examination, accurate anamnestic data, and laboratory tests are mandatory to assess the severity of the disease. Early treatment is necessary to avoid its progression and the onset of complications. Common laboratory initial assessments must always include a complete blood cell count, C-reactive protein (CRP) test, urine analysis, and blood protein electrophoresis [6]. Blood cultures should also be performed for clinical cases with high fever and distress, together with a comprehensive metabolic panel to evaluate for hypocalcemia, other electrolyte abnormalities, hypoalbuminemia, and renal and liver function [6].

5. Pathogenic mechanisms

GPP flares are usually idiopathic, but they may also be caused by internal and external triggers. Significant risk factors for GPP include infections [12,39–41], pregnancy [12], withdrawal of corticosteroids [10], intake of other drugs like ustekinumab [42] and tumor necrosis factor antagonists [43], and smoking, alcohol consumption, and obesity [41]. In addition, hypertension, diabetes, and hyperlipidemia are also more common in patients with GPP [41].

In 2011, the identification of loss-of-function mutations in the gene encoding the interleukin-36 receptor antagonist (*IL36RN*) emphasized the crucial role of this pathway in the

Table 2. Types of pustular psoriasis and definition for their diagnosis. Adapted from [5] and [85].

Types	*Clinical presentation*	*Subclassifier*	Reference
Generalized forms			
Generalized pustular psoriasis	Primary, sterile, macroscopically visible pustules on non-acral skin (excluding cases where pustulation is restricted to psoriatic plaques)	With or without systemic inflammation With or without psoriasis vulgaris Either relapsing (>1 episode) or persistent (>3 months)	[6]
Special forms of GPP			
Impetigo herpetiformis	Erythematous patches with marginal grouped sterile pustules mostly in the third trimester of pregnancy, primarily appearing in flexural regions, as they extend centrifugally, may develop erosion and crust and may even become secondarily infected (impetiginized)		[86]
Annular pustular psoriasis	Well-demarcated erythematous scaly plaques with central clearing		[87]
Localized forms			
Acrodermatitis continua of Hallopeau	Primary, persistent (>3 months), sterile, macroscopically visible pustules affecting the nail apparatus	With or without psoriasis vulgaris	[6]
Pustulosis palmoplantaris	Primary, persistent (>3 months), sterile, macroscopically visible pustules on palms and/or soles	With or without psoriasis vulgaris	[6]

pathogenesis of GPP [44] and showed that GPP is an autoinflammatory disease resulting from excessive expression of interleukin-1 family proteins in the skin and disinhibition of the signaling pathway that these proteins activate. Since then, *IL36RN* mutations have been reported in 10% to 82% of patients with GPP [23,45]. In addition, these mutations have been shown to account for 46–82% of cases of PP not associated with plaque psoriasis [46,47]. Although familial cases are commonly associated with homozygous *IL36RN* mutations, sporadic cases are more likely to be associated with compound heterozygous mutations [48,49]. However, there are cases in which these mutations have not been identified. A recent meta-analysis revealed that carriage of one or two *IL36RN* mutant alleles conferred a more severe clinical phenotype with an earlier age of onset and an increased risk of systemic inflammation compared with non-carriage [50].

A gene expression study on GPP and PV lesional biopsies [23] confirmed that even if their transcriptome overlaps, GPP is much more linked to the innate immune system, suggesting that keratinocytes, neutrophils, and monocytes are primarily involved with inflammatory processes mainly driven by IL-36, IL-1, TNF-α/IL-17A. The increased expression, processing, and activity of IL-36 cytokines might be a central mechanism that promotes neutrophil accumulation in the epidermis. GPP pathogenesis also appears to be mediated by other mutated genes. In Asian patients, mutations in the Caspase Recruitment Domain Family Member 14 gene (CARD14) have been associated with GPP; CARD14 facilitates the activation of nuclear factor-kB (NF-kB) in keratinocytes and other cell types [23,51–53]. Mutations in the myeloperoxidase (*MPO*) gene have also been associated with GPP [54–56] and are thought to cause a deficit of the myeloperoxidase protein, which physiologically regulates protease activity, neutrophil extracellular trap formation, apoptosis of neutrophils and their clearance by monocytes. Finally, mutations in the gene encoding the AP-1 complex subunit б1C (*AP1S3*), which regulates the expression of keratins in keratinocytes, have been identified in GPP patients [57]. These mutations may induce IL-1β, IL-36, and CXCL8 expression through the dysfunction of the NF-kB signaling pathway.

5.1. GPP treatment in clinical practice

Therapeutic goals in treating GPP can be classified as immediate/short-term and long-term. Immediate therapeutic goals during a flare include improving skin manifestations (stopping and preventing the development of pustules) and reducing the burden of systemic symptoms. The long-term therapeutic objectives for GPP revolve around minimizing or preventing new flares and disease progression. This involves implementing effective strategies for regular monitoring and clinical evaluation [9,51,58,59].

Despite the severity of this disease, treatment goals in GPP are not well-defined due to a lack of consistent therapy guidelines. Treatment choices are mainly driven by the extent of involvement, disease severity, and presence of risk factors, and often follow the guidelines for plaque psoriasis [60,61].

Typically, non-biologic systemic therapies including corticosteroids, acitretin, cyclosporine, and methotrexate, are administered as first-line options, although with minimal evidence supporting their use. Other agents with limited evidence include mycophenolate mofetil, hydroxyurea, apremilast, and colchicine. A summary of available treatment options, including specific details on spesolimab dosing and scheduling, is provided in Table 3. Considering the acute life-threatening characteristics of GPP flares, cyclosporine sometimes is preferred due to its rapid onset of action [9,59,62–66]. In Japan and other Asian countries, several biologics therapies targeting immunologic pathways have been approved for the treatment of GPP, including TNF inhibitors (infliximab, adalimumab, and certolizumab pegol), IL-17/IL-17 R inhibitors (secukinumab, brodalumab, and ixekizumab), and IL-23 inhibitors (risankizumab and guselkumab) [9,59,62–67]. In Italy, a multicenter, retrospective study compared the safety, effectiveness, and drug survival of IL-17 and IL-23 inhibitors among 27 erythrodermic psoriasis and 59 PP patients (36 with generalized GPP and 23 with PPP) [68]. Among GPP patients, the use of IL-17 inhibitors led to higher rates of the Generalized Pustular Psoriasis Area and Severity Index (GPPASI) 90 and GPPAS1 100 at week 12 compared to IL-23 inhibitors (IL-17 70% vs. IL-23 22%, $p = 0.022$ and IL-17 56% vs. IL-23 11%, $p = 0.019$), together with a higher GPPASI 90 response at week 24 (IL-17 63% vs. IL-23 56%, $p = 0.999$). A similar trend was shown when analyzing the response rates, where patients were considered responders if their Investigator's Global Assessment (IGA) score was 0 or 1 or at least two points lower than at baseline, although the differences were not statistically significant (IL-17 82% vs. IL-23 44% at week 12, and IL-17 85% vs. IL-23 22% at week 24). Literature is enriching of surveys showing biologics efficacy in GPP with more than 100 reported GPP cases treated with anti-TNF, anti-IL12/23, anti-IL17, or anti-IL23 so far [69].

5.2. Novel therapeutic agents targeting IL-36 R

The discovery of the central role of the IL-36 pathway in GPP favored the research of inhibitors of this pathogenic mechanism. Recently, the humanized IgG1 monoclonal antibody spesolimab has been developed to specifically bind the IL-36 R with high affinity and inhibit the signaling by IL-36 R agonists [70].

The safety and efficacy of spesolimab have been investigated in the Effisayil™ 1 study, a phase II, multicenter, double-blind, placebo-controlled trial [17] which showed a rapid control of skin symptoms within a week of treatment, further indicating that IL-36 pathway inhibitors might represent a potential therapeutic option for GPP patients [71,72]. In this study, patients with a GPP flare were randomized in a 2:1 ratio to receive intravenous spesolimab or placebo. The primary endpoint was a Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) pustulation subscore of 0 at the end of week 1. At baseline, 46% of the patients in the spesolimab group and 39% in the placebo group had a GPPGA pustulation subscore of 3, and 37% and 33%, respectively, had a pustulation subscore of 4. At the end of week 1, 54% of patients in the spesolimab group had a pustulation subscore of 0, as compared with 6% of patients in the placebo group (difference, 49% points; 95% confidence interval (CI), 21

Table 3. Treatment options for generalized pustular psoriasis.

Treatment option	Type	Indication	Dosing/Schedule	Key notes	References
Corticosteroids	Non-biologic	Acute flares	Variable; e.g. oral prednisone 0.5–1 mg/kg/day, tapered based on response.	Fast-acting but associated with significant side effects and risk of flare upon withdrawal.	[9,59,62]
Cyclosporine	Non-biologic	Acute flares	3–5 mg/kg/day; dose adjusted based on therapeutic response and tolerability.	Preferred for rapid action in severe cases.	[9,62,63]
Methotrexate	Non-biologic	Chronic management	15–25 mg weekly, with folic acid supplementation.	Evidence for use is limited; requires monitoring for hepatic and hematological toxicity.	[9,59]
Acitretin	Non-biologic	Chronic management	0.5–1 mg/kg/day; dose titrated based on efficacy and tolerability.	Effective for keratinization disorders; teratogenicity limits use in women of childbearing potential.	[9,59,62]
Anti-TNF agents (e.g. Infliximab, Adalimumab, Etanercept, Certolizumab pegol)	Biologic	Acute and chronic management	Dosage varies by agent; e.g. infliximab 5 mg/kg IV every 8 weeks after loading doses at weeks 0, 2, and 6.	Limited evidence for use in acute flares; primarily used for chronic inflammatory conditions.	[64,65,67]
Anti-IL-17 agents (e.g. Secukinumab, Brodalumab, Ixekizumab, Bimekizumab)	Biologic	Chronic management	Dosage varies by agent; e.g. secukinumab 300 mg subcutaneous weekly for 5 weeks, then monthly.	Shown to be effective in some GPP cases, particularly in patients with concomitant plaque psoriasis.	[9,62,68,69]
Anti-IL-23 agents (e.g. Guselkumab, Risankizumab, Tildrakizumab)	Biologic	Chronic management	Dosage varies by agent; e.g. guselkumab 100 mg subcutaneous every 8 weeks after loading doses at weeks 0, 4.	Primarily used for plaque psoriasis; limited data in GPP.	[62,67]
Spesolimab	Anti-IL-36 R Biologic	Acute flare treatment and prevention	900 mg IV as a single dose for acute flares; 300 mg subcutaneous every 4 weeks for maintenance.	Recently approved; rapid efficacy demonstrated in Effisayil trials. First GPP-specific biologic.	[17,71,74]
Imsidolimab	Anti-IL-36 R Biologic	Under investigation	Dosage under investigation in clinical trials.	Promising therapeutic option targeting IL-36 pathway.	[70,72]

to 67; $p < 0.001$). Finally, 43% of patients in the spesolimab group had a GPPGA total score of 0 or 1 at week 1, compared with 11% of patients in the placebo group (difference, 32% points; 95% CI, 2 to 53; $p = 0.02$).

The molecular profiles of the blood and skin of patients experiencing a GPP flare treated with spesolimab were analyzed and compared to healthy volunteers [71]. The results showed that spesolimab-treated patients presented a downregulation of the IL-36 pathway – related signatures, Th1Th1/Th17 and innate inflammation signaling, neutrophilic mediators, and keratinocyte-driven inflammation pathways, as early as week 1. Also, a decrease in the levels of the related serum biomarkers and cell populations was observed in skin lesions from patients with GPP, including CD31, CD11c1, and IL-36γ1 cells and lipocalin-2–expressing cells. In addition, rapid improvements were reported in the Visual Analogue Scale (VAS) pain scale, in the Functional Assessment of Chronic Illness Therapy – Fatigue Scale (FACIT – Fatigue), in the dermatology life quality index (DLQI), and in the Psoriasis Symptom Scale (PSS) scores [73], up to week 12. At week 4, a significant correlation ('Spearman's rank correlation coefficient) was observed between the GPPGA total score and all patient-reported outcomes (PROs), except for the FACIT – Fatigue score (pain VAS: $p < 0.05$; DLQI: $p < 0.001$; and PSS: $p < 0.05$). The proportion of patients achieving a GPPGA pustulation subscore of 0 and a GPPGA total score of 0 or 1 also mirrored the improvements in PROs scores from baseline over time. The Effisayil^{TM}2 study, a clinical trial investigating whether maintenance treatment with spesolimab can prevent flares and provide sustained disease control in GPP patients, has been recently completed [74]. Results from the Effisayil 2 study show that a loading dose of 600 mg followed by 300 mg every 4 weeks leads to an 84% reduction in risk of flares over 48 weeks compared with placebo, with no flares after the first subcutaneous dose at week 4. (HR of 0.157 and $p = 0.0005$). Moreover, the safety profile of spesolimab was favorable. Preventing GPP flares with a well-tolerated and effective treatment would cover a highly unmet need decreasing the impact of comorbidities and associated mortality [74].

6. Conclusions

In this review, we provided a comprehensive overview of the epidemiology of GPP and the pathogenic mechanisms underpinning the disease. We also described the clinical presentation of GPP, and challenges related to its diagnosis and treatment due to heterogeneity. We highlighted current and emerging treatment options available in the field and discussed challenges in the management of the disease.

7. Expert opinion

GPP is a severe and potentially life-threatening condition that must be promptly diagnosed and treated at early stages. However, given the rarity and complexity of this disease, it is common for GPP patients to be seen in emergency departments by non-expert physicians. A misdiagnosis of the disease or an inappropriate therapeutic intervention can worsen the

prognosis of GPP with a profound influence on patients' short and long-term outcomes. Medical education programs could increase clinical awareness to support the management of these patients [75] by facilitating a timely diagnosis and minimizing the severity of the disease and the onset and duration of complications. However, there are several major weaknesses in the current clinical management of GPP [10]. First, the definition and classification of GPP across studies in the literature are inconsistent and highly heterogeneous, thus impacting the possibility of developing consensus guidelines on disease management [6]. Consequently, at present, there is a lack of unified criteria that can be internationally adopted to diagnose GPP and its degrees of severity [6]. The recently published International Psoriasis Council (IPC) criteria for GPP in 2024 represent a significant step toward establishing standardized international diagnostic guidelines. These criteria provide a comprehensive framework for diagnosing GPP based on clinical presentation and histological findings, and they incorporate key elements to distinguish GPP from other pustular dermatoses such as AGEP. While the IPC criteria address the need for uniformity, their adoption in clinical practice remains limited, and further validation in diverse populations is required. Nevertheless, these criteria are an important milestone in reducing diagnostic ambiguity and facilitating consistent disease classification across clinical and research settings. Guidelines for GPP management in Europe are not yet available, while the Japanese Dermatological Society has recently updated its guidelines on GPP pathogenesis and treatment [7], and members of the National Psoriasis Foundation, a worldwide recognized organization, released a consensus statement on GPP management to support physicians and all the individuals affected [76]. Unified guidelines internationally recognized should be urgently developed to help physicians navigate the complexity of this disease and the needs of those affected. Two recently published Delphi processes further explored this aspect [77,78]. Puig [78] and colleagues highlighted the need for additional studies on differential diagnosis and triggers and proposed a management algorithm for practitioners. Prignano [77] and colleagues described the need for additional research to guide treatment during different GPP phases [61].

Different lines of evidence suggest that there is an urgent need also for therapeutic agents. Recent advances in targeting the IL-36 pathway have shown promise in addressing these therapeutic gaps. Spesolimab, the first IL-36 receptor antagonist approved for GPP flares, has demonstrated rapid efficacy in controlling acute symptoms and preventing future flares, as shown in the Effisayil studies [17,74]. These studies revealed that spesolimab provides substantial clinical benefit by reducing pustulation and improving patient-reported outcomes during flares, and it significantly reduces flare recurrence when used as maintenance therapy. This positions spesolimab as a key treatment option addressing the unmet needs of GPP patients. In a recent survey conducted in the US, among 29 dermatologists with experience in treating GPP, 67% considered treatment as inadequate in preventing new flares, 72% evaluated the treatment's effect as too slow to control a flare, and 83% of the interviewed dermatologists revealed that patients presented residual symptoms between flares, despite using the full range of available systemic and biologic therapies [66,79]. Of note, a recent study reported that most patients with GPP believed that their condition was not well-controlled and described a considerable emotional and physical impact [79]. This emerged also in an analysis of GPP disease characteristics in patients enrolled in the CorEvitas Registry for Psoriasis, where the individuals affected by the disease noted a significant impact of the disease on patients' quality of life and indicated that current treatment options do not adequately control GPP flares [80].

There is a profound need for GPP-specific therapeutic agents to be licensed in Europe, as they are currently available in other countries. In Japan, TNF inhibitors, IL-17/IL-17 R inhibitors, and IL-23 inhibitors are currently in use, although the evidence of their safety and effectiveness in treating acute flare is scarce and mainly coming from open-label trials or small case series [64,75]. Currently, treatments with high, sustained efficacy, also in the early phases of GPP, remain necessary. Recent data indicate that IL-36 pathway inhibitors (spesolimab and imsidolimab) represent novel potential therapeutic options for GPP patients [17,71,72,75,81]. Spesolimab received its first approval on 1 September 2022, in the US for the treatment of GPP flares in adults [82,83]. On 26 September 2022, it was approved in Japan for the treatment of GPP acute symptoms [84] and on 9 December 2022, it received EMA approval for treating flares in GPP adult patients, and in May 2024, it was granted updated labels in both the United States and China to expand its indications for GPP treatment.

It took over a century of research to achieve a more comprehensive understanding of the pathogenic mechanisms underpinning GPP due to the high heterogeneity and complexity of the disease. Historically, GPP has been classified as a variant of psoriasis vulgaris (PV), but recent clinical, histological, and genetic data show that it is a distinct clinical entity that requires specific diagnostic and therapeutic approaches. Future efforts in the field should be directed to develop an internationally shared definition of GPP and guidelines to inform clinical practice and facilitate early GPP diagnosis and treatment, preventing the onset of complications. Furthermore, the development and approval of new therapeutic agents with sustained efficacy should be a priority for future research, to decrease the impact of comorbidities and mortality associated with GPP and support the needs of these patients that remain currently unmet.

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Declaration of interest

A Balato has served as a scientific board consultant for AbbVie, Almirall, Amgen, Boehringer Ingelheim, BMS, Eli-Lilly, Janssen, LeoPharma, Novartis and UCB. P Calzavara-Pinton has served as a scientific board consultant for AbbVie, Leo Pharma, Galderma, Cantabria, Jannsen, Sanofi, Sun Pharma and

Incyte. A Chiricozzi has served as an advisory board member and consultant and has received fees and speaker's honoraria or has participated in clinical trials for AbbVie, Almirall, Boehringer-Ingelheim, Bristol Myers Squibb, Leo Pharma, Lilly, Janssen, Novartis, and Sanofi Genzyme, outside the submitted work. MC Fargnoli has served on advisory boards, received honoraria for lectures and/or research grants from Amgen, Almirall, AbbVie, Boehringer-Ingelheim, BMS, Galderma, Kyowa Kyrin, LEO Pharma, Pierre Fabre, UCB, Lilly, Pfizer, Janssen, MSD, Novartis, Sanofi-Regeneron and Sunpharma. P Gisondi served as a speaker for AbbVie, Amgen, Almirall, Boehringer Ingelheim, Eli Lilly, Novartis, Pfizer, Pieffe Fabre, Sanofi, Sandoz and UCB. AV Marzano reports consultancy/advisory boards disease-relevant honoraria from AbbVie, Boehringer-Ingelheim, Novartis, Pfizer, Sanofi, Janssen and UCB. S Piaserico has been a consultant and/or speaker for AbbVie, Almirall, Celgene, Janssen, Leo-Pharma, Eli Lilly, Merck Sharp & Dohme, Novartis, Pfizer, Sandoz and UCB. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Reviewer disclosure

A reviewer on this manuscript has disclosed honoraria from AbbVie, Novartis and Boehringer Ingelheim for research, advisory boards and lectures, sometimes relating to generalized pustular psoriasis. Peer reviewers on this manuscript have no other relevant financial relationships or otherwise to disclose.

Author's contribution

All authors contributed to the concept and design of the manuscript and commented on all previous versions of the manuscript. All authors have read and approved the final manuscript. The author(s) meet the criteria for authorship as recommended by the International Committee of Medical Journal Editors (ICMJE).

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