INSIDE THIS ISSUE:

How is pustular psoriasis distinct from plaque psoriasis?

How does pustular psoriasis most commonly develop and progress in patients?

What should providers look for when identifying potential cases of pustular psoriasis?

Why is pustular psoriasis potentially dangerous if not appropriately treated?

**The Pathophysiology of Pustular Psoriasis:**

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LEARNING OBJECTIVES

After participating in the activity, learners should be better able to:

• List core characteristics that differentiate the subtypes of pustular psoriasis
• Identify the primary risk factors of palmoplantar pustulosis (PPP) and generalized pustular psoriasis (GPP)
• Determine primary treatment pathways for patients with PPP and GPP
• Discuss the impact of pustular psoriasis on patient quality of life

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Any clinician working in dermatology is familiar with plaque psoriasis, which affects roughly 1 in 100 individuals in the United States. Pustular psoriasis, which comes in several forms, is a much less familiar entity. Generalized pustular psoriasis (GPP) is present in approximately 1 in 100,000 people in the United States. Its manifestations are so severe that experts have proposed the term “skin failure” to describe the condition, and deaths directly attributable to GPP occur in 2-16% of patients diagnosed with the condition. Palmoplantar pustulosis (PPP), a localized form of pustular psoriasis that affects the palms and the soles of the feet, is also rare, affecting only approximately 10 of every 10,000 people in the United States. However, PPP also takes a tremendous toll on patients, as its painful lesions can prevent individuals from using their hands and feet and, as a result, from going about their normal daily activities.

Historically, pustular psoriasis has been classified as a subtype of plaque psoriasis. However, mounting evidence indicates that pustular psoriasis is a distinct condition that requires a different treatment approach. In fact, experts have recently argued that GPP meets all of the European Medicines Agency’s criteria for an orphan disease and that it would be more accurate to classify it as an autoinflammatory keratinization disease.

Because pustular psoriasis can be so severe, it is critical to diagnose patients and start effective treatment as early as possible. However, the various subtypes of pustular psoriasis are so rare that evidence-based...
guidance about how to treat them is scant, and optimally managing symptoms to maximize patients’ quality of life can be quite challenging. Although in this article we focus primarily on the most common forms of pustular psoriasis—GPP and PPP—a brief description of other pustular psoriasis subtypes is included as well.

PUSTULAR PSORIASIS SUBTYPES

Pustular psoriasis can be divided into generalized subtypes (GPP, as well as pustular psoriasis of pregnancy and infantile/juvenile pustular psoriasis) and localized subtypes (PPP and acrodermatitis continua of Hallopeau, which primarily affects the fingers and toes, including the nail beds). Figure 1 includes illustrations of many of these conditions.6

GENERALIZED SUBTYPES OF PUSTULAR PSORIASIS

Generalized pustular psoriasis (GPP) typically emerges during adulthood,2 with the median age of onset between 40-50 years.9 It occurs in people of all races and is more common in women than men.10,11 Research shows that 65% of acute GPP cases occur in individuals with a prior diagnosis of plaque psoriasis,6 but it is common for years to elapse between the onset of plaque psoriasis and the onset of GPP.10

GPP flares are characterized by the widespread eruption of macroscopically visible pustules that expand and coalesce, often forming “lakes of pus.”6 Systemic symptoms, including fever, chills, malaise, anorexia, nausea, and severe pain, are also common in addition to the skin eruptions.6 GPP flares can lead to sepsis, acute respiratory distress syndrome, renal failure, and congestive heart failure.2 For this reason, hospitalization during flares is common.

Two subtypes of GPP have been identified on the basis of systemic symptoms.12 Among patients with the acute, von Zumbusch subtype, diffuse generalized pustular eruptions are present, along with associated systemic symptoms such as fever and arthralgia. Among patients with the milder exanthematic subtype, acute pustular eruptions are present but emerge without systemic symptoms, and lesions typically resolve after a few days. An annular subtype of GPP has also been identified, in which pustules emerge along the advancing edge of a ring. This subtype, however, is most often observed among children.

FIGURE 1
Representative photos of different types of pustular psoriasis, as well as of plaque psoriasis, for contrast.

The course of GPP can vary considerably from patient to patient. It can be relapsing or persistent; in patients with persistent disease, mild pustulation is continuously present, punctuated by flares of greater severity.\textsuperscript{2,13} While some patients with GPP have multiple severe flares per year, others only experience a flare every few years.\textsuperscript{13}

Recent research has shown that GPP is driven by alterations in biological pathways that are distinct from those observed in patients with plaque psoriasis. Plaque psoriasis is driven by dysregulation of the adaptive immune system, with the cytokine IL-17 playing a key role.\textsuperscript{2} GPP, meanwhile, appears to be driven primarily by dysregulation of the innate immune system, with the cytokine IL-36 playing a key role. For example, genetic alterations in the IL-36 receptor antagonist gene cause GPP in some patients.\textsuperscript{6} Patients with these alterations are unable to inhibit the effects of multiple IL-36–associated cytokines, leading to an increase in proinflammatory molecules. Other patients with GPP harbor alterations in the IL-1 receptor antagonist gene, which results in disinhibition of the proinflammatory cytokines IL-1a and IL-1b, and alterations in the \textit{CARD14} gene.\textsuperscript{6,14} \textit{CARD14} alterations result in abnormal activation of NF-kB, a key regulator of the inflammatory response.

These findings regarding the immunologic differences between GPP and plaque psoriasis may explain why many treatments for plaque psoriasis have limited effectiveness in patients with GPP, as well as why patients with GPP experience such severe symptoms and report more pain, fatigue, and itching than those with plaque psoriasis.\textsuperscript{15} A brief overview of some of the most important differences between GPP and plaque psoriasis can be found in Figure 2.

\textbf{Pustular psoriasis of pregnancy} is a life-threatening condition that typically occurs during the third trimester of pregnancy.\textsuperscript{16} It is believed to be a variant of GPP specific to pregnancy, with similar overall manifestations. Like GPP, pustular psoriasis of pregnancy can lead to fluid and electrolyte imbalances, loss of thermoregulation in the skin, and secondary infection and sepsis. If not treated aggressively, it can also lead to placental insufficiency.
intrauterine growth restriction, and stillbirth. Although pustular psoriasis of pregnancy typically resolves after childbirth, recurrence during subsequent pregnancies is common. In rare cases, it has been reported to arise during the postpartum period.

Infantile/juvenile pustular psoriasis accounts for up to 13% of pediatric psoriasis cases. The median age of onset is between 6 and 7 years, though it can also arise in infants. Due to a lack of research, even less is known about effective treatment for pediatric pustular psoriasis than adult pustular psoriasis.

**LOCALIZED SUBTYPES OF PUSTULAR PSORIASIS**

**Palmoplantar pustulosis (PPP)** is the most common subtype of pustular psoriasis. As with GPP, PPP is more common in women than men. PPP typically develops in middle-aged adults. Depending on the study cited, plaque psoriasis has been reported to be present in 14-61% of patients with PPP. PPP typically presents as sterile pustules with erythema, hyperkeratosis, and scaling on a patient’s palms and soles, often involving the arches of the feet. Pustules often expand and coalesce, and, after resolving, often leave a brown discoloration. Even though PPP is limited to the hands and feet, it can dramatically reduce patients’ health-related quality of life by making walking and other everyday activities difficult, as well as by causing psychiatric morbidity. Like GPP, PPP is associated with IL-36 and CARD14 mutations, and many experts believe it should be viewed as an entity independent from plaque psoriasis.

**Acrodermatitis continua of Hallopeau** primarily affects the fingers and toes, including the nail beds. The incidence of this rare disease is unknown. Initially, it presents as erythema on the distal digits, which later evolves into tender pustules and expands to involve the proximal digits. Eruptions typically, but do not always, occur after local trauma or infection. Acrodermatitis continua of Hallopeau is chronic and progressive, often resulting in permanent injury to a patient’s fingernails and toenails. Consequences can include nail loss, osteitis, and osteolysis of the distal digits.

In the remainder of this article, we will focus specifically on the diagnosis and treatment of GPP and PPP, the two most frequently encountered subtypes of pustular psoriasis in adults.

**MANIFESTATIONS, RISK FACTORS, AND DIAGNOSIS OF GENERALIZED PUSTULAR PSORIASIS**

GPP is clinically heterogeneous, which can make it difficult to recognize. In 2017, the European Rare and Severe Psoriasis Expert Network (ERASPEN) produced a consensus definition of GPP, stating that the condition was characterized by the presence of primary, sterile, macroscopically visible epidermal pustules on non-acral skin (see Figure 3). GPP can occur with or without systemic inflammation and with or without plaque psoriasis. It can also be either relapsing or persistent.
GPP typically begins with red papules or plaques that rapidly evolve into yellowish, superficial pustules on a red background. In practice, pain is the most common symptom documented during GPP flares, followed by rash and fever (see Figure 4). Some of the main features differentiating GPP from plaque psoriasis are pustulation, lesion painfulness, and a visibly ill appearance. Because inflammation during GPP flares is systemic, it can cause malaise, high-grade fever (occurring in 24-96% of patients), and diarrhea. Laboratory abnormalities during a GPP flare include elevated C-reactive protein and erythrocyte sedimentation rate, hypocalcemia, abnormal liver function tests, and leukocytosis with neutrophilia (the latter occurring in 30-70% of cases). Neutrophilic inflammation in GPP can cause cholestasis, uveitis, cholangitis, epigastric pain, arthritis, interstitial pneumonitis, oral lesions, acute renal failure, acute respiratory distress syndrome, cytokine storm, and congestive heart failure. Polymicrobial bacterial infections can also occur in pustular lesions, potentially leading to sepsis.

GPP should be suspected in any patient with a sudden onset of erythema and pustulosis. A diagnostic workup typically includes taking a patient history and reviewing their symptoms, performing a total body skin examination, reviewing a skin biopsy for hematoxylin and eosin staining, and ordering basic serologic studies. A history of psoriasis and a clinical course of rapid disease onset or relapsing episodes is suggestive of GPP, although clinicians should be aware that the absence of systemic symptoms does not exclude a diagnosis. Obtaining a thorough drug history is also essential to the diagnosis, as withdrawing or initiating certain drugs—such as systemic glucocorticoids—often incites flares.

When GPP is suspected, acute generalized exanthematous pustulosis (AGEP) should be ruled out. On the basis of clinical presentation, it is nearly impossible to distinguish AGEP from GPP, but approximately 90% of AGEP cases are associated with the use of certain types of medications, including antibiotics and calcium channel blocking agents such as aminopenicillins, pristinamycin, sulphonamides, quinolones, hydroxychloroquine, terbinafine, and diltiazem. In addition, AGEP has a more abrupt onset than GPP (signs/symptoms occur within 48 hours) and a shorter duration (it resolves within 1 to 2 weeks), does not recur, and is not associated with plaque psoriasis. Finally, biopsy findings of eosinophils and necrotic keratinocytes typically suggest a diagnosis of AGEP rather than GPP.

The differential diagnosis for GPP also includes localized forms of pustular psoriasis, IgA pemphigus (an autoimmune disease that causes blistering of the skin and the inside of the mouth, nose, throat, eyes, and genitals), and subcorneal pustular dermatosis (ie, Sneddon-Wilkinson disease). Histologically, GPP can be distinguished from plaque psoriasis by the infiltration of neutrophils into the epidermis.

Factors that can trigger GPP flares include pregnancy, upper respiratory tract infections, and stress, as well as use of corticosteroids, nonsteroidal anti-inflammatory drugs, terbinafine, ustekinumab (an IL-12/23 inhibitor), TNF inhibitors, and methotrexate. The use and withdrawal of systemic corticosteroids appears to be a particularly important cause of GPP. In one study of 102 patients with GPP flares, systemic glucocorticoids were determined to be a likely trigger in 44% of cases. Clinicians can help prevent GPP by avoiding an abrupt withdrawal of corticosteroids when treating patients for...
"Identifying evidence-based treatments for pustular psoriasis has been difficult because these diseases are so rare, making the conducting of clinical trials a challenge."

other conditions. Some dermatology clinicians find that GPP referrals from gastroenterologists are also common, as flares can occur in patients taking TNF inhibitors for issues such as inflammatory bowel disease. Finally, acute infections have been found to be either a trigger or exacerbating factor in 16% of patients with acute GPP.

MANIFESTATIONS, RISK FACTORS, AND DIAGNOSIS OF PALMOPLANTAR PUSTULOSIS

PPP is defined by ERASPEN as the presence of primary, persistent (>3 months), sterile, macroscopically visible pustules on a patient’s palms and/or soles, with or without plaque psoriasis (see Figure 3). These pustules are especially common on the arches of the feet. In one study of patients with PPP, palms alone were affected in 15% of patients, soles alone in 18%, and both palms and soles in 67%. In patients with PPP, lesions often coalesce and resolve after several days, leaving brown discoloration and hyperkeratosis. As with GPP, pain differentiates PPP from plaque psoriasis, with patients often describing a burning and/or itching sensation. In severe cases of PPP, cracking or fissuring occurs, resulting in severe pain. Nail changes, including onycholysis, pitting, pustules, dystrophy, ridging, discoloration, and thickening, are also present in roughly 40% of patients. Lesions are often symmetrical across appendages, but distribution of lesions may be unilateral at the onset of disease. Osteoarticular involvement is present in approximately 25% of PPP cases.

In some patients with PPP, non-pustular skin lesions occur in areas other than the hands and feet, such as the forearms, elbows, lower legs, knees, or buttocks. Though these lesions are non-pustular, they tend to be less pronounced and less well-demarcated than the lesions of classic plaque psoriasis. Estimates of the frequency of non-palmoplantar lesions in PPP vary widely, ranging from 4-73% depending on the study, although research suggests these lesions are more likely to occur in patients with severe PPP.

PPP is typically diagnosed based upon the clinical finding of a pustular eruption limited to the palms of the hands and/or soles of the feet, along with associated erythema and hyperkeratosis, when a clinical evaluation rules out other conditions. Performing a potassium hydroxide preparation or fungal culture is important for ruling out cutaneous fungal infection when the feet are involved. In patients with atypical presentations or refractory disease, a skin biopsy may be necessary but is not usually required. A full examination of the skin and nails should be performed to rule out other forms of pustular psoriasis such as GPP and acrodermatitis continua of Hallopeau.

The differential diagnosis for PPP also includes irritant contact dermatitis, pityriasis rubra pilaris (a rare skin disorder that causes inflammation of the skin, thickening of the nails, and sometimes shedding of the hair), and pompholyx (a type of eczema that affects the hands and feet). Due to its similar appearance to PPP, the most important of these possibilities to rule out is pompholyx. Histopathologic features that favor PPP include vesicles lacking spongiosis (ie, intercellular edema in the epidermis) and microabscesses on the edges of vesicles. Alternatively, features favoring a diagnosis of pompholyx include vesicles with spongiosis, neutrophils only on the top of vesicles, and no microabscesses on the edges of vesicles. Like GPP, PPP can be distinguished from plaque psoriasis histologically by the infiltration of neutrophils into the epidermis.
Risk factors for PPP include smoking, infection, the use of various medications (including TNFa inhibitors), trauma, stress, and metal sensitivities. Smoking is a particularly important risk factor: the prevalence of smoking among PPP patients ranges from 33-95%, depending on the study. Smoking is believed to activate various pro-inflammatory pathways in the body that contribute to PPP. When a patient quits smoking, it can lead to improvement and even near-resolution of their condition. Tonsillitis is the most commonly documented type of infection leading to PPP, and tonsillectomy has been shown to be beneficial for patients with the disease. Some evidence suggests that dental infection control and metal removal may also be beneficial. Finally, pathophysiological research suggests that an abnormality in sweating contributes to PPP; in support of this hypothesis, one study found that patients with PPP in Japan require more assistance from healthcare professionals to manage their condition during periods of hot weather vs. cold weather.

**PROGNOSIS AND TREATMENT FOR PUSTULAR PSORIASIS**

Unfortunately, there is no cure for pustular psoriasis. Recurrence is common, and symptoms typically persist even between flares. For example, in one study that followed patients with GPP for approximately 5 years, fewer than 5% had clear or almost clear skin between GPP flares, and 30% had persistent pustular lesions. Similarly, the severity of PPP and the risk of recurrence does not appear to attenuate over time. Therefore, treatment must be continuous and maintained long-term.

Yet while available treatments may not be able to cure patients with pustular psoriasis, they can dramatically improve patients’ symptoms. For patients with GPP, the goals of treatment are to improve a patient’s skin manifestations, alleviate systemic symptoms, and minimize their risk for developing life-threatening complications. For patients with PPP, the goals of treatment are to improve a patient’s skin manifestations and minimize bothersome or disabling symptoms. Of course, patients are likely to have their own, specific goals that can be discussed while creating a treatment plan.

Identifying evidence-based treatments for pustular psoriasis has been difficult because these diseases are so rare, making the conducting of clinical trials a challenge. Therefore, there is a lack of universally accepted, evidence-based treatment guidance. In the next segment of this issue, we’ll present a brief overview of the treatment guidelines that do exist for GPP and PPP, as well as the latest clinical data on specific agents; in the next issue of Dermatology Nurse Practice, we will explore this topic in more depth.

**MANAGING GENERALIZED PUSTULAR PSORIASIS**

The first and most important decision when dealing with a GPP flare is determining whether a patient should be hospitalized. This decision is based upon a global consideration of a patient’s status. In particular, hospitalization may be necessary for fluid management and to treat heart failure stemming from a flare. Research suggests that patients with renal disease, a history of myocardial infarction, liver disease, or diabetes mellitus are particularly likely to require hospitalization, and those with a history of myocardial infarction or psoriasis are particularly likely to develop fatal GPP. Specifically, after adjusting for age and sex, patients with a history of myocardial infarction are more than 5 times more likely to develop fatal GPP than those without, and those with a history of psoriasis are more than 3 times more likely to develop fatal disease. In any patient with these characteristics, as well as in elderly patients, hospitalization should be seriously considered.

If a drug is implicated in a patient’s GPP flare, clinicians should consider whether it can be discontinued. For example, if a TNFa inhibitor is the potential culprit, it may be possible to substitute another biologic with a different mechanism of action. If systemic corticosteroids are likely to blame, it may be possible to gradually taper them while also initiating therapy specifically for the amelioration of GPP symptoms.

Several different options, including systemic therapies, topical therapies, and phototherapy are available to treat pustular psoriasis. For patients with GPP, it generally makes sense to initiate systemic therapy first, as phototherapy takes longer to work. Topical therapy is not practical for controlling widespread disease and should primarily serve as an adjunct to systemic therapy. In general, there should be a low threshold to initiate systemic therapies, and combining systemic and topical therapies is encouraged. Antibiotic therapy may also be helpful in preventing secondary infection. Real-world data show that patients with GPP require more frequent use of antihypertensives than those with plaque psoriasis. In addition, supportive measures such as moisturizers, wet wraps, and oatmeal baths can be used to soothe skin symptoms.

According to the National Psoriasis Foundation (NPF) treatment guidelines for pustular psoriasis published in 2012, first-line therapies for GPP include acitretin (an oral retinoid), cyclosporine, or methotrexate, with acitretin considered the preferred option based on very strong evidence.
limited data. Recommended second-line therapies include adalimumab, etanercept, and combination therapy (typically a first-line systemic agent plus a biologic). Systemic steroids should generally be avoided in patients with GPP, given the risk of disease worsening upon their withdrawal. In fact, prescribing systemic steroids such as prednisone in a patient with a GPP flare is sometimes akin to throwing gasoline on a raging fire.

In the decade since the NPF guidelines were published, evidence has accumulated that biologics are the most effective treatment option for GPP. In Japan, TNFα inhibitors, IL-17/IL-17R inhibitors, and IL-23 inhibitors have all been approved to treat GPP based on clinical trial data. In addition, real-world data from Asia and Europe indicates that, compared to systemic treatment with non-biologic agents, treatment with biologics is associated with lower morbidity and mortality, and is significantly more likely to result in an excellent treatment response. IL-17 and IL-12/23 inhibitors appear to be especially effective at managing GPP. As a result of these emerging data, some experts propose that biologics be considered first-line therapy for patients with severe pustular psoriasis, while acitretin with or without photochemotherapy (ie, psoralen plus ultraviolet A, or PUVA) be considered first-line therapy for patients with mild-to-moderate disease.

Here, the classification of severe disease is made based on extent of inflammation, pustulation, scaling, affected area, general health, presence of fever, pain, and laboratory findings.

Furthermore, in the fall of 2022, the FDA approved spesolimab, the first agent indicated specifically for the treatment of GPP flares in the United States. Spesolimab is an IL-36 inhibitor that was developed because of the abundant data implicating IL-36 as a central player in GPP pathogenesis. The FDA’s approval of spesolimab was based on the results of the first randomized placebo-controlled trial ever conducted for GPP. This phase 2 trial found that spesolimab helped clear lesions in 54% of patients after 1 week of treatment. The most important adverse events associated with use of spesolimab included infections and systemic drug reactions. As more evidence available at the time, first-line local therapy for PPP consists of topical corticosteroids (used in 35% of episodes), opioids (21% of episodes), and oral treatments such as methotrexate, cyclosporine, and tacrolimus. Even during active flares, fewer than 5% of patients received oral retinoids or biologics. In addition, in almost 25% of flares, patients received no dermatologic treatment 30 days before, during, or 30 days after a flare. Thus, many patients with GPP would benefit from healthcare providers becoming more familiar with the latest data on effective treatment strategies for this challenging condition, as well as education on when to seek medical help.

**MANAGING PALMOPRANTAR PUSTULOSIS**

PPP is also notoriously difficult to manage. Patient responses to treatment tend to be highly variable and unpredictable. However, all patients with PPP should be advised to take steps to promote better health. First, they can regularly apply a bland, unscented, emollient moisturizer to help minimize the formation of cracks and fissures in their skin. Second, they can avoid skin irritants, taking special care to avoid washing items with detergents or soaps without wearing gloves. Third, they can quit smoking, given the strong link between smoking and PPP. Some data suggests smoking cessation alone improves PPP symptoms, and there is no doubt it improves overall health.

At present, there is insufficient evidence to guide treatment for PPP in a truly evidence-based fashion. According to the 2012 NPF guidelines for the treatment of pustular psoriasis, which were based on the best (scant) evidence available at the time, first-line local therapy for PPP consists of topical calcipotriene, topical corticosteroids, and PUVA, while second-line local therapy consists of photodynamic therapy and tacrolimus. In reality, topical treatment is seldom sufficient to result in remission among patients with PPP, so systemic therapy is often necessary and should not be delayed. The NPF guidelines recommend acitretin as the first-line systemic therapy option, with second-line options including cyclosporine and biologics, including TNFα inhibitors and the IL-12/23 inhibitor ustekinumab.
Since the publication of the NPF guidelines, new evidence has emerged regarding the efficacy of biologics in treating PPP. A phase 3 trial has shown that the IL-23 inhibitor guselkumab is effective and safe for patients with PPP. However, some small clinical studies indicate that other biologics are either no more effective than placebo (the IL-17 inhibitor secukinumab), result in either no or only moderate improvement in symptoms (the IL-17 inhibitor brodalumab), or improve symptoms in some patients while worsening them in others (the TNFa inhibitor etanercept). Available efficacy data for the IL-12/23 inhibitor ustekinumab is mixed.

Currently, IL-1 and IL-36 inhibitors are being investigated for the treatment of PPP. Given the clinical and genetic similarities between PPP and GPP, it is possible that IL-36 inhibitors may be found to be effective for PPP, as well as for GPP.

**SUPPORTING PATIENTS WITH PUSTULAR PSORIASIS**

During a flare, pustular psoriasis affects virtually every facet of a patient’s life, from their ability to wear shoes to their ability to be intimate with a partner (see Figure 5). For many patients, such problems persist to some degree even between flares. Thus, from the moment a patient is diagnosed, it can be helpful to prepare them for the path that lies ahead. Pustular psoriasis is often difficult to treat, and it is rare for patients to achieve “100% clear” status, even between flares. Many different treatment strategies may need to be tested before a patient finds one that controls their symptoms and meets their needs. Through careful listening and clear communication, clinicians can set a foundation for a productive therapeutic relationship in which the patient understands that they will be treated as a partner in finding therapies that work best for them.

Controlling skin and systemic symptoms is certainly an essential part of treating pustular psoriasis, but many patients also require psychological support. Their lesions can be highly stigmatizing, and many patients also fear that their current treatments may eventually stop working. Not surprisingly, depression and anxiety are common among patients with pustular psoriasis. In fact, in a recent survey of patients with GPP, respondents reported that a change in mood was the most burdensome symptom associated with flares. In addition, many reported they felt that their clinician did not understand the level of emotional, psychological, or physical pain caused by GPP. By simply validating patients and acknowledging their pain, clinicians can provide a critical aspect of care that is often neglected. In addition, linking patients to therapy can make a meaningful difference in how they are able to adapt to living with pustular psoriasis.

**FIGURE 5**

The patient experience of flares, derived from a survey of 66 patients with generalized pustular psoriasis (Adapted from Reisner et al, 2022)

<table>
<thead>
<tr>
<th>Impacted During a Flare</th>
<th>Activity</th>
<th>Impacted Outside of a Flare</th>
</tr>
</thead>
<tbody>
<tr>
<td>58%</td>
<td>Physical activity</td>
<td>21%</td>
</tr>
<tr>
<td>39%</td>
<td>Important life events</td>
<td>15%</td>
</tr>
<tr>
<td>47%</td>
<td>Wearing shoes</td>
<td>15%</td>
</tr>
<tr>
<td>44%</td>
<td>Running errands</td>
<td>14%</td>
</tr>
<tr>
<td>52%</td>
<td>Intimacy with a partner</td>
<td>23%</td>
</tr>
<tr>
<td>38%</td>
<td>Household Chores</td>
<td>11%</td>
</tr>
<tr>
<td>41%</td>
<td>Socializing</td>
<td>12%</td>
</tr>
</tbody>
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*Proportion of patients reporting a high impact on the activity in question (defined as 8-10 on a scale of 0-10)

**CONCLUSION**

Pustular psoriasis is a dramatic and devastating condition, and managing this rare and challenging disease can feel overwhelming for both patients and clinicians. In one recent survey, only one-third of patients with GPP felt their disease was well-controlled. Often, a trial-and-error approach to management is necessary, as no two patients will respond to treatment in the same way. The difficulty of finding an effective treatment plan can make patients and their healthcare providers feel helpless at times. However, the first medication specifically indicated for pustular psoriasis was recently approved in the United States, making the future look more hopeful. As we learn more about the biologic basis of the different subtypes of pustular psoriasis, it is likely that additional novel treatments will be developed. In the meantime, clinicians should diagnose patients with pustular psoriasis as quickly as possible and offer them the treatments supported by the strongest evidence. By persisting in the endeavor to find an effective treatment plan for each patient, clinicians can improve lives—and sometimes even save them.
REFERENCES


When I educate healthcare colleagues on the nuances of psoriasis, I emphasize the importance of breaking down the entity into its two pieces. Just like on your own birth certificate, psoriasis often gets a first and last name. But instead of “Julie Smith,” it’s plaque psoriasis or guttate psoriasis or palmoplantar pustulosis. This method reminds us that there is important uniqueness to each psoriasis subtype that requires a different approach to diagnosis and management. The subtype often heralds the geographic location of the rash or scales and clues us in to the direction of optimal treatment.

While there is some commonality among many of the psoriasis subtypes, pustular psoriasis is in a class of its own. Plaque psoriasis is the most common subtype of the disease, so let’s say a “Julie Smith.” Pustular psoriasis is more like a “Baron Chester von Grangerton.”

As detailed throughout this issue of Dermatology Nurse Practice, patients with pustular psoriasis have subtle, sterile pustules in their psoriatic plaques that are often located in specific areas (ie, borders rather than centers, palmar and plantar arches). It takes a focused eye to locate these pustules. Pustular psoriasis requires us to be stealth detectives, to see subtleties and look at the entire body as a puzzle. While pathways such as tumor necrosis factor alpha, interleukin (IL)-17, IL-23, and IL-12 play a key role in the development of many immunologic conditions, including plaque psoriasis, there is increasing evidence that IL-36 is the key disease pathway driving the development of several pustular psoriasis subtypes.¹

A recent patient of mine, James, tested all my clinician detective skills. I first met James in the summer...
of 2021. He came to our practice with a 20-year history of plaque psoriasis that initially presented in his early adulthood, most often involving his scalp and less frequently his trunk and extremities. James went through a series of flares and remissions over the course of his adult life, with a disease that was always fairly manageable.

In the spring of 2021, James presented to a local urgent care with a hacking cough and signs of an upper respiratory infection. He was diagnosed with bronchitis and prescribed a short course of oral glucocorticoids as well as a cough suppressant. He told me that his skin was completely clear prior to this health episode, but a few days after his last glucocorticoid dose, his rash exploded not only on his scalp, but also on his hands, feet, trunk, and extremities. He returned to urgent care, where he was given a repeat course of oral glucocorticoids and referred to our dermatology clinic for follow-up.

By the time of his initial visit to our practice, James’ rash had been flaring for several weeks. He could not wear shoes due to intense pain in his feet or turn doorknobs due to severe sensitivity in his fingertips. His rash covered his scalp, trunk, and extremities, with marked redness on his hands and feet. James was unable to close his fist and was having such trouble with mobility that he had been forced to take disability leave from work. Additionally, he said he just wasn’t feeling well in general, with a mild but persistent fever, general malaise, and poor sleep. His fingernails had all fallen off several weeks ago, accompanied by a significant amount of purulent drainage, and had not grown back.

There were several key clues in James’ history and workup that pointed us in the direction of generalized pustular psoriasis (GPP). First, James was a chronic smoker, with a pack-a-day history since late adolescence. Smoking is one of the primary risk factors for the development of GPP. Second, James’ rash seemed to be exacerbated by his recent use and withdrawal of systemic glucocorticoids. This is a hallmark sign of GPP. If you remember nothing else about this essay, please remember to be extremely cautious about prescribing systemic glucocorticoids in patients with psoriasis—while this can help alleviate symptoms in the short term, it can make things much worse in some patients. Other diagnostic clues of GPP were James’ marked hand and feet erythema (better known as erythroderma in the dermatology setting), anonychia (complete absence of toenails or, in this case, fingernails), mild yet persistent fever, and hypocalcemia.

While I was certain James had GPP following our comprehensive physical exam, I wanted to make sure I wasn’t missing anything, so I ran through a mental list of other possible diagnoses.

- Pemphigus foliaceus? No, because James’ rash involved pustules on his trunk, palms, and soles instead of blisters or bullae.
• Dermatitis herpetiformous? Not without a history of celiac disease, gastrointestinal intolerance to gluten, or another food allergy or intolerance.

• Septicemia? His systemic symptoms (fever, malaise, poor sleep, and hypocalcemia) made this unlikely.

• Superinfected atopic dermatitis? There was no atopy, eczema, allergies, or asthma, so this was ruled out as well.

Nonetheless, to cement the diagnosis, I ordered wound cultures of pustules on James’ abdomen and feet. I also performed a punch biopsy of one of the newer plaques on his abdomen and ordered a battery of routine lab tests (ie, CBC with differential, CMP, chest X-ray). All of the results came back consistent with a diagnosis of GPP.

So what now? To make immediate inroads, James was initially placed on systemic therapy with oral glucocorticoids (40 mg PO daily for 5 days, 30 mg PO daily for 5 days, 20 mg daily for 5 days, 10 mg PO daily for 5 days, then 5 mg PO daily for 10 days). I know what you are thinking—didn’t I just say that glucocorticoids can lead to or exacerbate GPP? Yes, but what’s important is the dose regimen of the prescription. Systemic glucocorticoids can be used in many patients with psoriasis, including those with GPP, as long as the taper is controlled over an extended period of time. Few dermatology practices will ever prescribe a glucocorticoid dose pack for a patient with psoriasis—while the brief “honeymoon” phase is often grand, the rebound flare often results in a worse rash than before. In James’ case, his symptoms quickly improved thanks to our regimented use of systemic glucocorticoids as well as clobetasol ointment that was applied to his fingertips and itchy areas up to twice daily. To maintain his improvement, James was placed on guselkumab. He remains rash and pain free 1 year later.

While 90% of our practice as dermatology providers may involve the care of patients with more common conditions, it is those diagnostic zebras such as James that test our detective skills. It is important in these patients that we carefully consider all potential options before (hopefully) coming to the appropriate conclusion.

REFERENCES


The outlook for patients with plaque psoriasis has improved tremendously over the course of the last 20-plus years ever since biologic therapies entered our arsenals for this common dermatologic condition. Providers have welcomed these therapies with open arms, understanding how much of an impact they can have on our patients’ physical and emotional well-being. Today, we have even been able to refine the art of addressing hard-to-treat areas of pustular psoriasis. Consequently, there are few patients we can’t help with this condition once they enter our practices.

It's unfortunately a much different story with pustular psoriasis patients. Not only is this disease more difficult to treat, but the diagnosis is often delayed or missed entirely both by primary care and dermatology providers. Patients’ pustules are commonly misinterpreted as being infectious in nature, resulting in the prescription of needless (and completely ineffective) antibiotics. These patients present with a variety of other signs and symptoms, including erythema on the hands, face, or throughout the body, chills, fatigue, and skin/joint pain. In some cases, especially in patients with generalized pustular psoriasis (GPP), hospitalization is necessary due to life-threatening erythroderma that requires IV fluids and careful monitoring of kidney function. Some patients may require a modified Goeckerman regimen that involves the application of topical triamcinolone 0.025% wet wraps applied in 4-hour on/4-hour off cycle.¹

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While there is some clinical trial data specific to the treatment of pustular psoriasis—and specifically GPP and palmoplantar pustulosis (PPP)—most studies have been small in nature with limited enrolled patients. While the body of evidence is slowly growing, its dearth has led many providers to base clinical decisions on real-world, first-person experience.

Let’s start first with GPP. Here is what I have learned in my personal clinical experience managing patients with this condition:

1. The use of conventional, oral systemic and biologic therapies that are so useful in the treatment of plaque psoriasis and other dermatologic conditions have not yielded adequate efficacy and durability for the treatment of most patients with GPP. Consequently, many patients with GPP require frequent medication changes to achieve even moderate control of this chronic and episodic condition.

2. While cyclosporine works well to quiet severe and episodic disease flares, it is not appropriate for all patients. And even for those who do benefit from its use, cyclosporine cannot be used as a long-term therapeutic solution.

3. While suggested by some providers based on small case reports, I have personally had poor success treating GPP patients with narrow-band ultraviolet B (NBUVB) or psoralen UV A (PUVA) phototherapy. In fact, in many of my GPP patients, phototherapy has worsened their erythema and caused flaring of pustules.

Because of the lack of historically proven therapies, the majority of GPP patients who I manage are treated with some combination of oral systemic and biologic therapies. It is often frustrating for providers and patients because we can rarely hope for better than a few months of disease control on one medication or one medication combination before things begin to exacerbate again and we move onto another regimen.

Fortunately, there is finally a glimmer of hope on the horizon for our patients with GPP. In September 2022, spesolimab became for the first therapy specifically approved for the treatment of GPP flares in patients ages 18 and older. Spesolimab is an interleukin-36 receptor antagonist delivered via intravenous infusion at a dose of 900 mg. If the patient’s flare persists, an additional 900 mg dose can be given a week later because all of my current GPP patients are stable on their current medication regimens, I do not yet have any real-world experience with spesolimab, but based on clinical trial research and FDA approval, I will not hesitate to recommend its use to my patients if their disease flares.

So what about patients with PPP? These are patients who struggle through cycles of moderate-to-severe flares on the hands and feet that are extremely painful, sometimes rendering them unable to walk or use their hands to complete the simplest of daily tasks. Patients with PPP often are accompanied to appointments by friends or family members since their disease flares render them unable to grip a steering wheel or wear normal shoes. They often present with hands in a curled position due to deep pustules in various stages of waxing and waning, general fissures, and peeling plaques with erythema.

Here is what I have learned in my personal clinical experience managing patients with PPP:

1. Topical corticosteroids provide little to no relief in the majority of patients. It’s the same with use of moisturizers or wearing cotton gloves.

2. Use of topical tapinarof, an aryl hydrocarbon receptor-modulating agent, is effective for some patients. Topical roflumilast, a selective phosphodiesterase-4 inhibitor, is also sometimes beneficial. Please note that the use of both of these agents is off label.

3. Topical pimecrolimus and tacrolimus often cause severe burning and discomfort. I avoid their use in patients with PPP.

4. I have not seen good success with NBUVB or PUVA in patients with PPP and find that they often cause disease flares.
"While I am personally grateful for the incredible strides we’ve made in the treatment of some of our more common dermatologic conditions... it’s some of our more uncommon, ‘unicorn’ conditions like pustular psoriasis where we continue to grasp at straws"

As in GPP, there is no consistent strategy to the successful treatment of patients with PPP, and approaches must regularly be evaluated and modified. Systemic therapies that are commonly included within our PPP patient regimens include methotrexate, cyclosporine (limited to select patients), acitretin, and apremilast. It is important to note that both methotrexate and acitretin are contraindicated in pregnancy so their use should be avoided in any woman trying to conceive. While there are clinical trials underway testing the use of other biologics in the treatment of PPP, studies testing spesolimab in these patients unfortunately did not meet efficacy endpoints. Nonetheless, clinical development in this disease category continues since patients with PPP carry such a high physical and psychological burden.

While I am personally grateful for the incredible strides we’ve made in the treatment of some of our more common dermatologic conditions such as psoriatic arthritis and plaque psoriasis, it’s some of our more uncommon, “unicorn” conditions like pustular psoriasis where we continue to grasp at straws. I eagerly await the day when we’re able to change the lives of these patients for the better.

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