COMPASS

Coordinating care and improving outcomes in patients with pustular psoriasis

GENERALISED PUSTULAR PSORIASIS

CONTENTS

OVERVIEW OF GENERALISED PUSTULAR PSORIASIS

Generalised pustular psoriasis (GPP) is a rare but severe and potentially life-threatening form of psoriasis.[1,2] GPP typically occurs in adulthood, with a peak incidence between 40 and 59 years of age, but infants and children can also be affected.[1] An earlier age of onset tends to occur among patients with GPP without plaque psoriasis.[1] Without prompt treatment, GPP can be fatal, with life-threatening complications that include sepsis, acute respiratory distress syndrome, and cardiac failure.[3]

The exact prevalence of GPP is unknown, but it appears to be more prevalent in Asian (7.46 per million in a Japanese population) than in Western populations (0.64–1.76 per million in a French population).[1-3] GPP affects women most commonly, although this gender discrepancy is inconsistently reported.[1] Approximately 10% of patients have a preceding history of plaque psoriasis characterised by persistent erythematous scaly plaques.[4] GPP is also frequently associated with inflammatory polyarthritis and metabolic syndrome, including obesity, hypertension, dyslipidaemia, and diabetes.[1]

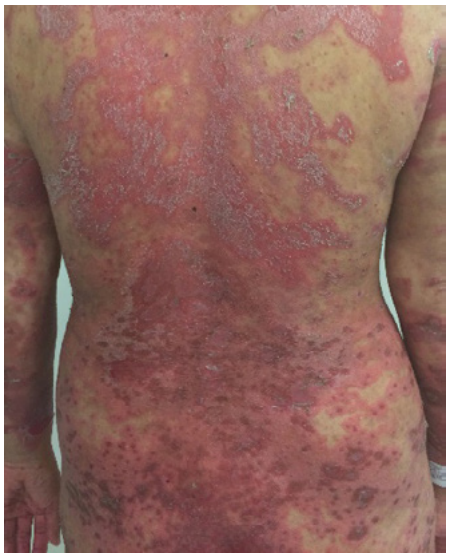

Figure 1. Generalised pustular psoriasis. ©Waikato District Health Board. Source 🖹. *Used with permission from* **DermNet New Zealand**. *Licensed under* **CC BY-NC-ND 3.0 NZ**.

Click **here** to view other images of GPP

CLINICAL PRESENTATION

The clinical course of GPP is highly variable.[2] GPP presents as acute flares characterised by the abrupt appearance of sheets of sterile pustules on an erythematous base covering most of the body (*see Figure 1),* causing painful, burning sensations, as well as fever, chills, and general debility.[1,4] Flares are triggered most commonly by steroid withdrawal and by certain medications, as well as by infection, psychological stress, and pregnancy.[1,4]

CLINICAL COURSE

Flares may occur 0–3 times per year and can last up to 12 weeks.[5] Hospitalisation of up to 8 days to manage flares is common.[5] Remission occurs when skin reverts to its previous state or with the development of erythroderma.[4] *Figure 2* presents the responses of dermatologists to the Corrona Psoriasis Registry cross-sectional survey.[5]

During an acute episode, intense inflammation occurs and patients are systemically unwell.[1] Complications may also occur, including secondary bacterial infection, high-output cardiac failure, and renal and hepatic impairment.[4] Older individuals are at greatest risk of complications.[4] Prognosis is improved with the identification of a clear trigger, such as pregnancy.[1]

SIGNS AND SYMPTOMS

Recurrent acute flares are characteristic of GPP.[4] Initially, cutaneous dryness, redness, and tenderness occur, which is soon followed by the appearance of 2–3 mm pustules that eventually coalesce to form lakes of pus.[4] Once these have dried and peeled, a glazed and smooth surface appears, on which new pustules may appear, erupting and reappearing every few days or weeks.[4]

OVERVIEW OF DIAGNOSIS

Diagnosing GPP can be difficult not only because of its rarity, but also because of its variable presentations and lack of consistent classification.[3]

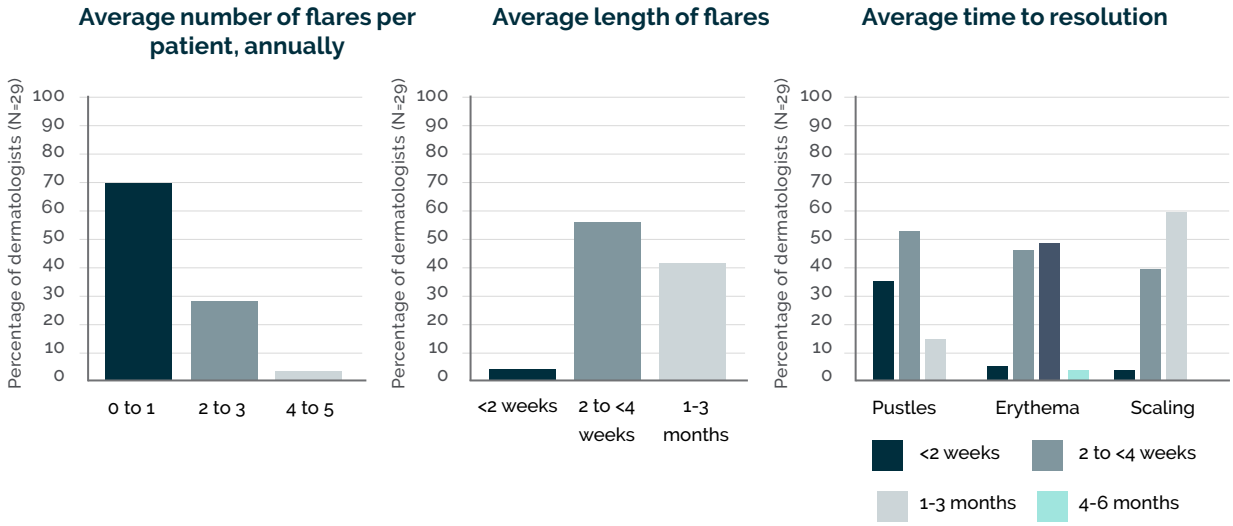

Figure 2. Dermatologists in the Corrona Psoriasis Registry describing the natural history of GPP.[5] (Adapted from Strober B, Kotowsky N, Medeiros R, et al. Dermatol Ther (Heidelb). 2021 Apr;11(2):529–541.)

Importantly, recognition of acute GPP is critical because it is a potentially fatal subtype of psoriasis requiring initiation of therapy without delay.[3]

Reviewing current real-world standards of care in GPP, Strober et al.[5] reported that misdiagnosis of GPP is common, along with late referral and treatment initiation. Emergency department and primary care physicians are likely to encounter patients with pustular psoriasis, however, they have limited understanding of the presentation and pathogenesis of GPP, and may often mistake the flares of sterile pustules for infection.[6] Healthcare providers encountering patients presenting with recurrent, acute, widely distributed pustular eruptions should not hesitate to contact a dermatologist for help.[6]

However, it should be noted that some dermatologists who can diagnose GPP may have limited knowledge of available treatments,[5] and may need to refer to a colleague with more experience in GPP management, thus delaying patient management even further.

DIAGNOSTIC CRITERIA

GPP should be suspected in patients with acute onset of erythema and pustulosis.[3] Diagnosis is made by clinicopathologic correlation that considers findings from physical examination of the skin and oral mucosa, symptom review, and histopathology, along with patient history.[3] (*See Table 1.*)

DIFFERENTIAL DIAGNOSES

The differential diagnoses for GPP are numerous and include several cutaneous pustular diseases, with acute generalised exanthematous pustulosis (AGEP) being the most critical to exclude.[3,6] Like GPP, AGEP presents as sterile pustules on an erythematous base, with AGEP typically starting on the face or armpits and groin before becoming widespread.[3,7] However, AGEP has a more abrupt onset (occurring within 48 hours) and shorter duration (resolving within 1–2 weeks) than GPP.[3,6] Unlike GPP, AGEP also does not recur and there is no apparent personal or familial history of psoriasis vulgaris.[3] The vast majority of cases of AGEP are triggered by medication use, particularly beta-lactam antibiotics.[3,7]

Read more about AGEP **here**.

DIAGNOSTIC CRITERIA

Consensus guidelines for GPP from the European Rare and Severe Psoriasis Expert Network (ERASPEN)[8] and the Japanese Dermatological Association[9] are available, which aim to present a standard classification based on clinical and genetic insights to improve diagnosis and enable early treatment.[3] (*See Table 2.*) The diagnostic criteria for GPP based on these guidelines indicate the clinical presence of histopathologically confirmed pustules and disease recurrence, with the exclusion of AGEP. Despite the availability of these consensus diagnostic criteria, a need exists for unified and universally applicable criteria to allow further characterisation of GPP.[2,3]

Table 1. Overview of the clinicopathologic considerations in diagnosing GPP

Consideration	Details
Physical examination and symptom review[3]	• Critical to evaluate the extent of skin involvement • Cutaneous symptoms include pain, burning, pruritus • Mucosal findings include geographic or fissured tongue, cheilitis, ocular involvement • Nail abnormalities, arthralgia, jaundice, lower extremity oedema may occur
Patient history[3]	• Patient may have a history of concurrent or previous psoriasis vulgaris, but not all patients have a history of psoriasis • Although some cases may appear idiopathic, potential identified triggers should be considered
Histopathology[3]	• Skin biopsy required to confirm diagnosis • Histopathology is characterised by Kogoj's spongiform pustules (i.e., neutrophil accumulation under the stratum corneum) and classic findings of psoriasis • Oedema and inflammatory cell infiltrate are greater than seen with psoriasis vulgaris

Table 2. Overview of consensus guidelines for diagnosis of GPP[3]

ERASPEN (2017)[8]	Japanese Dermatological Association (2018)[9]
Primary, sterile, and macroscopically visible epidermal pustules on non-acral skin Subclassifications include: ▪ ± systemic inflammation ▪ ± plaque psoriasis ▪ Relapsing (>1 episode) or persistent (>3 months)	Systemic or extensive flush coupled with multiple sterile pustules Neutrophilic subcorneal pustules histopathologically characterised by Kogoj's spongiform pustules Systemic symptoms (e.g., fever, fatigue) Recurrence of clinical and histological findings *A definitive diagnosis is made in the presence of all four features; suspected diagnosis is made with the first two features.*

SEVERITY CRITERIA

The Japanese Dermatologic Association uses a total score that combines the rating of skin symptoms and systemic inflammation and laboratory findings to classify the severity of GPP as *mild* (total score: 0–6), *moderate* (total score: 7–10), or *severe* (total score: 11–17).[9] *(See Table 3.)*

Remission is considered to have occurred if recurring skin symptoms are no longer observed or the disease has changed into psoriasis vulgaris in the absence of disease-specific treatment; no complications are observed during the acute or chronic phase; and all impairments in activities of daily living are resolved.[9]

TREATMENTS AND TREATMENT GUIDELINES

Treatment of GPP requires specialist care, typically under hospitalisation because of the risk of complications.[3,4,6] The goals of treatment are to improve the skin, prevent complications such as fluid loss, hypothermia, and electrolyte imbalance, and prevent the recurrence of flares.[6,9,10] If a medication triggered the flare of GPP it should be discontinued if possible.[2]

To minimise disease severity and complications and decrease disease burden, optimal treatment for GPP would have a rapid onset of action to alleviate acute flares and a rapid time to complete disease clearance.[2] Available GPP treatment options do not adequately prevent new flares nor resolve residual symptoms, and only some are considered sufficiently fast acting to help control severe flares.[5] This suggests the lack of fast-acting and long-lasting treatments specifically for GPP flares. There is also a lack of effective long-term maintenance therapy for GPP to help prevent repeated flares.[2] Unfortunately, the rarity of GPP impedes conducting large clinical trials to establish appropriate treatments for this patient population.[2]

AVAILABLE TREATMENT OPTIONS

In GPP, topical treatments to the affected areas include compresses and low-potency steroid creams, which may be used as an adjunct to systemic therapy or to treat mild cases.[2,4] Antibiotics may be used to treat associated infections.[4,6] Systemic medications include acitretin, methotrexate, colchicine, ciclosporin and biologic agents with a rapid speed of onset

Table 3. GPP severity criteria based on the Japanese Dermatological Association guidelines[9]

Evaluation of skin symptoms				
	Score			
	Severe	Moderate	Mild	None
Area of erythema (whole body)[a]	3	2	1	0
Area of erythema and pustules[b]	3	2	1	0
Area of oedema[b]	3	2	1	0

Evaluation of systemic systems and laboratory findings			
	Score		
	2	1	0
Fever	≥38.5˚C	37.0˚C–<38.5˚C	<37.0˚C
White blood cell count, mL^{-1}	≥15,000	10,000–<15,000	<10,000
C-reactive protein, mg/dL	≥7.0	0.3–<7.0	<0.3
Serum albumin, g/dL	<3.0	3.0–<3.8	≥3.8

[a]Percentage of body surface area: severe ≥75%; moderate 25%–<75%; mild <25%.

[b]Percentage of body surface area: severe ≥50%; moderate 10%–<50%; mild <10%.

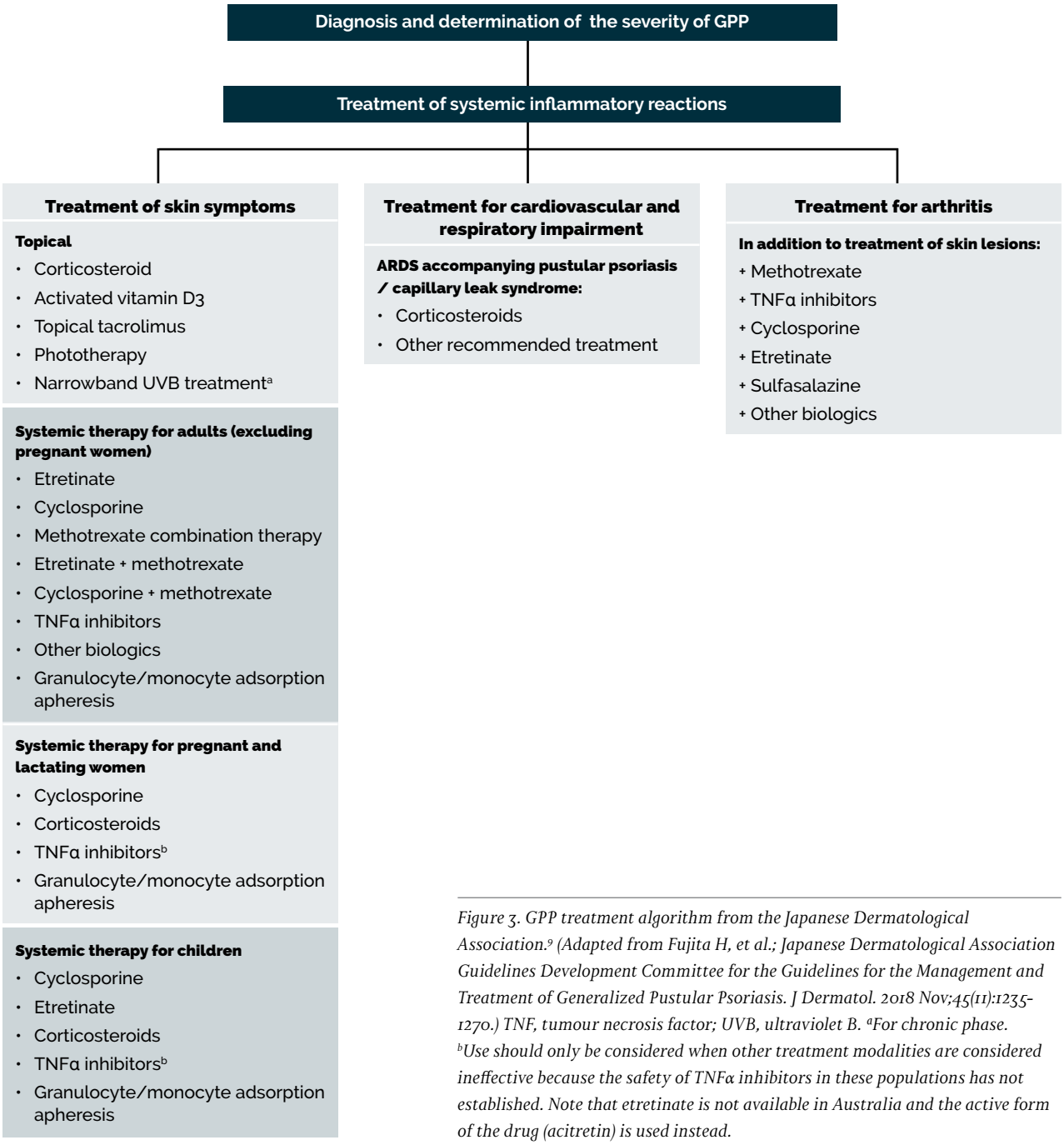

Figure 3. GPP treatment algorithm from the Japanese Dermatological Association.[9] (Adapted from Fujita H, et al.; Japanese Dermatological Association Guidelines Development Committee for the Guidelines for the Management and Treatment of Generalized Pustular Psoriasis. J Dermatol. 2018 Nov;45(11):1235-1270.) TNF, tumour necrosis factor; UVB, ultraviolet B. [a]For chronic phase. [b]Use should only be considered when other treatment modalities are considered ineffective because the safety of TNFα inhibitors in these populations has not established. Note that etretinate is not available in Australia and the active form of the drug (acitretin) is used instead.

(i.e., infliximab, ixekizumab, adalimumab and secukinumab).[2,4] Combination therapy of a biologic plus another systemic agent or sequential use of two biologics may be required to achieve disease control.[6]

With no approved treatments for GPP in Australia, the Therapeutic Goods Administration granted spesolimab, a humanized IgG1κ antibody that blocks the activation of IL-36 receptor involved in the pathogenesis of neutrophilic skin diseases including GPP, an orphan drug designation in early 2022.[11]

OVERVIEW OF TREATMENT GUIDELINES

The Japanese Dermatological Association guidelines include a treatment algorithm for GPP.[9] *(See Figure 3.)* It is noted that because GPP is a potentially life-threatening inflammatory disease, treatments without a well-established safety profile may be necessary.[9]

SUMMARY

- GPP is a potentially life-threatening form of psoriasis. GPP exhibits a fluctuating clinical course that is characterised by recurrent acute flares. Diagnosis is difficult because the presentation is variable but is critical as early initiation of therapy is required to avoid serious sequelae including death. Several differential diagnoses for GPP exist, with AGEP being the most critical to exclude.
- ERASPEN and Japanese Dermatological Association consensus guidelines for the diagnosis of GPP use clinical and genetic parameters to improve diagnosis and enable early treatment. These diagnostic criteria include the clinical presence of histopathologically confirmed pustules, and disease recurrence, with the exclusion of AGEP. However, the availability of unified and universally applicable criteria is an unmet need.
- GPP treatment requires specialist care, with the aim of improving the skin, preventing complications and limiting recurrence. GPP treatments are limited because of a lack of fast-acting and long-lasting therapies to manage flares, and of long-term maintenance therapies to prevent relapse. Available treatments include topical agents and systemic medications. No agents are specifically approved in Australia for the treatment of GPP.

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