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Generalized pustular psoriasis: A global Delphi consensus on clinical course, diagnosis, treatment goals and disease management

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Abstract

Background: Generalized pustular psoriasis (GPP) is a rare and highly heterogeneous skin disease, characterized by flares of neutrophilic pustules and erythema. As a rare disease with few clinical studies and no standardized management approaches, there is a paucity of knowledge regarding GPP.

Objectives: Conduct a Delphi panel study to identify current evidence and gain advanced insights into GPP.

Methods: A systematic literature review was used to identify published literature and develop statements categorized into four key domains: clinical course and flare definition; diagnosis; treatment goals; and holistic management. Statements were rated on a Likert scale by a panel of dermatologists in two rounds of online questionnaires; the threshold for consensus was agreement by ≥80%.

Results: Twenty-one panellists reached consensus on 70.9%, 61.8%, 100.0% and 81.8% of statements in the 'clinical course and flare definition', 'diagnosis', 'treatment goals' and 'holistic management of GPP' domains, respectively. There was clear consensus on GPP being phenotypically, genetically and immunologically distinct from plaque psoriasis. Clinical course is highly variable, with an extensive range of complications. Clinical and histologic features supporting GPP diagnosis reached high levels of agreement, and although laboratory evaluations were considered helpful for diagnosis and monitoring disease severity, there was uncertainty around the value of individual tests. All acute and long-term treatment goals reached consensus, including rapid and sustained clearance of pustules, erythema, scaling and crust, clearance of skin lesions and prevention of new flares. Potential triggers, associated comorbidities and differential diagnoses achieved low rates of consensus, indicating that further evidence is needed.

Conclusions: Global consensus between dermatologists was reached on clinically meaningful goals for GPP treatment, on key features of GPP flares and on approaches for assessing disease severity and multidisciplinary management of patients. On this basis, we present a management algorithm for patients with GPP for use in clinical practice.

INTRODUCTION

Generalized pustular psoriasis (GPP; von Zumbusch type) is a rare autoinflammatory skin disease characterized by widespread eruption of sterile, neutrophilic pustules.[1,2] The prevalence of GPP varies between studies and countries, with reports of 0.02 per 10,000 people in France, 0.07–0.09 per 10,000 in Brazil, 0.15 per 10,000 in Sweden, 0.2 per 10,000 in Japan, 0.9 per 10,000 in the USA, 1.1 per 10,000 in South Korea and 1.4 per 10,000 in Germany.[3–7]

GPP is a heterogeneous disease with variable clinical course and manifestations; patients may experience recurrent GPP flares with periods of clear skin or persistent disease with flares of increased severity.[1,8] Flares can be triggered by several factors including infections, medication withdrawal and pregnancy and can be associated with systemic symptoms and markers of inflammation such as fever, fatigue and elevated C-reactive protein (CRP) levels.[9–12] If left untreated, systemic inflammation associated with GPP may develop into life-threatening complications such as sepsis and multisystem organ failure.[13]

The European Rare and Severe Psoriasis Expert Network (ERASPEN) and the Japanese Dermatological Association (JDA) have published guidelines on the phenotypic classification and diagnostic criteria of GPP, respectively;[1,9] however, the evidence base for these guidelines is limited. Owing to the rarity of GPP, large-scale clinical trials are not feasible. This, combined with a lack of international consensus on clinical criteria for diagnosis and treatment goals, has resulted in few clinical studies and a general paucity of information to inform effective clinical management of patients with GPP.

We conducted a Delphi panel study to gain advanced global insights into the clinical course, diagnosis, treatment goals and management of GPP.

MATERIALS AND METHODS

Study design overview

The objective of this global Delphi panel study was to achieve consensus on four key domains related to GPP: clinical course and flare definition; diagnosis; treatment goals; and holistic management. Statements relating to these domains were developed following a systematic literature review (SLR) and discussion with a steering committee of clinical experts. Statements were then evaluated within the framework of a Delphi panel of physicians.[14] Details on the SLR methodology, steering committee and Delphi panellists are available in the Supplementary Material.

Delphi panel study

Data from the Delphi panel were collected via two rounds of questionnaires housed on a secure online platform (IQVIA). Panellists anonymously evaluated statements, indicating their agreement on a Likert Scale from 1 (strong disagreement) to 7 (strong agreement). A free-text field was available for additional comments. After round 1, statements with low agreement or suggestions from panellists were discussed by the steering committee; revised statements were included in the questionnaire for round 2 (statements with ≥80% agreement were not revised). For statements for which a useful revision was not possible, 'no consensus' was declared and no further evaluation was conducted.

Data analysis

Descriptive statistical analysis was conducted using SAS® software V9.3 or later (SAS Institute). Continuous variables were described by number, mean, standard deviation, median and range values; categorical variables were described as the total number and relative percentage per category. To calculate consensus rates, each statement was counted equally with no weighting. Consensus was reached when ≥80% of panellists scored a statement within the thresholds for agreement (5–7) or disagreement (1–3).

RESULTS

Systematic literature review

The SLR identified 3070 publications, of which 237 were used to generate 78 main statements for use in the Delphi panel study (Figure S1).

Demographics of Delphi panellists

All panellists were dermatologists. Of 21 panellists who participated in round 1, 19 completed round 2. The panellists provided global opinions; 38.1% were based in Asia, 23.9% in Europe, 4.8% in the USA, 14.3% in South America and 9.5% in Africa (see Supplementary Material). Over half of the panellists (52.4%) worked in a hospital setting with in- and outpatient practice; 14.3% in a hospital with in-patient practice only; 28.6% in both a hospital and from an office; and 4.8% were exclusively office based. There were more male (71.4%) than female (28.6%) panellists, and the majority (>95%) were aged ≥40 years.

Delphi panel study findings

Figure 1 summarizes the number of statements reaching consensus or no consensus in each Delphi panel round, and the number that required revision after round 1. In round 1, 141 of 185 statements (76.2%) achieved consensus (Table 1). Following steering committee review, round 2 included 28 revised statements, of which 16 (57.1%) reached consensus

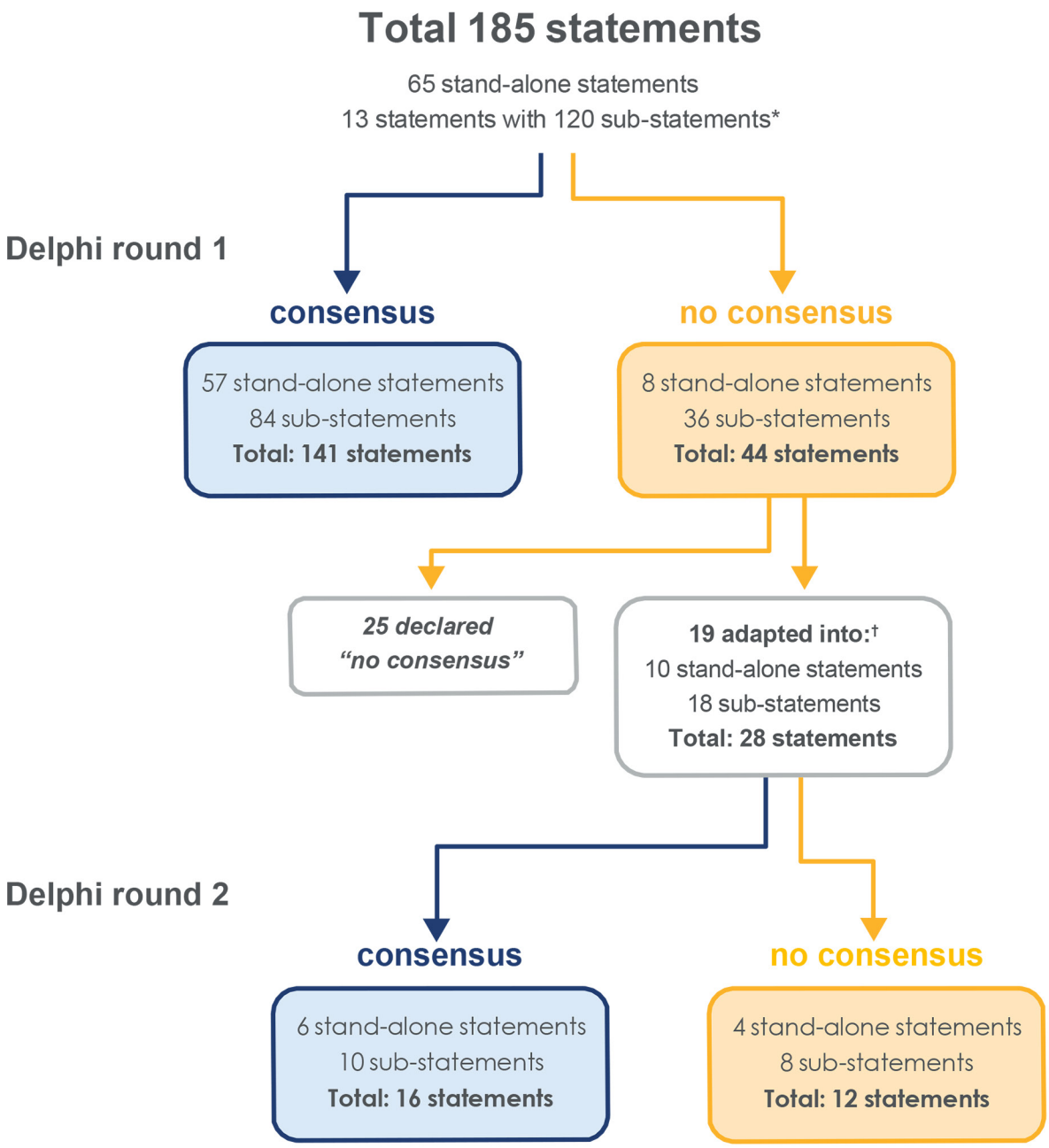

FIGURE 1 Flow chart of consensus on statements following Delphi rounds 1 and 2. Flow chart showing the numbers of statements included in the two rounds of questionnaires. The chart shows how many statements reached consensus after each round, how many were revised after round 1 and included in round 2 and how many did not reach consensus. *For statements with sub-statements, only the sub-statements were voted on; †"Adapted" refers to statements that were revised, split or complemented.

(Table 1). After both Delphi panel rounds, consensus was reached for 157 of 213 statements (73.7%) and no consensus for 56 of 213 statements (26.3%); all statements that reached consensus are presented in Table 2 and those without consensus in Table 3. Additional breakdown of agreement rates reached after each Delphi round and for individual domains is provided in the Supplementary Material (Tables S1–S4).

Based on the consensus statements agreed by this global panel of experts, we have developed detailed (Figure 2) and concise (Figure 3) clinical management algorithms for GPP, covering the four domains of clinical course and flare definition; diagnosis; treatment goals; and holistic management of GPP. Key statements that will inform clinical practice and have contributed to the management algorithm are outlined later.

Domain 1: Clinical course and flare definition

Consensus was reached on the key characteristics of GPP, which were defined as follows: primary, macroscopically

TABLE 1 Proportion of statements reaching consensus after each round of the Delphi process.

Domain/subdomain	Statements, n	Agreement, n (%)
Round 1		
Total	185	141 (76.2)
Domain 1: Clinical course and flare definition		
GPP definition/classification	21	16 (76.2)
Flare definition and GPP clinical course	9	9 (100.0)
Potential triggers and disposing factors	27	13 (48.1)
Prognosis	24	23 (95.8)
Domain 1 total	81	61 (75.3)
Domain 2: Diagnosis		
Criteria	2	2 (100.0)
Clinical diagnosis of GPP	3	3 (100.0)
Laboratory tests relevant for the diagnosis of GPP	15	9 (60.0)
Genetic screening in GPP diagnosis	2	1 (50.0)
Histopathologic features of GPP	5	4 (80.0)
Differential diagnosis	14	5 (35.7)
Domain 2 total	41	24 (58.5)
Domain 3: Treatment goals		
Flare/acute phase treatment goals	9	9 (100.0)
Long-term goals	8	8 (100.0)
Domain 3 total	17	17 (100.0)
Domain 4: Holistic management of GPP		
Domain 4 total	46	39 (84.8)
Round 2		
Total	28	16 (57.1)
Domain 1: Clinical course and flare definition		
GPP definition/classification	3	0
Potential triggers and disposing factors	2	0
Domain 1 total	5	0
Domain 2: Diagnosis		
Laboratory tests relevant for the diagnosis of GPP	3	1 (33.3)
Genetic screening in GPP diagnosis	2	2 (100.0)
Histopathologic features of GPP	7	7 (100.0)
Differential diagnosis	2	0
Domain 2 total	14	10 (71.4)
Domain 4: Holistic management of GPP		
Domain 4 total	9	6 (66.7)
Rounds 1 and 2		
Total	213	157 (73.7)

Abbreviation: GPP, generalized pustular psoriasis.

visible pustules of variable size on inflamed skin, classically affecting non-acral areas, associated with systemic symptoms. GPP is phenotypically, genetically and immunologically distinct from plaque psoriasis; however, GPP can occur with or without plaque psoriasis. Extracutaneous signs and symptoms of GPP that reached consensus were fever, chills, malaise, arthritis, arthralgia, asthenia, fatigue, neutrophilic cholangitis, nail abnormalities, cardiovascular shock, liver abnormalities, oedema and laboratory abnormalities. Other extracutaneous symptoms of GPP identified from the SLR, including conjunctivitis, uveitis, and otitis media, did not reach consensus (Table 3).

There was consensus that the clinical course of GPP is highly variable; it can be relapsing or persistent and is generally unstable and prolonged without treatment. Characteristics of a GPP flare consist of acute onset of a rapidly disseminating erythema covered with aseptic pustules, crusts and scales, with pustules often merging to form lakes of pus. Flares are also associated with systemic symptoms such as fever, arthralgia and asthenia. Severity of flares varies between patients and episodes in the same patient, and even in the postflare phase, there may be residual disease.

Experts reached consensus on treatment with or withdrawal of systemic corticosteroids or antipsoriatic therapy, and bacterial or viral infections as potential triggers for GPP flares. However, there was no agreement on non-steroidal anti-inflammatory drugs (NSAIDs), antihypertensives, exposure to sunlight, seasonal variation or menstruation as potential triggers. Patients with a family history of plaque psoriasis, GPP or another form of pustular psoriasis may be predisposed to GPP, and genetic mutations such as *IL36RN*, *CARD14*, *AP1S3* and *SERPINA3* are potentially associated with GPP. Other risk factors include stress and pregnancy.

The aetiology of GPP in pregnancy is unclear but typically presents during the last trimester and may be associated with hypocalcaemia and hypoparathyroidism; it is associated with severe negative outcomes such as placental insufficiency leading to an increased risk of stillbirth, neonatal death and foetal abnormalities. Although GPP is rare in children, it may present as a severe and potentially life-threatening disorder. Elderly patients may also have a poor prognosis, driven by systemic complications of GPP. Consensus was reached on an extensive list of complications associated with GPP (Table 2), with only secondary amyloidosis not reaching consensus. Due to the multiple complications that can occur during a flare, GPP can be potentially life-threatening.

Domain 2: Diagnosis

There was consensus among panellists that the ERASPEN criteria and JDA diagnostic criteria can be used to classify/define GPP (Table 2). GPP should be suspected in patients with acute onset erythema and pustulosis, and a complete medication history should be explored.

A number of laboratory tests were agreed as helpful in diagnosing GPP, including complete blood cell count, erythrocyte sedimentation rate, CRP levels and blood chemistries (Table 2). By contrast, elevated plasma immunoglobulin (IgG, IgA) levels, hypo/hyperkalaemia and hyponatraemia were not considered informative for GPP diagnosis (Table 3).

TABLE 2 Statements on generalized pustular psoriasis with expert consensus.

Domain/subdomain	Statement (round 1/round 2; R1/R2)	Agreement
Domain 1: Clinical course and flare definition		
GPP definition/classification	Generalized pustular psoriasis (GPP) is defined as primary, macroscopically visible pustules of variable size on inflamed skin classically affecting non-acral areas associated with systemic symptoms. (R1)	95%
	GPP is historically considered a variant of psoriasis but is indeed phenotypically, genetically, immunologically and histopathologically distinct from psoriasis vulgaris/plaque psoriasis. (R1)	100%
	GPP can occur with or without plaque psoriasis. (R1)	91%
	Skin symptoms are pain, burning and pruritus. (R1)	100%
	Extracutaneous signs and symptoms of GPP at any stage during the disease course may include:	
	• Fever, chills and malaise (R1)	100%
	• Arthritis and arthralgia (R1)	91%
	• Asthenia and fatigue (R1)	95%
	• Neutrophilic cholangitis (R1)	81%
	• Nail abnormalities (R1)	95%
	• Cardiovascular shock (R1)	81%
	• Liver abnormalities and jaundice (R1)	86%
	• Oedema (mostly lower extremity) and oedema in recumbent parts (R1)	100%
	• Laboratory abnormalities as in erythroderma (hypoalbuminemia, hyposideremia, electrolyte alterations, hypocalcaemia, leukocytosis with/without eosinophilia, thrombocytosis, anaemia) (R1)	100%
	GPP can be classified according to genetic and clinical characteristics (time of onset and distribution). (R1)	100%
	GPP is rare in children but may present as a severe and potentially life-threatening disorder. (R1)	100%
	Impetigo herpetiformis, or GPP during pregnancy, has a typical onset in the last trimester and, while the aetiology is unclear, associations with hypocalcaemia and hypoparathyroidism have been suggested in some cases. (R1)	91%
Flare definition and GPP clinical course	A GPP flare consists of the acute onset of a rapidly disseminating erythema covered with aseptic pustules, crusts and scales and associated with systemic symptoms: fever, arthralgia and asthenia. (R1)	100%
	GPP can be either relapsing (more than one episode of flares) or persistent (disease maintained over the course of more than 3 months). (R1)	95%
	Flares may occur as often as several times per year or with long dormant periods between activity. (R1)	100%
	Flaring frequency is unpredictable in most cases of GPP. (R1)	100%
	The spectrum of severity of flares varies widely among patients and also varies across flare episodes in the same patient. (R1)	100%
	GPP presents with mainly three phases: prepustular phase, flare phase, postflare phase/between flares. (R1)	95%
	The prepustular phase may or may not include psoriatic lesions and may start several years prior to the first GPP flare. (R1)	86%
	During a flare, pustules often merge to big lakes of pustules and can last for days or weeks. (R1)	100%
	In the postflare phase/between flares, patients still may have residual disease, most commonly with symptoms such as minimal skin scaling and crusts, and minor erythema. (R1)	100%
Potential triggers and disposing factors	GPP may erupt due to internal or external triggers or idiopathically. (R1)	100%
	Flares or relapses can be seen after treatment discontinuation, during maintenance treatment or following infection. (R1)	100%
	Pustular flares of psoriasis, including GPP, have been reported to be potentially triggered by medications, including:	
	• Treatment or withdrawal of systemic corticosteroids, or antipsoriatic treatment (e.g. cyclosporine, TNF-α inhibitors, secukinumab and ustekinumab) in patients with psoriasis vulgaris (R1)	91%
	Bacterial and viral infections have been reported as potential triggers of GPP flares. (R1)	100%
	The benefit of COVID-19 vaccination for patients with GPP outweighs the potential risk of triggering a GPP flare. (R1)	91%
	Mutations/genetic disposition potentially associated with GPP include:	
	• Positive family history: Plaque psoriasis, and/or GPP, and/or other forms of pustular psoriasis (R1)	95%
	• Gene mutations in *IL36RN*, deficiency of IL-36 receptor antagonist or unopposed IL-36 signalling in general (R1)	100%
	• Gene mutation in *CARD14* (R1)	100%
	• Gene mutation in *AP1S3* (R1)	86%
	• Gene mutation in *SERPINA3* (R1)	81%
	Other risk factors potentially triggering GPP flares include:	
	• Pregnancy, with a typical onset in the last trimester (R1)	95%
	• Stress (R1)	91%
	• Severe hypocalcaemia secondary to hypoparathyroidism (R1)	81%

(Continues)

TABLE 2 (Continued)

Domain/subdomain	Statement (round 1/round 2; R1/R2)	Agreement
Prognosis	The clinical course of GPP is highly variable, generally unstable and prolonged without treatment. (R1)	100%
	The prognosis in older patients may be poorer than in younger patients and this is driven by the systemic complications of GPP, including cardiorespiratory failure and chance of infection and sepsis. (R1)	100%
	GPP in pregnancy is associated with severe negative outcomes, including placental insufficiency leading to an increased risk of stillbirth, neonatal death and foetal abnormalities. (R1)	95%
	GPP can be potentially life-threatening and result in death due to its multiple complications during a flare. (R1)	100%
	Complications in GPP patients include:	
	• Death (septic shock and cardiac failure) (R1)	95%
	• Infections (R1)	100%
	• Systemic capillary leak syndrome (R1)	95%
	• Superinfection (R1)	100%
	• Septicaemia (R1)	100%
	• Sepsis (R1)	100%
	• Intestinal malabsorption (R1)	86%
	• Liver diseases: (spontaneous, bleeding and toxic hepatitis) (R1)	81%
	• Acute renal failure (R1)	91%
	• Heart failure (R1)	86%
	• Arthritis (R1)	91%
	• Aseptic purulent arthritis (R1)	81%
	• Myalgias and polymyalgia (R1)	86%
	• Polyarthralgia (R1)	95%
	• Bronchopneumonia (R1)	86%
	• Acute respiratory distress syndrome (psoriasis-related sterile pneumonitis) (R1)	100%
	• Pulmonary capillary leak syndrome (R1)	91%
	• Mucosal lesions (R1)	86%
	• Iatrogenic complications (steroids: hypocortisolism, Cushing syndrome, osteoporosis; infliximab: arthritic lupus, arterial thrombosis; cyclosporine: renal failure) (R1)	91%
Domain 2: Diagnosis		
Criteria	ERASPEN criteria can be used to classify GPP (primary, sterile, macroscopically visible pustules on non-acral skin [excluding cases where pustulation is restricted to psoriatic plaques]). (R1)	86%
	JDA diagnostic criteria can be used to define GPP. (Diagnostic criteria: a) systemic symptoms such as fever and fatigue; b) systemic or extensive flush accompanied by multiple sterile pustules that sometimes merge to form lakes of pus; c) neutrophilic subcorneal pustules histopathologically characterized by Kogoj's spongiform pustules; d) the clinical and histological features a)-c) recur repeatedly. Exclusion criteria for GPP: a) clear cases of psoriasis vulgaris with transient pustule formation after the application of corticosteroids; b) in general, the circinate annular form is excluded because of mild systemic symptoms; c) cases where the diagnosis of subcorneal pustular dermatosis or pustular drug eruptions (including AGEP) is made after careful observation for a certain period). (R1)	81%
Clinical diagnosis of GPP	The diagnosis of GPP should be suspected in patients with acute onset erythema and pustulosis. (R1)	100%
	Medical history (history or family history of psoriasis vulgaris or pustular psoriasis) is useful to confirm a diagnosis of GPP. (R1)	86%
	A complete medication history should be explored. (R1)	100%
Laboratory tests relevant for the diagnosis of GPP	Laboratory evaluations are helpful for diagnostic and therapeutic purposes in GPP. (R1)	100%
	Complete blood cell count:	
	• Leukocytosis with left shift with/without eosinophilia (R1)	100%
	• Neutrophilia (R1)	100%
	Elevated ESR. (R1)	91%
	Elevated CRP. (R1)	95%
	Blood chemistries:	
	• Decreased albumin (R1)	86%
	• Decreased calcium and zinc (R1)	81%
	• High blood urea nitrogen and creatinine if the patient is oligemic (R1)	86%
	• Elevated liver function enzymes (aspartate transaminase, alanine transaminase) in the case of liver damage; alkaline phosphatase, bilirubin (R1)	91%
	Urinalysis can be positive for albumin but is not a diagnostic measure. (R2)	90%

TABLE 2 (Continued)

Domain/subdomain	Statement (round 1/round 2; R1/R2)	Agreement
Genetic screening in GPP diagnosis	When available genetic testing helps to diagnose GPP. (R1)	86%
	When available, genetic testing for *IL36RN* mutations is recommended. (R2)	84%
	Screening for mutations other than *IL36RN* may be considered, if available. (R2)	84%
Histopathologic features of GPP	Histopathological examination of a skin biopsy is useful to confirm diagnosis of GPP in some patients and is useful for differential diagnosis purposes. (R1)	91%
	Histological findings in skin biopsies include:	
	• Neutrophilic subcorneal pustules histopathologically characterized by Kogoj's spongiform pustules (R1)	100%
	• Intense neutrophilic epidermal and dermal infiltration and forming pustules with subcorneal localization as well as acanthosis, spongiosis and exocytosis in epidermis (R1)	95%
	• Munro's micro-abscesses and superficial perivascular mononuclear cell infiltrations can also be observed (R1)	95%
	• Intraepidermal pustules (R2)	100%
	Histological findings of psoriasis vulgaris which can be present in GPP include:	
	• Parakeratosis (R2)	95%
	• Acanthosis (R2)	95%
	• Hyperkeratosis (R2)	84%
	• Elongation of rete ridges (R2)	90%
	• Diminished stratum granulosum (R2)	100%
	• Capillary dilation of the papillary dermis (R2)	100%
Differential diagnosis	The most important diagnosis to exclude is AGEP. (R1)	95%
	Other differential diagnosis to exclude are:	
	• Subcorneal pustular dermatosis/Sneddon–Wilkinson disease (R1)	95%
	• IgA pemphigus (R1)	81%
	• Erythrodermic psoriasis (R1)	81%
	• Infectious diseases: acute generalized pustular bacterid, bullous or non-bullous impetigo, multiple sweat gland abscesses, sepsis and fungal infections (R1)	81%
Domain 3: Treatment goals		
Flare/acute phase treatment goals	Achieve rapid and sustained clearance of pustules. (R1)	100%
	No fresh pustules being observed. (R1)	100%
	Achieve rapid and sustained clearance of inflammatory erythema. (R1)	95%
	Achieve rapid and sustained clearance of scaling and crust. (R1)	91%
	Achieve complete and sustained clearance of skin lesions. (R1)	95%
	Improved control of consequences of systemic inflammation (including but not limited to acute respiratory distress syndrome, cardiovascular aseptic shock, heart failure, prerenal kidney failure and severe infections). (R1)	100%
	Rapidly alleviate systemic symptoms. (R1)	100%
	Reduce pain. (R1)	100%
	Favourable safety profile. (R1)	100%
Long-term goals	Prevention of new flares. (R1)	100%
	Sustained resolution of skin and systemic symptoms (no symptoms):	
	• No pustules over time (R1)	95%
	• No erythema over time (R1)	95%
	• No crust and scaling over time (R1)	100%
	• No pain over time (R1)	95%
	• No itching over time (R1)	95%
	No safety concerns with long-term exposure. (R1)	100%
	Normalize health-related quality of life. (R1)	100%
Domain 4: Holistic management of GPP		
	Quality of life should be assessed on an ongoing basis. (R1)	100%
	Diagnosis and treatment of GPP should be provided at centres with dermatologists experienced in managing GPP. (R1)	100%
	The following assessments are useful for assessing/monitoring disease severity in GPP in clinical practice:	
	• GPPGA: Generalized Pustular Psoriasis Physician Global Assessment (R1)	95%
	• GPPASI: Generalized Pustular Psoriasis Area and Severity Index (R1)	95%
	• Body surface area affected by GPP lesions (R1)	95%
	• Systemic symptoms during flares (R1)	95%

(Continues)

TABLE 2 (Continued)

Domain/subdomain	Statement (round 1/round 2; R1/R2)	Agreement
	• Laboratory markers of systemic inflammation including, but not limited to, WBC count, serum CRP, ESR, procalcitonin assessment and albumin levels (R1)	95%
	Laboratory evaluations are strongly recommended and deemed necessary for assessment of severity and potential complications associated with GPP. (R1)	100%
	Tools to assess patient-reported outcomes (e.g. DLQI, SF-36 and pain VAS) are useful to assess the impact of disease or treatment interventions on patients in clinical practice. (R1)	95%
	During flares, emergency care may be required, especially when a patient presents with fever, severe pain, elevated markers of systemic inflammation or signs of infection. (R1)	95%
	Systemic management and drug therapy are an essential part of GPP treatment because untreated patients have an increased risk of systemic complications, including cardiorespiratory failure. (R1)	100%
	During pregnancy, GPP flares should be treated promptly and monitored closely to prevent any further complications that may impact the mother and the foetus' well-being. (R1)	100%
	Treatments with rapid onset of action during GPP flares are essential. (R1)	100%
	Treatment should be continued according to disease severity. (R1)	100%
	During flares, patients should be carefully monitored by a dermatologist. (R1)	100%
	GPP is associated with multiple comorbidities. The following comorbidities impact management of GPP and/or affect treatment decisions for GPP:	
	• Obesity (R1)	86%
	• Diabetes mellitus (R1)	95%
	• Infections (R1)	100%
	• Psoriasis vulgaris (R1)	95%
	• Psoriatic arthritis (R1)	95%
	• Polyarthritis and arthritis (R1)	91%
	• Hypertension (R1)	95%
	• Hormonal/metabolic conditions (R1)	81%
	• Autoimmune conditions (R1)	86%
	• Liver disease (R1)	95%
	• Inflammatory skin conditions (R1)	81%
	• Subcutaneous tissue infections (R1)	91%
	• Septicaemia during hospitalization (R1)	100%
	• Cardiovascular disease (R1)	95%
	• Ischaemic heart disease (R1)	91%
	• Chronic renal insufficiency (R1)	86%
	• Acute renal failure (R1)	91%
	• Depression (R1)	91%
	• Anxiety (R1)	91%
	• Fluid and electrolyte disorders (R1)	91%
	A multidisciplinary approach is required and patients should be referred to other relevant specialties according to the patient's specific symptoms including, but not limited to:	
	• Acute respiratory distress syndrome (R1)	100%
	• Capillary leak syndrome (R1)	100%
	• Cardiovascular impairment (R1)	100%
	• Arthritis (R1)	95%
	Consultation with GP:	
	• May be required according to systemic symptoms as needed (R2)	84%
	Consultation with internist:	
	• May be required according to systemic symptoms, as needed	90%
	Consultation with infectologist to evaluate secondary infections/sepsis risk should be done as needed. (R2)	90%
	Consultation with specialists (e.g. rheumatologist, endocrinologist, ophthalmologist, gastroenterologist, genetic counsellor and obstetrician) should be done as needed. (R2)	100%
	Blood chemistries should be monitored for appropriate disease management:	
	• Hypo/hyperkalaemia (R2)	95%
	• Hyponatraemia (R2)	95%

Abbreviations: AGEP, acute generalized exanthematous pustulosis; CRP, C-reactive protein; DLQI, Dermatology Life Quality Index; ERASPEN, European Rare and Severe Psoriasis Expert Network; ESR, erythrocyte sedimentation rate; GP, general practitioner; GPP, generalized pustular psoriasis; IgA, immunoglobulin A; IL-36, interleukin-36; JDA, Japanese Dermatological Association; R1, round 1; R2, round 2; SF-36, Short Form-36; TNF-α, Tumour Necrosis Factor alpha; VAS, Visual Analog Scale; WBC, white blood cell.

TABLE 3 Statements on generalized pustular psoriasis with a lack of expert consensus.

Domain/subdomain	Statement (round 1/round 2; R1/R2)	Agreement
Domain 1: Clinical course and flare definition		
GPP definition/classification	Extracutaneous signs and symptoms of GPP at any stage during the disease course may include:	
	• Conjunctivitis, uveitis, otitis media (R1)	76%
	• Conjunctivitis (R2)	47%
	• Uveitis (R2)	58%
	• Otitis media (R2)	16%
	• Epigastric pain and cholestasis (R1)	67%
	• Intestinal malabsorption (R1)	52%
	• Interstitial pneumonitis (R1)	76%
	• Prerenal renal failure (R1)	76%
Potential triggers and disposing factors	Pustular flares of psoriasis, including GPP, have been reported to be potentially triggered by medications, including:	
	• NSAIDs and antihypertensives (R1)	67%
	• Antibiotics and terbinafine (R1)	76%
	• Antibiotics (R2)	58%
	• Terbinafine (R2)	53%
	• Lithium carbonate, fluoxetine (R1)	67%
	• Progesterone (R1)	67%
	• Vaccinations (e.g. monovalent H1N1) (R1)	76%
	Mutations/genetic disposition potentially associated with GPP include:	
	• Gene mutation in MPO (R1)	71%
	• Patients with TNF-238A may be more susceptible to paediatric-onset GPP (R1)	62%
	Other risk factors potentially triggering GPP flares include:	
	• Allogeneic haematopoietic SCT (R1)	67%
	• Turner syndrome (R1)	52%
	• Sun exposure (R1)	71%
	• Seasonal variation (R1)	57%
	• Salicylates (R1)	52%
	• Exertion (R1)	52%
	• Menstruation (R1)	62%
Prognosis	Complications in GPP patients include:	
	• Secondary amyloidosis (R1)	62%
Domain 2: Diagnosis		
Laboratory tests relevant for the diagnosis of GPP	Blood chemistries:	
	• Elevated plasma globulins (IgG, IgA) (R1)	67%
	• Hypo/hyperkalaemia (R1)	76%
	• Hyponatraemia (R1)	76%
	Urinalysis: positive for albumin. (R1)	62%
	Pustule smear and cultures: negative results indicate the absence of bacterial and fungal infection. (R1)	67%
	Pustular smear and cultures should be performed to rule out superinfection. (R2)	53%
	Blood examinations: procalcitonin. Elevation is an indication of systemic bacterial infection (R1)	76%
	Elevation of procalcitonin supports systemic bacterial infection. (R2)	79%
Genetic screening in GPP diagnosis	Genetic testing is not used in clinical practice for the diagnosis of GPP, but only as a research tool. (R1)	76%
Histopathologic features of GPP	Histological findings in skin biopsies include:	
	• Parakeratosis, acanthosis, hyperkeratosis, elongation of rete ridges, diminished stratum granulosum and capillary dilation of the papillary dermis. (R1)	67%

(Continues)

TABLE 3 (Continued)

Domain/subdomain	Statement (round 1/round 2; R1/R2)	Agreement
Differential diagnosis	Other differential diagnoses to exclude are:	
	• Pemphigus foliaceus (R1)	57%
	• SAM syndrome (R1)	52%
	• DIRA (R1)	71%
	• TEN (R1)	48%
	• Palmoplantar pustulosis (R1)	52%
	• ACH (R1)	43%
	• Psoriasis vulgaris/plaque psoriasis (R1)	71%
	Poststreptococcal pustulosis (pustulosis acuta generalisata) (R1)	57%
	Psoriasis vulgaris and GPP can be easily distinguished. (R1)	76%
	Palmoplantar pustulosis may occasionally coexist with GPP. (R2)	68%
	ACH may occasionally coexist with GPP. (R2)	74%
Domain 4: Holistic management of GPP		
	The following assessments are useful for assessing/monitoring disease severity in GPP in clinical practice:	
	• JDA severity index of GPP (R1)	76%
	GPP is associated with multiple comorbidities. The following comorbidities impact management of GPP and/or affect treatment decisions for GPP:	
	• Dyslipidaemia (R1)	76%
	• Thyroid disorder (R1)	62%
	• Malignancies (R1)	76%
	Consultation with a GP, internist or rheumatologist is always required. (R1)	71%
	Consultation with a GP is always required. (R2)	26%
	Consultation with an internist is always required. (R2)	32%
	Consultation with an infectologist to evaluate secondary infections/sepsis risk. (R1)	76%
	Consultation with an endocrinologist, ophthalmologist, gastroenterologist, genetic counsellor and obstetrician as needed (R1)	76%
	Blood chemistries should be monitored for appropriate disease management:	
	• Elevated plasma globulins (IgG, IgA) (R2)	53%

Abbreviations: ACH, acrodermatitis continua of Hallopeau; DIRA, deficiency of the interleukin-1 receptor antagonist; GP, general practitioner; GPP, generalized pustular psoriasis; IgA, immunoglobulin A; IgG, immunoglobulin G; JDA, Japanese Dermatological Association; MPO, myeloperoxidase; NSAID, non-steroidal anti-inflammatory drug; R1, round 1; R2, round 2; SAM, severe dermatitis, multiple allergies, and metabolic wasting; SCT, stem cell transplantation; TEN, toxic epidermal necrolysis; TNF, tumour necrosis factor.

Moreover, there was no consensus on the role of pustule smears and cultures in diagnosing GPP. Genetic testing is helpful for GPP diagnosis, when available; screening for *IL36RN* mutations is recommended, while screening for other mutations associated with GPP may be considered if available.

Experts agreed that histopathologic examination of a skin biopsy is useful in differential diagnoses to confirm GPP. Histologic features of GPP include neutrophilic subcorneal pustules characterized by Kogoj's spongiform pustules, intense neutrophilic epidermal and dermal infiltration, intraepidermal pustules and Munro's micro-abscesses (Table 2). The panel agreed that parakeratosis, acanthosis, hyperkeratosis, elongation of rete ridges, diminished stratum granulosum and capillary dilation of the papillary dermis are histologic findings of plaque psoriasis, which may also be present in GPP.

Consensus rates were lowest for statements relating to differential diagnoses. Although panellists agreed that the most important diagnosis to exclude is acute generalized exanthematous pustulosis (AGEP), consensus was not reached for other differential diagnoses, for example deficiency of the interleukin-1 receptor antagonist (DIRA), palmoplantar pustulosis, acrodermatitis continua of Hallopeau (ACH) and plaque psoriasis.

Domain 3: Treatment goals

Consensus was reached for all statements relating to treatment goals in GPP. In the acute phase, therapeutic strategies should aim at achieving rapid and sustained clearance of pustules, inflammatory erythema, scaling, crust and skin lesions; no fresh pustules should be observed. Flare treatment

FIGURE 2 Detailed management algorithm for GPP based on consensus statements after two Delphi panel rounds. All statements that achieved consensus after two rounds of questionnaires were summarized and incorporated into a detailed flow chart. AGEP, acute generalized exanthematous pustulosis; ARDS, acute respiratory distress syndrome; ERASPEN, European Rare and Severe Psoriasis Expert Network; GP, general practitioner; GPP, generalized pustular psoriasis; GPPASI, generalized pustular psoriasis area and severity index; GPPGA, generalized pustular psoriasis physician global assessment; IL-36R, interleukin-36 receptor; JDA, Japanese Dermatological Association; QoL, quality of life.

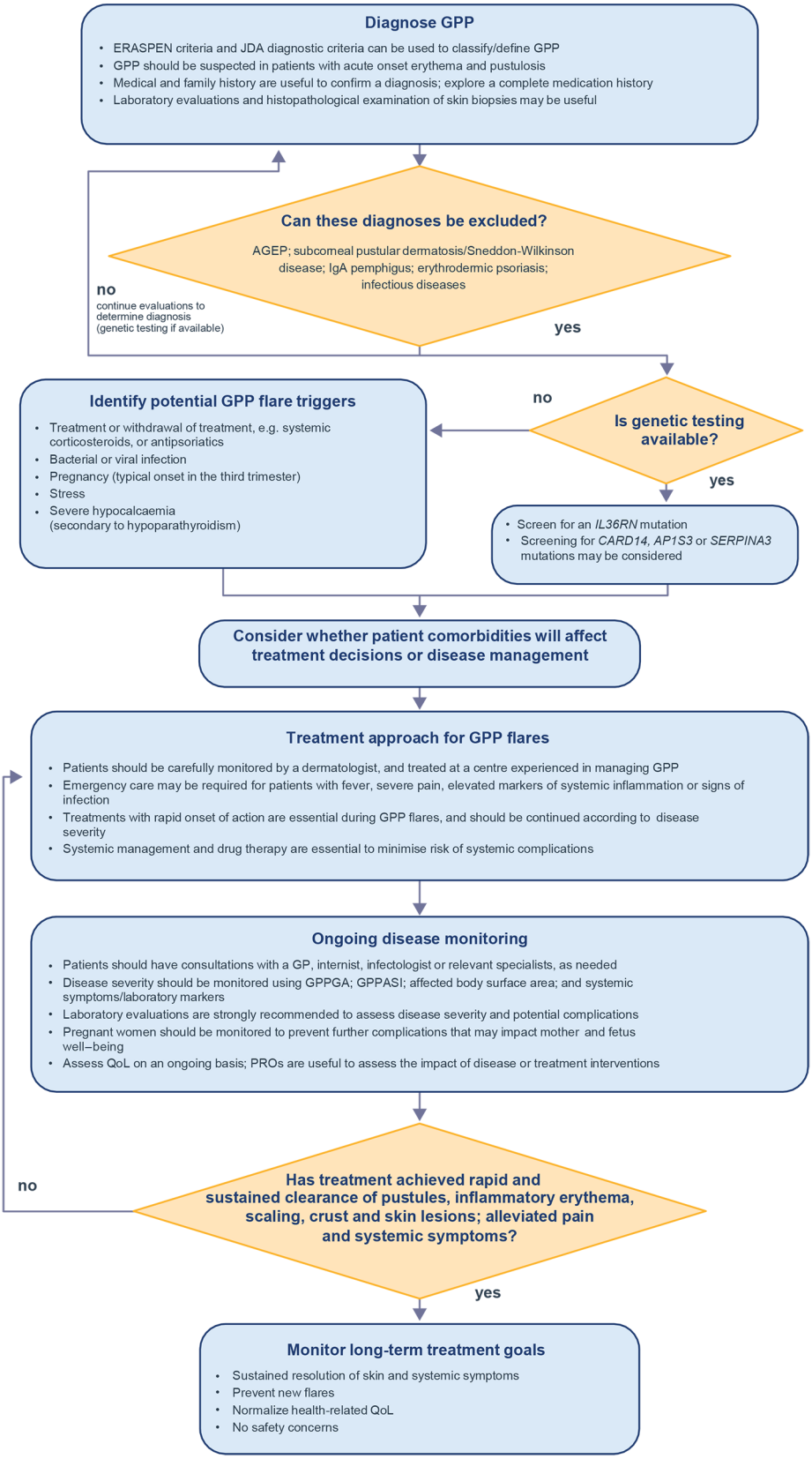

FIGURE 3 Clinical management flow diagram for GPP based on consensus statements after two Delphi panel rounds. Consensus statements with potential clinical implications were summarized and used to develop a disease management algorithm to inform and guide clinicalpractice. AGEP, acute generalized exanthematous pustulosis; ERASPEN, European Rare and Severe Psoriasis Expert Network; GP, general practitioner; GPP, generalized pustular psoriasis; GPPASI, generalized pustular psoriasis area and severity index; GPPGA, generalized pustular psoriasis physician global assessment; IgA, immunoglobulin A; JDA, Japanese Dermatological Association; PRO, patient-reported outcome; QoL, quality of life.

should also rapidly alleviate systemic symptoms and reduce pain while maintaining a favourable safety profile. In the long term, treatment for GPP should prevent the occurrence of new flares, achieve sustained resolution of skin and systemic symptoms, and normalize health-related quality of life. Prolonged exposure to treatment should not present any safety concerns (Table 2).

Domain 4: Holistic management of GPP

It was agreed that treatments with rapid action are essential and should be provided at centres with dermatologists experienced in treating and managing patients with GPP. Patients should be carefully monitored by a dermatologist throughout a flare, and the following clinical assessments are useful for monitoring disease severity: Generalized Pustular Psoriasis Physician Global Assessment (GPPGA), Generalized Pustular Psoriasis Area and Severity Index (GPPASI), body surface area, systemic symptoms and laboratory markers of systemic inflammation; however, consensus was not reached for the JDA severity index. Although hypo/hyperkalaemia and hyponatraemia were not considered informative to diagnose GPP, they should be monitored as part of appropriate disease management. Quality of life should also be assessed on an ongoing basis, and patient-reported outcomes such as the Dermatology Life Quality Index, Short Form-36 and pain-Visual Analog Scale are useful in assessing the impact of disease/treatment interventions on patient well-being and daily activities.

Several comorbidities associated with GPP may impact disease management, including obesity, diabetes mellitus, infections, plaque psoriasis and psoriatic arthritis (Table 2). However, there was no agreement that dyslipidaemia, thyroid disorders or malignancies may influence disease management decisions (Table 3).

A multidisciplinary approach is required for GPP disease management. Therefore, patients should be referred to other relevant specialists according to their symptoms, which can include acute respiratory distress syndrome, capillary leak syndrome, cardiovascular impairment and arthritis. There was consensus that consultations with referring general practitioners, internists, infectologists or other specialists should be carried out as needed.

DISCUSSION

To date, there has been a lack of international consensus on the clinical course and treatment goals of GPP and an absence of recommendations to support physicians in diagnosing and managing GPP. With panellists spanning 12 countries worldwide, this Delphi study presents expert, consensus-based guidance on the clinical course, diagnosis, treatment goals and management of GPP. The findings have been translated into an evidence-based disease management algorithm that can be implemented in clinical practice.

While the results of this Delphi panel reveal areas of agreement between dermatologists, they also highlight areas of GPP requiring further investigation. With regard to extracutaneous manifestations of GPP, panellists agreed on many of the systemic symptoms including fever, fatigue and oedema,[8,15–17] whereas there was uncertainty on organ-specific manifestations, such as conjunctivitis, uveitis, cholestasis, intestinal malabsorption and prerenal renal failure. Therefore, the latter may represent conditions for which further evidence is needed or that show greater variation between patients.[17,18]

Similarly, there were differing opinions relating to laboratory tests that can support GPP diagnosis. The diagnostic value of pustule smears and cultures was highlighted as an area lacking clarity, with panellists either agreeing or disagreeing, but none expressing neutrality. Disagreeing panellists commented that antibiotics should be given based on clinical evaluation and that pustule smears and cultures may be considered only for patients with refractory disease.[19] Agreement was particularly low for differential diagnosis, including on the coexistence of conditions such as palmoplantar pustulosis and ACH with GPP.[1,20] GPP and ACH are both associated with mutations in *IL36RN* and *AP1S3*; co-occurrence of the two diseases, as well as progression from ACH to GPP, have been reported.[20–24] It is possible that in patients with overlapping manifestations, the pustular rash may be attributed solely to the predominant disease, potentially affecting whether those diseases are considered to coexist. Given the rarity and heterogeneity of GPP, in areas for which there was no consensus, panellists may have insufficient experience of the many clinical manifestations of GPP and/or variable experience in distinguishing GPP from concomitant or similar diseases. While consensus was reached that GPP is distinct from plaque psoriasis, panellists acknowledged that it can be difficult to distinguish GPP from plaque psoriasis with pustules, and that early cases of GPP may be diagnosed as plaque psoriasis. These findings highlight the importance of establishing a clear diagnostic algorithm, because misdiagnoses can result in delayed or inappropriate treatment.

The need for more evidence to support potential triggers and predisposing factors for GPP flares was also highlighted. Although almost all panellists agreed on treatment with or withdrawal of systemic corticosteroids or antipsoriatic therapy as potential triggers, there was no consensus regarding medications such as NSAIDs, antibiotics, lithium carbonate, progesterone or vaccinations.[8,25–29] Severe hypocalcaemia secondary to hypoparathyroidism was agreed as a potential trigger for GPP flares. The role of vitamin D in cell differentiation and proliferation in the skin may underpin the link between hypoparathyroidism and GPP;[30] however, very few cases are reported in the literature and greater awareness of this potential risk factor is needed.[30] Agreement was also low on the role of environmental factors such as sun exposure and seasonal variation, and physiologic factors such as exertion and menstruation; these factors may not be widely observed because they were reported by a single study.[31]

Complications associated with GPP was an area of high consensus. The exception was secondary amyloidosis, which was identified as a fatal complication in one patient with GPP in a French review from 1965 to 1985.[32] Given the lack of consensus on this potential complication within the Delphi panel and the date of the report, further evidence is required to support the link between secondary amyloidosis and GPP. Similarly, agreement was reached on a broad range of GPP comorbidities that may impact disease management, with the exception of dyslipidaemia, thyroid disorder and malignancies.[8,33,34] Despite the lack of consensus, conditions such as dyslipidaemia are likely to influence management decisions, because acitretin and cyclosporine, which are commonly used to treat GPP, can affect serum lipid levels.[35,36] Although thyroid dysfunction may not be directly related to GPP, it does reflect systemic inflammation,[37] which suggests that the lack of consensus reflects the need for additional evidence from studies investigating comorbidities associated with GPP.

It is particularly striking that experts strongly agreed on all acute and long-term treatment goals, marking an important step towards establishing a framework for evaluating the effectiveness of existing and new treatments. Immunosuppressive drugs such as cyclosporine and methotrexate are often used as first-line therapies to suppress acute inflammation, but responses can be slow and flare control inadequate.[8,38–40] Spesolimab was recently approved for use in the European Union, Japan, China and the United States based on data from the randomized controlled Effisayil 1 study.[41–43] In Japan, several biologic therapies targeting immunologic pathways have been approved for GPP treatment, providing more treatment options;[8,44–48] however, evidence supporting the efficacy of these therapies is limited to case reports or small, single-arm studies. Therefore, achieving these goals is challenging with current treatment options, highlighting the high unmet need for GPP-specific targeted therapies.

Treatment goals were mirrored in statements that reached consensus regarding the management of GPP. The GPPGA and the GPPASI are newly developed GPP-specific tools that have been implemented in clinical trials of spesolimab,[41,42] and 95% of panellists recognized their role in the assessment of GPP severity and the value of expanding and establishing their use in clinical practice. This highlights the importance of using disease severity measures that capture skin pustulation, as this is a key manifestation of GPP. To achieve long-term treatment goals and improve patient quality of life, consultations with several disease specialists as part of a multidisciplinary approach are recommended to treat the numerous complications and systemic manifestations associated with GPP. It should be noted that regional preference does appear to influence the choice of methods for assessing disease severity, with all except the JDA severity index reaching consensus. We also note that access to medications can vary by country, and management approach may vary from physician to physician, with decisions influenced by resources and setting, whether at a hospital, university or private practice.

Overall, the findings of this Delphi panel confirm that GPP is a serious and potentially life-threatening disease that is distinct from plaque psoriasis, although both conditions may occur in one patient. Greater knowledge is needed regarding the triggers of GPP, associated comorbidities and differential diagnoses, and future studies should focus on generating much-needed evidence in these areas. Nevertheless, global consensus was clear on key clinical and histologic features supporting GPP diagnosis and flare definition, as well as treatment goals of rapid and sustained control of cutaneous and systemic symptoms.

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CONFLICT OF INTEREST

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DATA AVAILABILITY STATEMENT

To ensure independent interpretation of clinical study results and enable authors to fulfil their role and obligations under the ICMJE criteria, Boehringer Ingelheim grants all external authors access to clinical study data pertinent to the development of the publication. In adherence with the Boehringer Ingelheim Policy on Transparency and Publication of Clinical Study Data, scientific and medical researchers can request access to clinical study data when it becomes available on Vivli - Center for Global Clinical Research Data, and earliest after publication of the primary manuscript in a peer-reviewed journal, regulatory activities are complete, and other criteria are met. Please visit Medical & Clinical Trials | Clinical Research | MyStudyWindow for further information.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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