**Title:** Pyoderma Gangrenosum

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**Competing interests**

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**Abstract:** Pyoderma gangrenosum (PG) is a rare neutrophilic dermatosis that is difficult to diagnose and treat. Patients with PG present with painful skin ulcerations hallmarked by undermined borders and a distinct violaceous color. The etiology of PG is not well understood, but it is generally considered to be an autoinflammatory disorder. Current knowledge about PG pathophysiology has come from characterizing humans with autoinflammatory syndromes that present with PG-like lesions and animals harboring defects in innate immune genes. Other studies have focused on the role of T cells, especially at the wound margin. These cells may support the destructive innate immune autoinflammatory response. Epidemiologic studies have identified the average age of PG onset to be mid 40’s with an incidence of approximately 6 per million person-years. PG is associated with a variety of other immune-mediated diseases, the most common being inflammatory bowel disease (20%) and rheumatoid arthritis (12%). Although PG remains a diagnostic challenge, recent diagnostic criteria have been established and validated. However, PG-specific outcome measures are still lacking, and there are only a handful of PG quality of life studies published. Herein, we review all of these topics in detail and provide a PG treatment algorithm to aid in clinical decision making.

**Introduction**

Classic ulcerative pyoderma gangrenosum (PG) is a rare neutrophilic dermatosis characterized by rapidly evolving painful ulcers, with undermined borders and peripheral erythema (red skin).1 Of note, the term PG is a misnomer, as PG is not an infection (pyoderma historically refers to a bacterial skin infection that produces pus), nor is it a classical gangrenous condition. Undermining of a PG ulcer edge occurs when the skin partially splits, separating the epidermis and upper papillary dermis from the lower dermal layer.2 The disease can present as a solitary lesion (usually at the site of trauma, see below) but also as several new lesions at the same time; patients with PG can have chronic, relapsing or self-remitting (reversible) disease.

PG was first described by the French dermatologist Louis-Anne-Jean Brocq, who in 1908, published a report on “geometric phagedena” (phagédénisme géométrique), a rapidly spreading ulceration of soft tissue.3 However, the modern name of the disease was coined in a 1930 clinical study by Louis A. Brunsting, William H. Goeckerman and Paul A. O’Leary. Although these authors incorrectly proposed an infectious etiology for PG, their classic description of the presentation, clinical behaviour, and disease associations of PG forms the basis of how PG is taught and diagnosed today.3-6 Among the most striking observations in this study is the description of pathergy, a major skin injury that occurs after minor trauma. The authors demonstrated that new non-healing ulcers occurred at skin graft donor sites, and they also observed that PG frequently occurs in the setting of other co-morbidities, specifically chronic ulcerative colitis. Today, the link between PG and a variety of underlying autoimmune and autoinflammatory diseases has been firmly established.7 However, PG pathophysiology remains poorly understood.

Most researchers consider PG to be a prototypical ND. NDs are a group of cutaneous disorders characterized histologically by a neutrophilic infiltrate with no evidence of underlying infection or vasculitis. Clinically, patients with ND present with erythematous oedematous papules, plaques, nodules or sterile (non-infectious) pustules. Secondary include abscesses, blisters and ulcers. Rarely, internal organ involvement may also be noted,8 and this finding has led to the related term neutrophilic diseases.9,10 However, herein, we will refer to PG as a ND, as this classification best represents the typical presentation of PG.

The predominant view is that PG and other NDs result from autoinflammation, a process by which innate immune cells cause host tissue damage in the absence of an infectious stimulus.11,12 Autoinflammation can be initiated by aberrant production and/or signalling of inflammatory cytokines. Several ND-related syndromic diseases exist, which result from genetic mutations that activate pathways of innate immunity that lead to the overproduction of inflammatory cytokines.10,13-15 (Table 1) These monogenic autoinflammatory syndromes can be referred to as types of syndromic PG, as they present with lesions that resemble classical ulcerative PG. This finding suggests that these syndromic autoinflammatory diseases share a common pathogenetic mechanism with the NDs. In fact, many patients with ND have similar mutations, which led to the hypothesis that NDs are a spectrum of polygenic autoinflammatory conditions.10,15-17

PG remains one of the most difficult dermatologic diseases to diagnose and treat. At the time of writing, there are only two published randomized clinical trials which means that PG treatments are largely based upon anecdotal data and small case studies. Although this Primer will focus mainly on classical ulcerative PG, over the years, several PG subtypes (Table 2) and PG-like diseases (Table 3) have been proposed.

**Epidemiology**

**Incidence, prevalence and mortality**

There are only a few population-based studies assessing the epidemiology of PG, and the difficulty in correctly diagnosing PG could affect the accuracy of estimates. Of these population-based studies, the largest was a cross-sectional study from the USA that used a validated algorithm and data derived from Explorys, a cloud-based IBM platform for analysis of longitudinal electronic health record data. This study identified 1,971 individuals with PG from a database containing >31 million adult patients.18 A population-based study conducted in the UK reported the incidence of PG to be ~6 per million person-years, and another study in the USA reported the prevalence as 58 per million adults.18,19

Most other studies in European regions have relied upon historical data generated from specialist center cases or from analysis of specific at-risk populations, such as those with inflammatory arthritis or inflammatory bowel disease (IBD), and have focused on the proportion of these populations developing PG.20,21

Although PG can occur in any age group, 22-30 all studies to date indicate that PG presents most frequently in older individuals (~50 years) across multiple countries.18-20,31-33 For example, a cohort study involving participants from the UK General Practice Research Database revealed that the median age of a patient with PG is 59 years (interquartile range 41-72).19 Similarly, a cross-sectional US-based study demonstrated that nearly 70% of PG with PG were of ≥50 years of age.18 Both of these studies also reported a slightly higher prevalence and incidence of PG in women than in men , comprising ~59–68% of cases.18,19,33 Another study from the USA has demonstrated that the average age of PG onset is 44.6 years (SD+19.7), with similar estimates from studies from other regions, including Italy and Switzerland.20,31,32 However, one important caveat to consider when interpreting these findings is that distinguishing PG from other ulcerative diseases affecting elderly individuals can be challenging.

In addition to the severe morbidity associated with having painful PG wounds, historical studies have also demonstrated that PG is associated with an increased mortality.19,34 One population-based study utilizing the UK General Practice Research Database reported that patients with PG have a mortality rate three-fold higher than that of age-matched and sex-matched controls, and when compared with patients with other inflammatory diseases, patients with PG still had a higher risk of death.19 For example, patients with PG had a 72% higher risk of death than patients with IBD, after adjusting for age, sex and comorbidity.19 A study from the USA found that during inpatient hospitalizations, 3.2% of patients with PG died (from any cause of death) during their stay, although the authors did not address how this percentage compares with that of other patient groups of the same age and sex admitted to the hospital.35 Further studies are still needed to better elucidate why patients with PG have increased mortality and how much of it can be attributed to PG-associated comorbidities, immunosuppression, infection, or iatrogenic occurrences.36

**Comorbidities**

Although nearly a century has passed since the first report of the association between PG and other diseases, such as chronic ulcerative colitis, modern epidemiological studies are still trying to quantify the frequency of these disease associations. Thus far, results have varied, with some groups reporting that as many as 50% of patients with PG have a second underlying immune-mediated disease, whereas others have found such associations at a somewhat lower frequency.19,37 Most studies have not focused on the time of onset of the associated immune-mediated disease, although clinical reports strongly suggest that these diseases usually precede PG onset. For example, in the UK General Practice Research Database, 33% of individuals with PG had a second immune-mediated disease; of these diseases, the most common were IBD (20.2%), rheumatoid arthritis (11.8%) and haematological malignancies (3.9%).19 Similar results were found in a large meta-analysis of 21 studies including 2,611 patients; in this study, the prevalence of immune-related systemic diseases in PG was 56.8%,37 with IBD reported in 17.6% of patients, inflammatory arthritis in 12.8%, haematological malignancies in 8.9% and solid malignancies in 7.4%. Although PG is highly associated with these diseases, PG itself is a rare disease. Thus, whereas it is common for patients with PG to have an associated illness, the reverse is not true. For example, the relative risk (odds ratio) for a patient with IBD to develop PG is high (29.2, CI 21.0-40.8), but only an exceeding small fraction (0.5%) of patients with IBD will have PG.38

**Mechanisms/pathophysiology**

The best documented factor that can induce PG ulcerations is trauma, which is known to induce the release of cytokines and danger signals that can support innate immune responses. Two of the aberrantly expressed cytokines detected in early PG lesions are known to be associated with trauma. Trauma induces the release (mainly from keratinocytes) of IL-36 (Ref39), a cytokine thought to have a major role in PG pathophysiology.40Minor trauma to the skin has also been shown to increase *IL8* expression, which encodes IL-8, another putative PG-driving cytokine.41. Tissue damage can also cause the release of autoantigens.42 These events may be sufficient to induce PG, especially in patients harboring mutations in genes involved in the inflammasome pathway (see below).

*Autoinflammation*

Studies on PG pathophysiology in humans are limited; much of what we know has been inferred from characterizing animal models of autoinflammation and the ND-related syndromic diseases in humans (Table 1).4344 One protein that seems to be relevant is tyrosine-protein phosphatase non-receptor type 6, also commonly referred to as SHP-1 and encoded by *PTPN6*. It modulates signals transmitted by tyrosine-phosphorylated cell surface receptors, which include various cytokine receptors, and also modulates signals originating from receptors on cells of the adaptive immune system, such as the T cell receptor (TCR).45,46 Studies in a mouse model homozygous for a loss of function *Ptpn6* variant that results in a protein with decreased enzymatic activity (*Ptpn6meB2/meB2* mice) 47 showed that these mutant mice develop an autoinflammatory disease characterized by sterile neutrophilic skin lesions that resembles ND in humans.47 The discovery of patients with PG with mutations in *PTPN6* supports the involvement of this pathway in human PG.44

Similarly, patients with PG with mutations in *PSTPIP1,* another classic autoinflammatory gene encoding proline-serine-threonine phosphatase interacting protein 1, have also been identified.44,48 *PSTPIP1* mutations are well known to cause pyogenic arthritis, PG and acne (PAPA) syndrome, a syndromic PG.49 PAPA syndrome-associated *PSTPIP1* mutations increase binding affinity of PSTPIP1 to pyrin, (encoded by *MEFV*); this binding induces the assembly and hyperactivation of the inflammasome, an intracellular cytosolic protein complex that cleaves inactive precursors forms of IL-1β, IL-18, and IL-33 to generate their active proinflammatory counterparts (FIG. 1).50 Thus, patients with PAPA syndrome have increased activation and secretion of IL-1β.13,50,51 IL-1β overproduction triggers uncontrolled release of various other proinflammatory cytokines, including those that mediate neutrophil recruitment and activation, resulting in neutrophil-mediated autoinflammation.13,16,43,50-52 The connection between PG to autoinflammation is further demonstrated by the finding that patients with classic ulcerative PG, as well as those with a syndromic PG, can harbour mutations in a number of autoinflammatory genes, including *MEFV*, *NLRP3* (encoding NACHT, LRR and PYD domains-containing protein 3), *NLRP12* (encoding NACHT, LRR and PYD domains-containing protein 12), *LPIN2* (encoding phosphatidate phosphatase LPIN2, also known as lipin 2), *NOD2* (encoding nucleotide-binding oligomerization domain-containing protein 2) and *PSTPIP1* (FIG. 1).53-56 PG, acne and suppurative hidradenitis (PASH) syndrome and pyogenic arthritis, PG, acne and suppurative hidradenitis (PAPASH) syndrome are other types of syndromic PG53-56 that are highly similar to PAPA syndrome but also present with hidradenitis suppurativa (HS). HS is a debilitating disease that manifests as nodules, abscesses, fistulae and hypertrophic scars and mainly affects apocrine gland-bearing skin, such as the skin folds of the axillae (armpits), groin and perianal regions.57 Like PG, HS has been proposed to have an autoinflammatory aetiology.58 These observations support the hypothesis that classic PG being a polygenic autoinflammatory condition hallmarked by dysfunction of the innate immunity and elevated levels of markers of inflammation.15,16,43,59-61

In addition to IL-1 IL-1α has been implicated as a major driver of autoinflammation, although it seems to function through a unique mechanism entirely independent of the IL-1β-activating inflammasome pathway. The discovery of the role of IL-1in PG stemmed from studies of *Ptpn6spin* mice,62-64 which are another model of ND. In these mice, a missense mutation in *Ptpn6* (encoding a Tyr208Asn substitution at the carboxy terminus of the Ptpn6 protein) results in chronic footpad oedema, neutrophilia, and suppurative inflammation.62-64 The phenotype is crucially mediated by IL-1α (regulated by receptor-interacting serine/threonine-protein kinase 1 (RIPK1)) and not by IL-1β-driven events.63 Further elucidation of the *Ptpn6spin* model has revealed that the *Ptpn6spin* phenotype is also mediated by mitogen-activated protein kinase kinase kinase 5 (MAP3K5) and MAP3K7, which are serine/threonine protein kinases that mediate signal transduction, and by the caspase recruitment domain-containing protein 9 (CARD9).62-65 The identification of these pathways in mice will hopefully pave the way to novel drug targets to treat ND in humans.

*Inflammatory cytokines*

In addition to the IL-1 family members just described, gene expression analyses have identified elevated levels of numerous other pro-inflammatory cytokines in PG, including C-C motif chemokine 3 (CCL3, encoded by *CCL3*),CCL5 (*CCL5*),C-X-C motif chemokine 9(CXCL9, encoded by *CXCL9*),CXCL10 (*CXCL10*),CXCL11 (*CXCL11*),IFNγ (*IFNG*),tumour necrosis factor (*TNF*),IL-1α (*IL1A*),IL-8 (*CXCL8*),IL-15 (*IL15*),pro-IL-16 (*IL16*),IL-17A (*IL17A*),IL-23 (*IL23A*), IL-25 (*IL25*),IL-36α (*IL36A*) andIL-36γ (*IL36G*).11,54,56,66-70 IL-36α and IL-36γ are also members of the IL-1 family of cytokines. IL-36 cytokines are of particular interest because they have an important role in psoriasis, pustular psoriasis, acute generalized pustulosis and the PG-associated diseases ulcerative colitis, Crohn's disease and HS.71-76 As a general rule, *IL36A* and *IL36G* are highly expressed by epithelial cells in the setting of inflammation and, owing to their pathogenetic role in several PG-associated diseases, they probably also have a yet to-be-described function in PG. One possibility is that inactive IL-36 cytokines precursors are proteolytically processed and activated by proteases released from neutrophil granules. Once activated, these cytokines can fuel an inflammatory loop leading to recruitment of more neutrophils and subsequently enhanced activation of additional pro-inflammatory cytokine precursors. This excessive inflammatory response ultimately results in tissue damage.

IL-25 (also known as IL-17E) is an IL-17 family member that has been implicated in PG and several other NDs.77 Multiple cell types can secrete IL-25, including keratinocytes, eosinophils, basophils, dendritic cells and type 2 T helper (TH2) cells.78 Although IL-25 was initially thought to promote TH2 cell-mediated immune responses,79,80 for example, in atopic dermatitis, more-recent data suggest that it has a pathogenetic role in neutrophilic inflammation.77,81 In this setting, IL-25 may induce secretion of the neutrophil-recruiting chemokines CXCL1, CXCL10 and CCL20 by macrophages.81 Other neutrophil-attracting cytokines with upregulated expression in PG include IL-8, CCL3 and CCL5.40,56,66,82,83 Each of these cytokines attracts neutrophils by a different mechanism. For instance, IL-8 acts by binding to C-X-C chemokine receptor type 1 (CXCR1) and CXCR2 (Ref84). Also, IL-16 (which is cleaved by caspase-3 from pro-IL-16 indirectly attracts neutrophils by inducing neutrophil chemoattractant expression.85 It is unique in that it does not function through a classical cytokine receptor but rather via its interaction with cell surface glycoprotein CD4.

Finally, the success of anti-TNF therapies in treating PG highlights TNF as one of the most clinically relevant PG-associated cytokines.86 TNF is produced by numerous cell types and has a broad range of inflammatory functions. With regard to PG, TNF can increase the expression of blood vessel adhesion molecules to support neutrophil binding and migration, and it can also induce production of IL-8.87-90 A direct role for TNF in PG autoinflammation is supported by data showing that the TNF–TNF receptor pathway can contribute to inflammasome activation (FIG. 1).91

*Role of adaptive immunity*

Although the majority of studies on PG pathophysiology have focused on the innate immune response and autoinflammation, it is increasingly evident that the adaptive immune system may also play an important part. This evidence has emerged from studies of the inflammatory infiltrate in very early lesions in patients with PG . One approach to study the disease-initiating immune process has been to biopsy the erythematous border just peripheral to the outmost edge of the PG ulcer, as the inflammatory process underlying the expansion of PG lesions occurs in this area. Histological analysis of this region has revealed a predominance of lymphocytes,92 including clonally expanded T cells, which would indicate an antigen driven phenomenon.93 The nature of the antigen(s) recognized remains to be elucidated, but on the basis of the distribution of the PG inflammatory response, dermal or follicular antigens are implied.40

An alternative approach to study the PG-initiating process has been to biopsy a PG papule at the earliest possible stage, rather than the ulcer edge. However, because PG papules rapidly evolve into pustules and then ulcerate,1 finding an early papule is difficult. Gene-expression analysis of such papules revealed robust expression genes encoding T cell attractant chemokines (*CXCL9*, *CXCL10* and *CXCL11*) and several cytokines, including *IL8, IL17A, TNF, IFNG and IL36G*.40 IL-36γ is known to induce immune cells and keratinocytes to secrete cytokines that can attract macrophages, T cells, and neutrophils.94 The expression of cytokines and transcription factors involved in TH1 cell-mediated and TH17 cell-mediated immune responses is also predominant. For example, the TH1 cell-promoting transcription factors *STAT1* and *STAT4* are upregulated, whereas the TH2 cell-promoting transcription factor *GATA3* is downregulated.40 Matching these gene expression patterns, histological analysis of the early PG papule revealed a robust infiltrate of CD4+ T cells accumulating perivascularly and around pilosebaceous units (FIG. 2).40 This distribution of T cells is also supported by early histological studies of PG as well as the clinical observation that PG lesions typically do not to affect anatomical areas devoid of pilosebaceous units, such as palms, soles and the areolas.40,95 In addition, the cytokine profile of the T cell response of the early PG papule is similar to that observed in PG-associated diseases,19 namely Crohn’s disease, ulcerative colitis, inflammatory arthritis and HS,96,97 suggesting that IL-23 and its downstream cytokines are a common denominator that links together these poorly understood disease associations.40,98,99

In PG lesions, there also seems to be a TH17 cell – regulatory T (Treg) cell imbalance, hallmarked by a reduction in Treg cells and concurrent overexpression of TH17 cell-associated.40,100 These cytokines may be one of the early drivers of the PG autoinflammatory response. Thus, a TH17 cell-mediated immune response could contribute to the recruitment of neutrophils, which are the main cell type within the bed and beneath the undermined border of an active PG ulcer.7,68,99 (FIG. 2) This recruitment is probably in part mediated by IL-23 (Ref[44](#_ENREF_43)), which is produced by dendritic cells, Langerhans cells, monocytes and macrophages, usually in response to some biochemical insult occurring at a barrier site, such as the skin and gut .101 IL-23 maintains and expands TH17 cells by initiating signaling cascades involving the tyrosine-protein kinase JAK2 (also known as Janus kinase 2) and signal transducer and activator of transcription (STAT) 3 pathways.102 These signaling cascades constitute the backbone of the IL-23–IL-17 axis, ultimately stimulating the production of IL-17A, a cytokine known to be essential for neutrophil migration.102,103 The overexpression of IL-23–IL-17 axis cytokines in PG links the adaptive immune system with the autoinflammatory pathways thought to drive PG pathophysiology. The IL-23–IL-17 axis will be an important topic for future investigations, especially as biologics that target these cytokines are readily available to be tested in PG clinical trials. Finally, recent data suggest that other cell types, such as neutrophils, CD8+ T cells and γδ T cells, can be potential sources of IL-17.(Ref104) Single cell sequencing may help to determine whether any of these cell types are also a major source of IL-17A in PG.

It is of interest to note that some PG ulcers will heal spontaneously. The mechanism is unknown but this natural disease course follows the general relapsing remitting course seen in other autoimmune diseases.105 Clearly, in an active PG ulcer there are a variety of anti-inflammatory cytokines expressed in addition to the pro-inflammatory ones described above.40 Among these IL-10 is known to IL-10 can block NF-κB activity, inhibit expression of Th1-associated cytokines, and downregulate MHC expression.106 The Treg transcription factor, FoxP3, is also up-regulated in PG lesions.40 Thus, it is possible that in some cases these anti-inflammatory regulatory pathways may eventually lead to ulcer healing.

**Diagnosis, screening and prevention**

*Diagnostic work-up*

Clinical presentation.

Evaluating a suspected PG lesion should start with a thorough medical history to assess for associated risk factors, including a history of IBD, autoimmune arthritis, and/or malignancy;30 although the onset of PG does not have to coincide with a flare of a patient’s underlying IBD or autoimmune arthritis. It is also important to determine the temporal evolution of the ulcer (for example, how fast the ulcer formed) and whether there was a triggering event. PG ulcers usually form rapidly, often following minor trauma (pathergy). Medications should be documented, as some investigators believe certain drugs can induce a PG-like diseases. On physical examination, the location of the lesions, characteristics of the ulcer border, and the presence and appearance of scars at sites of prior ulcerations should also be noted (FIG. 3). PG scars typically appear cribriform (with numerous small indentations similar to pockmarks)— or alternatively look wrinkled (cigarette paper-like) A PG ulcer border is typically undermined with a characteristic violaceous color. Finally, a PG lesion most commonly is located on the anterior lower extremities, probably because accidental trauma to this area is common.

A classic presentation is a minor trauma to a lower extremity that resulted in a tender inflammatory papule, nodule or pustule, which thereafter rapidly breaks down over a few days and becomes a necrotic ulceration.1 A violaceous undermined border is a sign of disease activity and of the impending enlargement of the ulcer(s); although at the time of this review there are no validated scores or outcome measures to quantify disease activity or severity. Macular erythema (redness) is often present peripherally to the undermined border in active lesions, or it can replace the undermined border in less active lesions. In partially treated or resolving ulcers, the violaceous color and the undermined border may be absent, a fact that can complicate diagnosis. When expanding, ulcers usually increase in size symmetrically or asymmetrically by following the growth of their undermined edge, or, alternatively, they can extend through the appearance of new peripherally located pustules. In severe cases, ulcers can appear without history of trauma, often initially presenting as one or more small pustules, sometimes closely grouped.

The base of a PG ulcer usually does not extend past the adipose tissue underlying the dermis , but rarely lesions involving the fascia (the connective tissue under the skin that covers the muscles) have been reported.107 The appearance of ulcers can vary, depending on how long they have been present and whether or not the patient is on immunosuppression for their PG. A typical PG ulcer initially has an oozy exudative base, which can transition over the course of weeks to exuberant granulation tissue (FIG. 3). With appropriate immunosuppression and wound care, the granulation tissue flattens, and re-epithelialization begins. Thus, it is important to document not only the size of the ulcer, but also the appearance of its border and base: once immunosuppression is initiated, a PG ulcer loses its characteristic features, including its violaceous undermined border, and ultimately looks very similar to ulcers of other aetiologies.

Laboratory tests

A PG diagnostic work-up typically continues with a biopsy, with the specimen preferentially obtained from the ulcer edge. Histological features include dermal oedema, suppurative inflammation and sometimes sterile abscess formation. If the biopsy sample is obtained from the periphery of the lesion, perivascular or periadnexal (usually perifollicular) lymphocytes may also be found. Additional staining of the biopsy sample may be required to help to rule out bacterial and fungal infections, and additional tissue may be obtained for bacterial and fungal cultures, as deep fungal infections, syphilis, leishmaniasis, and mycobacterial infections can clinically mimic PG. Severe insect bites can also mimic PG. Other differential diagnoses to consider include factitious (that is, self-inflicted) ulcerations, vasculitis, parasitic infections, venous insufficiency, antiphospholipid antibody syndrome, malignancy and other inflammatory disorders.108,109 To evaluate for these alternative diagnoses, laboratory diagnostic tests could include a rapid plasma reagin or venereal disease research laboratory test (for syphilis), perinuclear anti-neutrophil cytoplasmic antibodies (pANCA) or cytoplasmic anti-neutrophil cytoplasmic antibodies (cANCA) tests (for autoimmune diseases, in particular vasculitis), complete blood count and peripheral blood smear, anti-Saccharomyces cerevisiae antibodies (for Crohn’s disease), and serum and urine protein electrophoresis.7 When the diagnosis of PG seems probable and the patient presents with concomitant joint or gastrointestinal symptoms, additional work-up may include radiological imaging of the affected joints and/or a colonoscopy to rule out inflammatory arthritis and ulcerative colitis, respectively.

PG can also present as a paraneoplastic phenomenon, frequently observed in patients with myelodysplastic syndromes , multiple myeloma, polycythaemia vera, paraproteinaemia (also known as monoclonal gammopathy) and leukaemia.36,110,111 **112** These patients can have an atypical presentation with vesiculobullous lesions or more-superficial ulcerations with a blue-gray bullous border, which can occur at uncommon sites, such as the hands, forearms and face.7,31,110,111,113 Owing to the link between PG and cancer, all patients should be up-to-date with their age-appropriate cancer screenings.

*Validated diagnostic criteria*

Making a PG diagnosis can be challenging, owing to the variable presentation of PG, clinical overlap with other conditions and absence of defining histopathological and laboratory findings. Unsurprisingly, diagnostic delays and misdiagnoses are common. There are also numerous reports about ulcers initially attributed to PG that were subsequently re-classified under an alternative diagnosis after additional information about the case emerged, for example, identification of a malignancy, infection, vascular or a nutritional disorder.109,114-119 Such errors can pose substantial risk to the patient, as therapeutics used to treat PG are often contraindicated in patients with other ulcerative diseases.

Historically, PG was classified as a diagnosis of exclusion,120 which meant that all other potential aetiologies for the ulcer had to be excluded before it could be attributed to PG. Ultimately, this diagnostic strategy was impractical and costly.12,121,122 In addition, without established diagnostic criteria, patient selection into clinical trials can be particularly difficult and prone to misclassification. To bridge this clinical gap, two separate independent approaches have been taken.12,123,124 The PARACELSUS PG diagnostic tool uses a point scale with major, minor and additional criteria that are awarded three, two and one point, respectively. The assignment of a parameter into one of these three categories is based upon the specific prevalence of that parameter in the general population of individuals with PG. For example, PARACELSUS major criteria, such as a reddish-violaceous wound border, are present in >95% of patients with PG. Patients who receive a PARACLELSUS score of ≥10 are considered highly likely to have a diagnosis of PG.123

The second set of diagnostic criteria was established by an international panel of experts.12 Using a two-step approach, the team first established preliminary criteria using the Delphi method developed by the Research and development (RAND) Cooperation and the University of California, Los Angeles (UCLA). As part of this method, individual PG experts were asked to score statements regarding PG findings that could aid in the diagnosis of PG. Mathematic calculations outlined in the RAND–UCLA protocol were then applied to determine the degree of appropriateness of each statement and the level of expert agreement. Preliminary criteria established by the Delphi were then refined and mathematically cross validated against a set of published PG mimickers.12 The resulting international PG diagnostic criteria (FIG. 4) assign equal points to criteria that fall under four categories (histology, history, clinical examination and response to therapy). For example, a history of a papule or pustule that rapidly ulcerates would be awarded one point. Scores above 5 support a diagnosis of PG, but clinicians are encouraged to re-apply the diagnostic criteria as additional clinical data emerge.

**Management**

There are multiple case reports, small case series and open-label studies on PG treatments but, at the time of writing, only two published randomized trials.86,125 This overall paucity of clinical data means that important and practical clinical questions remain unanswered, including what initial steps should be taken after the diagnosis of PG, whether topical therapies work and, if so, which one(s) are the most effective , who the patients who should start systemic therapy are, how PG wounds should be dressed and how disease recurrence can be prevented. Until additional studies are conducted, we can only offer our expert opinion on these issues. First, PG is an immune-mediated disease. Thus, the primary goal of therapy is to halt the aberrant inflammatory process, and this goal is usually achieved with immunosuppression.126,127 Second, PG is an ulcerative disease that requires appropriate wound care. Regardless of aetiology, wounds can be slow to heal and, therefore, a regimen of cleansing and bandaging must be strictly followed.31 Third, PG-associated diseases and concurrent illnesses contribute to a patient’s ability to heal. Concurrent illnesses need to be taken into account when designing a treatment strategy.Fourth, PG is associated with considerable pain and psychosocial issues.128 These issues need to be addressed early with education and, when necessary, appropriate referrals to psychiatry and pain management clinics. Lastly, PG can be chronic, relapsing, or self-remitting (reversible). Once all lesions have healed, a decision needs to be made on treatment duration, as some patients will need lifelong therapy, whereas others will remain in remission after treatment discontinuation. In all cases, a prevention strategy or early treatment plan should be designed and tailored to each patient’s needs, especially in patients planning future surgical procedures.

*Treatment approaches*

On the basis mainly of expert opinion, a few investigators have attempted to develop algorithm approaches to treat PG.129-131 An approach agreed upon by this panel of authors is outlined in FIG. 5. From our experience, it is reasonable to start with a fast-acting immunosuppressive agent, such as cyclosporine or a corticosteroid (for example, prednisone), as PG is a rapidly evolving disease. Afterwards, the clinician should decide whether or not to add a second steroid-sparing agent. As can be extrapolated from their use in other disease settings, most steroid-sparing immunosuppressive drugs, such as mycophenolate mofetil and the majority of biologics, are slow-acting agents that demonstrate maximum effectiveness between 1-4 months.132,133 Thus, a reasonable strategy is to add a steroid-sparing agent to the therapy as soon as possible (see systemic agents below) to enable the down titration of the fast-acting agent(s) used to initially quench the pathogenetic pro-inflammatory immune response. Once therapy has been initiated, the clinician should reassess the patient in 1-3 weeks for an appropriate response to therapy, which would include no new ulcers, cessation of spread of existing ulcers, improvement in ulcer border and resolution of peripheral erythema. Later signs of improvement would include a decrease in the wound size or the appearance of “Gulliver's sign”, which is finger-like projections of new epithelium extending towards the ulcer’s center,134 and pain cessation or reduction.

Additionally, physicians need to consider the presence of coexisting disease(s) when selecting the treatment strategy. For example, if the patient has concurrent inflammatory bowel disease (IBD), agents approved for treatment of IBD, such as the anti-TNF antibodies adalimumab, certolizumab pegol or infliximab, are reasonable treatment options.135-137 If a patient with PG is having a suboptimal response to a biologic agent, then addition of an immunosuppressant such as methotrexate would be reasonable, as these combinations have been extensively studied in other diseases. In this setting, improved effectiveness may result either from the ability of methotrexate to enhance the activity of the primary agent or its ability to reduce the antigenicity of the primary agent.138-140 Treating patients with PG and hematologic malignancies pose a particular challenge, as some immunosuppressants will be contra-indicated depending on the type of cancer.

*Topical and intralesional therapies*

Several topical immunosuppressive agents have been employed as monotherapy to treat PG, but none have been formally studied in randomized trials.141 Thus, there is minimal information available to help guide the physician when selecting an appropriate topical medication, its strength, frequency of application, and the dressing best suited for use in conjunction with the topical agent. In our opinion, PG is frequently a rapidly evolving disease and, therefore forgoing systemic therapy for a topical regimen should be limited to patients with mild disease or contraindications to systemic therapy. Agents that have been used topically include superpotent corticosteroids, calcineurin inhibitors (particularly tacrolimus) to reduce cytokine production, dapsone (an antibiotic), 4% disodium chromoglycate (an anti-histaminic agent), 5-aminosalicylic acid (an anti-inflammatory agent) and nicotine (usually in a patch formulation presumably to lower inflammatory leukotriene production).142-144 Perhaps in the future, topical JAK inhibitors may also be used, as this drug class is being tested systemically.145-147

In addition to topical therapy, intralesional therapy has also been reported as an effective local treatment. Most commonly, intralesional triamcinolone (a glucocorticosteroid agent) is used but intralesional cyclosporine and intralesional methotrexate have also been reported to have an effect.148-150 In our opinion, it may be best to consider topical and intralesional management strategies as adjuvant therapies in conjunction with systemic agents.151

*Systemic therapies*

Historically, PG has been managed with systemic corticosteroids. However, results of a large randomized controlled trial have revealed that cyclosporine may be equally efficacious but have fewer serious adverse events (that is those that lead to hospitalization or death). In this pragmatic trial, 47% of patients achieved healing (defined as the time at which sterile dressings were no longer required) at 6 months in both treatment arms, with either cyclosporine (28/59 patients) or prednisolone (25/53 patients). Disease recurrence on therapy was similar, at 30% and 28%, respectively, and in both arms approximately two-thirds of patients experienced adverse events. However, serious adverse events, primarily infections, were more common in the patients treated with prednisolone than in those who received cyclosporine.152

The other randomized controlled trial compared infliximab (an anti-TNF monoclonal antibody) with placebo. In this study, patients were randomized to treatment with infliximab (n = 13) or placebo (n = 17) intravenously. After an assessment at 2 weeks, both groups were carried forward into an open-label extension phase, during which all patients received infliximab. At 2 weeks, clinical improvement was significantly better, defined by physician global assessment, in the infliximab arm (46%) than in the placebo group (6%, p=0.025). Although this study had a high percentage of responders, 69% (20/29) at 6 weeks, only 20% (6/29) achieved remission at week 6, and many patients (31%) failed to respond altogether (9/29).86

Although substantial progress has been made, all PG clinical studies to date have been hindered by a variety of shortcomings, most importantly, a lack of a validated PG outcome measure.153 Standard measures commonly applied to other ulcerative diseases are not ideally suited to accurately assess change (that is, “responsiveness” or “sensitivity to change”) in patients with PG ulcers, as PG ulcers are due to an aberrant inflammatory response, whereas traditional ulcer trials assess ulcer size but not inflammation. In addition, until recently, there were no accepted PG diagnostic criteria, a lack that made enrollment of a uniform population of individuals with PG into a clinical trial difficult.

*Multi-drug approaches*

PG is a rapidly progressing, debilitating disease. Thus, even short delays in achieving disease control can result in severe worsening of disease burden. Unfortunately, biologics and traditional steroid-sparingimmunosuppressive agents , such as mycophenolate mofetil, take 2 to 4 months to reach maximum effectiveness, and additional delays might occur if the patient needs to acquire insurance authorization to gain access to some drugs. In this setting, systemic corticosteroids and cyclosporine remain attractive first-line therapeutic options, owing to their extremely rapid onset of action (hours to days). However, a relatively high dose of systemic corticosteroids and/or cyclosporine is typically required to achieve a desired clinical effect. This high dosage combined with a long duration of therapy to achieve ulcer healing increases the risk of drug-related adverse events, as nearly everyone on high-dose cyclosporine or systemic corticosteroids will experience some adverse event during their therapy.152 Thus, steroid-sparing agents have been studied, including immunosuppressive antibiotics (for example, dapsone, sulfasalazine and minocycline);154,155 traditional immunosuppressives (for example, azathioprine, mycophenolate mofetil and methotrexate);156-159 alkylating agents (for example, chlorambucil and cyclophosphamide);160 biologics, including anti-TNF agents (for example, infliximab, adalimumab, golimumab and certolizumab),161-167 an anti-IL-12–IL-23 agent (ustekinumab),68,168 an anti-IL-23 agent (tildrakizumab),169 an anti-IL-17 agent (secukinumab),170 a IL-1 receptor antagonist (anakinra),171 anti-IL-1 agents (canakinumab and gevokizumab),172,173 an anti-IL-6 receptor agent (tocilizumab);174 intravenous immune globulin (an immune modulator);175-177 a phosphodiesterase-4 inhibitor (apremilast);178 and JAK–STAT inhibitors (for example, tofacitinib and ruxolitinib).145-147 However, the data on the success of all these durgs as steroid-sparing agents are based on uncontrolled observations in small numbers of patients, usually in the setting of concomitant therapeutics. This limitation combined with a lack of a validated PG outcome measure hinders the interpretation of the results. The only agent that was being studied in a randomized double-blind, placebo-controlled trial was gevokizumab, but this study was halted owing to a change in focus of the company manufacturing the drug.173

*Wound care*

As in other ulcerative diseases, bacterial colonization, oedema and several other factors can impede PG wounds healing. However, despite being one of the most important aspects of appropriate PG management, these factors are often overshadowed by the urgent need to suppress the pathogenetic inflammatory response. Nevertheless, an ideal PG treatment strategy should employ excellent wound care in parallel with the administration of immunosuppressive medications.31 Unfortunately, there are no controlled studies addressing this issue, which leaves only expert opinion to guide clinicians.

Cleansing and dressing

Most clinicians would agree that, at the minimum, gentle daily wound cleansing is indicated. In general, any solution applied to a PG wound should be at least room temperature, to avoid inhibiting the wound healing process and to minimize pain. If wound pain is a limiting factor, gentle cleansings can be substituted with wound soaks. Providers may use warm tap water or sterile solutions per regional preferences, as there is no evidence for superiority.179 The effectiveness of cleansing agents has not been extensively studied (for example, povidone-iodine versus benzoyl peroxide 5% soap)180,181, and some experts make arguments against soaps altogether, as they may damage fragile cells in the wound bed.182 Dilute vinegar (0.5% acetic acid) soaks have significant antimicrobial effects and may be beneficial in other ulcerative diseases183,184 but can be painful.

Antibiotics are usually not indicated, but it can be difficult to distinguish a PG flare from an infected PG wound. In addition, bacterial colonization and biofilm formation should not be mistaken for infection, as biofilm is best treated topically. New onset peripheral erythema and increased pain in a patient with PG who had previously shown improvement on immunosuppression would suggest infection. In such cases, cultures of wound tissue may help to guide antibiotic therapy.

With regards to dressings, wet-to-dry dressings should be avoided, as early PG wounds are usually exudative in nature, which hinders the effectiveness of these dressings. In later stage wounds, wet-to-dry dressings can be associated with substantial pain, which decreases our enthusiasm for this strategy. Absorbent antibacterial dressings (for example, silver-impregnated calcium alginate dressings) can be considered for early stage wounds that usually produce large amounts of fluid (FIG. 3). Dressings for these wet, often exudative wounds may need to be changed more than once a day. Given that protease-expressing neutrophils are abundant in early stage PG ulcers protease absorbent dressing can also be considered, which have been shown to be effective for other ulcerative diseases.185 In less exudative wounds, providers can consider decreasing bacterial colonization with topical antimicrobials, such as silver sulfadiazine, iodosorb, hydrofera blue and xeroform, among others. Some PG wounds pass through a stage with exuberant granulation tissue, which can resolve on its own if the patient is appropriately immunosuppressed. Later stage wounds can be dry, and some are covered by eschars (dark dead tissue adherent to the wound). Thus, dressing strategies should be adopted early and tailored to match the wound characteristics as it evolves. Generally, it is wise to avoid overly drying out of the wound base. The use of topical analgesics, particularly the use of topical medical cannabis on wounds as recently reported,186 is intriguing, but existing data are insufficient to enable recommendations in this regard.

PG wounds often occur on the lower legs, which should be monitored for oedema. Many of the medications used to treat PG, including prednisone and mycophenolate mofetil, can cause oedema, which can also be a direct result of the pro-inflammatory destructive PG immune response. When present, providers may consider compression therapy, with commercially available three-layer or four-layer compressive dressings. Elastic bandage wraps and compression stockings (as low as 20 mmHg, if limited by pain) may also be viable options. However, until the patient is appropriately immunosuppressed, there is a risk that excessive compression may result in new lesions forming by pathergy.

Impaired healing

Underlying medical conditions, such as diabetes mellitus, can also impede wound healing. Patients should be monitored for diabetes mellitus, especially those that are being treated with prednisone (which frequently increases glucose levels). Many of the medications used to treat PG unfortunately can also delay wound healing, especially prednisone, methotrexate and mycophenolate mofetil. In particular, methotrexate and mycophenolate mofetil directly inhibit keratinocyte proliferation, among other things.187 Impaired wound healing by immunosuppressive medications should be considered as a possible factor when patients are slow to heal despite being on adequate immunosuppression. In such cases, alternative agents may be considered, such as biologics or intravenous immunoglobulin.

Surgical management

Wound debridement can exacerbate PG ulcers, which is why it is contraindicated under most circumstances. Unfortunately, it is not uncommon for patients with PG to present to dermatology clinics with rapidly progressing disease after receiving surgical debridement.188,189 In such cases, the PG ulcer(s) were originally attributed to another aetiology prior to the patient’s paradoxical reaction to wound debridement. Surgical trauma can also be the inciting event that induces a PG ulcer to occur. When patients with post-surgical PG also have accompanying signs and symptoms of fever, sepsis and leukocytosis, they might be misdiagnosed as necrotizing fasciitis or another severe infection. Aggressive wound debridement in this setting can have devastating outcomes including amputation.115,190 Haag, C. K. *et al.* Pyoderma gangrenosum misdiagnosis resulting in amputation: A review. *J Trauma Acute Care Surg* **86**, 307-313, doi:10.1097/TA.0000000000002096 (2019).

The necrotizing nature of some PG wounds has prompted investigators to prefer the term necrotizing neutrophilic dermatosis in such severe cases.191 Indeed, pathergy makes management of PG ulcers very difficult. However, it is also controversial whether or not all patients with PG demonstrate pathergy. One study estimated that pathergy only occurs in ~32% of patients with PG.128 Although it is difficult to know the actual percentage because ulcers of other etiologies are often misdiagnosed as PG.192-200 However, patients become more resistant to pathergy once they are appropriately immunosuppressed. This finding has led some experts to manage slow healing PG ulcers in well-immunosuppressed patients similar to ulcers caused by other aetiologies, which would include the use of skin grafting and wound debridement.22 201

*Pain and psychosocial issues*

Excessive pain can be debilitating and may limit a patient’s ability to receive appropriate wound care. Oral agents for pain relief are usually helpful; however, when possible, opioids should be avoided. If needed, a pain management referral may be considered. The effect of PG on other aspects of the patient’s quality of life should also be addressed. Owing to the rapidly evolving nature of the disease,1 patients often live in constant fear of recurrence or disease worsening. Some become obsessive with avoiding minor trauma, which could trigger pathergy and new ulcer formation. In addition, PG ulcers usually have a foul odor and are unsightly, which may compel patients to avoid going out in public. The characteristic wrinkled-paper appearances of PG scars can also be quite distressful. All of these issues need to be addressed with the patients, and, when necessary, psychiatry consultation may be needed.

*Prevention strategies*

After all PG ulcers have healed, a decision whether or not to discontinue therapy needs to be made. Unfortunately, no data exist to guide this decision. We believe it is reasonable to discontinue all therapy if the patient has no underlying PG-associated condition and has remained disease-free for several months. However, many patients with PG have chronic disease and will relapse once immunosuppression has been discontinued. Thus, prior to discontinuing therapy, a plan to deal with potential relapses should be prepared. Such a plan would include instructions on how to immediately seek expert medical care at the first signs of relapse. Also, select patients may be candidates for keeping medications on-hand to self-administer if their disease relapses. This precaution is especially important for patients who plan to undergo a surgical procedure or any other pathergy-inducing stimulus.202 A small retrospective study revealed that 15.1% of patients with a history of PG will develop a recurrence if they undergo a surgical procedure, a finding that does not appear to depend on the time elapsed since the original PG diagnosis or the location of the surgical procedure.202,203 It is unclear whether prophylactic immunosuppressive agents are beneficial in these situations.203 Ideally, patients and their surgeons should be well-educated on the potential for pathergy.

**Quality of life**

Quality of life (QoL) research for PG has not yet received the same attention as other dermatologic diseases have. The lack of a validated PG-specific QoL measure may be one reason why PG has lagged behind other skin diseases in QoL research.204 Currently, patients with PG were included in the development and validation of only one non-disease specific wound-QoL questionnaire .205 In the absence of a PG-specific patient reported outcome measure, the prospective PG QoL studies that do exist have employed standard dermatological questionnaires, mostly the Dermatology Life Quality Index (DLQI)86,144,206 and/or the European Quality of Life 5 Dimensions (EQ-5D) instruments.86,144,152 Albeit limited in number, these studies have begun to quantify how PG severely affects patients' QoL. Specifically, patients with PG have DLQI scores between 8.4 (± 6.0) and 14.9 (± 8.0), indicating that they have severely impaired QoL.144,206 This score is higher than that for other dermatological diseases, such as non-melanoma skin cancer (2.25), Behçet's disease (5.70) or acne vulgaris (7.45).207 Similarly, mean baseline EQ-5D scores have been reported between 0.48 and 0.59, which are comparable to the scores of patients with mild to severe heart failure but lower than those of patients with IBD.208,209

There are many ways PG can negatively affect a patient’s QoL. PG is a severely painful skin disease,152,210 and pain is one of the major factors that negatively affect the health-related QoL of a patient with PG.206,211 For example, when DLQI components are analyzed separately, pain-related questions comprise the highest DLQI subscore, 2.1 (± 1.0) out of 3, and PG-associated pain seems to be independent of disease location, number of flares and comorbidities, such as IBD and/or rheumatoid arthritis.206 When assessed on a separate validated scale, patients with PG had an average pain score of 7.5 out of 10.206 As it is the case for other debilitating diseases, PG-associated pain has been linked to other comorbidities, especially depression. In one study, 10% of all patients with PG (n=50) developed depression.206 These findings were recapitulated in a retrospective case series, which revealed that 14% (n=103) of patients with PG have concomitant major depressive disorder Finally, there is some evidence that treatment can successfully improve a patient’s QoL. One prospective cohort study clearly demonstrated improved PG-related QoL upon treatment, according to both skin-specific (DLQI) and general health status (EQ-5D-3L) questionnaires.144 However, which therapy has the greatest effect on PG QoL has yet to be determined.

Related to QoL, disability-adjusted life year (DALY) is a measure of disease burden that considers QoL and quantity of years lived. In an observational study measuring the worldwide burden of skin diseases, the DALY values determined for PG were slightly lower than those attributed to melanoma but significantly higher than those attributed to pressure ulcers.212 Taken together, these studies clearly demonstrate that PG has a severe physical and psychosocial burden that considerably reduces QoL.

**Outlook**

*Development of PG outcome measure*s

Outcome measures can be broadly classified as physical examination-based, laboratory-based or patient-reported. Compared with other ulcerative diseases, PG has a unique pathophysiology and, therefore, assessing the severity of PG in any of the aforementioned categories requires the development and validation of appropriately tailored outcome measures. Applying an outcome measure developed and validated for another ulcerative disease to PG is a suboptimal option. Establishing validated PG-specific outcome measures will aid investigators in accumulating standardized clinical data and in conducting appropriately powered clinical trials. In the meantime, in the absence of a PG-specific outcome measure, clinical trials have assessed disease severity in various ways. A pilot study of ustekinumab for PG (EUCTR2011-002920-41-DE) used an adaptation of the RECIST criteria (a cancer outcome measure that evaluates a limited number of lesions), whereas the PG STOP GAP randomized comparative trial used a “pyoderma gangrenosum-specific global treatment response” score (a seven point Likert scale ranging from completely clear through to worse) to assess treatment response. For blinded assessment, photographs were used for scoring.152,210,213 Although these attempts at scoring PG severity represent a step in the right direction, the development of validated PG-specific outcome measures will hopefully improve the accuracy of our ability to measure PG disease severity.

*Biomarkers and molecular models*

Easily quantifiable, naturally occurring proteins, lipids, glycans and genetic elements involved in or altered by disease pathophysiology may have clinical utility as diagnostic or predictive classifiers (biomarkers ). Multi-analyte classifiers can be determined through molecular modeling techniques that combine two or more individual analytes together to form a composite classifier with superior accuracy than any of its individual constituents. Currently, numerous PG-associated inflammatory mediators and PG-associated genetic variants have been identified.11,53-56,66-70 The next logical step will be to characterize the utility of these molecules and genetic variants as diagnostic, prognostic and/or predictive classifiers. Such classifiers might enable physicians to identify patients who are likely to respond to a particular therapy or, alternatively, they may help to predict the probability that a patient will experience a chronic or self-limiting disease course. Eventually, prediction models may guide physicians on the most appropriate initial therapy and its duration. Classifiers could also help to identify which patients will be most at risk for a particular PG-associated comorbidity. With the exception of a limited study on osteopontin, the utility of PG-associated cytokines and other immune mediators as predictive classifiers has not been explored.214 However, such studies are gaining attention in IBD and rheumatoid arthritis, which are the most common PG-associated diseases.215,216 Owing to the shared pathological mechanisms of these diseases, it will be of interest to conduct parallel classifier studies in PG.

*Current and future clinical studies*

Now that many of the immune-mediated events that initiate and drive PG autoinflammation have been described, identifying which of these pathways are appropriate therapeutic targets is of the utmost importance. Thus far, some success has been garnered with the TNF antagonists, but several other highly specific biologics and small molecule kinase inhibitors are poised to be evaluated in PG. Of these, IL-1-targeting agents are of particular interest, including gevokizumab, described above, and canakinumab, which has been tested in steroid-refractory PG.172 A phase II open-label study (NCT01965613) of bermekimab, an anti-IL-1α monoclonal antibody, has been registered as complete; however the data have not yet been publicly communicated. C5a is another possible treatment target for PG217,218, owing to its neutrophil-attracting capacity and the potential to initiate neutrophil-mediated autoinflammation,. IFX-1, an anti-C5a-specific monoclonal antibody, is currently under investigation (NCT03971643). Also currently recruiting is a single-arm study to assess the potential effect of anti-IL-17 agents (secukinumab) in the treatment of PG (NCT02733094); however, anti-IL17A agents should be used with extreme caution given their ability to exacerbate IBD, a known PG-associated disease that can be subclinical at PG presentation. Perhaps a more promising target could be IL-23, a cytokine upstream of IL-17 that promotes IL-17 production and stimulates PG-relevant neutrophil recruitment but does not negatively affect IBD.219 As additional case reports and retrospective case series emerge, we will have a better idea about the most appropriate agents to move forward to larger randomized controlled clinical trials.

Table 1. Pyoderma gangrenosum syndromes

|  |  |  |
| --- | --- | --- |
| **PG syndrome** | **Clinical presentation** | **Gene(s)** |
| PAPA49 | Pyoderma gangrenosum, Acne, Pyogenic sterile Arthritis | *PSTPIP1 (mutation)* |
| PASH53,220 | Pyoderma gangrenosum, Acne, Hidradenitis Suppurativa | *MEFV, NOD2, NLRP3, PSMB8, NCSTN* |
| PAPASH221 | Pyogenic Arthritis, Pyoderma gangrenosum, Acne, and Hidradenitis Suppurativa | *PSTPIP1, IL1RN, MEFV* |
| SAPHO222,223 | Synovitis, Acne, Pustulosis, Hyperostosis, Osteitis | *PSTPIP2, LIPN2, NOD2 (polymorphisms)* |

*IL1RN* = interleukin-1 receptor antagonist, *LIPN2* = lipin 2, *MEFV* = Mediterranean fever, *NCSTN* = nicastrin, *NLRP3* = NOD-like receptor family, pyrin domain containing 3, *NOD2* = nucleotide-binding oligomerization domain-containing protein 2, *PSMB8* = proteasome [prosome, macropain] subunit beta type 8, *PSTPIP1* = proline-serine-threonine phosphatase-interacting protein 1, *PSTPIP2* = proline-serine-threonine phosphatase-interacting protein 2

Table 2. Clinical variants of pyoderma gangrenosum

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Variant**1-12 | **Clinical presentation** | **Common location(s)** | **Histopathology** | **Reported associated systemic disease(s)** |
| Ulcerative224 | Tender inflammatory nodule(s) or pustule(s) that rapidly evolve into necrotic ulcers with violaceous undermined borders and surrounding erythema | Most commonly occurs at sites of trauma, frequently on the anterior lower extremities | Findings depend on location and stage of lesions. Biopsies taken from the ulcer edge show perivascular lymphocytic infiltrates with dermal oedema, whereas biopsies taken from the center show a predominately neutrophilic infiltrate. Vascular damage with fibrin deposition, thrombosis, and red blood cells extravasation is common | Inflammatory bowel disease (IBD), haematological malignancies, rheumatoid arthritis, seronegative arthritis (negative for rheumatoid factor (RF) and cyclic citrullinated peptides (CCP)-specific antibodies), monoclonal gammopathy |
| Bullous225 | Rapidly evolving, painful bulla(e) that can progress to erosion and/or ulcer | Face, upper extremities more often than lower extremities | Subcorneal, subepidermal and intra-epidermal bullae with dermal neutrophilic infiltrate and microabscess formation. Immunofluorescence is negative or non-specific, which helps to rule out immunobullous diseases | Myeloproliferative disorders (especially acute myeloid leukaemia) and IBD |
| Pustular226 | Pustule(s) **[Au: so “pustule(s)”?]** with symmetric erythematous borders | Legs and trunk | Neutrophilic infiltrate and accumulation underneath the stratum corneum (subcorneal), around hair follicles and in the derma, with subepidermal oedema | IBD |
| Vegetative227 | Non-painful, slow growing, non-purulent single superficial ulcer; borders are not undermined and less violaceous; readily responsive to therapy | Trunk | Palisading granulomatous reaction (mononuclear cells with elongated or spindle-shaped nuclei palisaded around the edge of the central necrotic zone.) and neutrophilic abscesses with sinus tracts | None |
| Peristomal228 | Papule(s) that erode into ulcers with undermined borders; often difficult to distinguish from other peristomal erosive lesions | Immediately adjacent to the stoma | Dermal neutrophilic infiltrates with granulation tissue | IBD, enteric malignancy, connective tissue disease and monoclonal gammopathy |
| Postoperative229 | Erythema at the surgical site, followed by wound dehiscence or ulcerations that coalesce. Pain out of proportion to exam. | At the surgical site | Dermal oedema, neutrophilic infiltrate | Commonly associated abdominal and breast surgery |

**Figure Legends**

**Figure 1. IL-1 and examples of the monogenic autoinflammatory syndromes.** Autoinflammatory syndromes resulting from monogenic mutations in inflammasome proteins are depicted in red adjacent to their corresponding protein defects. The NLR Family Pyrin Domain Containing 3 (NLRP3) and the pyrin inflammasomes are shown. Inflammasome priming (signal 1, left side of figure) occurs following binding of inflammatory cytokines (e.g. IL-1 and TNF) to their cell surface receptors. Priming can also occur following detection of pathogen-associated molecular patterns (PAMPs), either by cell surface or intracellular cytosol receptors, depending on the type of pathogen molecule detected. Shown here, intracellular Nucleotide Binding Oligomerization Domain Containing 2 (NOD2) recognizes muramyl dipeptide (MDP), a bacterial component. Also depicted here is TLR activation by lipopolysaccharides (LPS), a component of the outer membrane of gram-negative bacteria. Following PAMP recognition, NFB is translocated to the nucleus, leading to the transcription of *IL1B*, *IL18*, and *NLRP3*, among other genes. Inflammasome activation (signal 2, right side) occurs by oligomerization-inducing signals originating from PAMP or damage-associated molecular pattern (DAMP) recognition. Specifically, pyrin is an innate immune sensor to detect bacterial toxin-induced Rho guanosine triphosphatase (Rho GTPase)-inactivation. In contrast, NLRP3 can be activated by ATP, pore-forming toxins and particulate matter (nigericin, uric acid crystals, amyloid-β fibrils). NEK7, an essential component of NLRP3 inflammasome activation, is a specific K+ sensor. Cryopyrin-Associated Autoinflammatory Syndromes (CAPS) are a group of illnesses due to genetic defects in *NLRP3* (also called cryopyrin). Pyogenic Arthritis, Pyoderma Gangrenosum, and Acne (PAPA) is caused by a mutation in *PSTPIP1* (Proline-Serine-Threonine Phosphatase Interacting Protein 1). Mediterranean fever (MEFV) is caused by defects in the *MEFV* gene, which encodes the protein pyrin. NLRP3 and PSTPIP1/pyrin interact independently with ASC to form an inflammasome complex, allowing caspase-1 to process pro-IL-1β and pro-IL-18 into their active forms. The mutations in *NLRP3*, *PSTPIP1, MEFV* that result in their respective monogenic autoinflammatory syndromes, all increase activation of IL-1β. This pathway is thought to be one of the drivers of PG pathophysiology. More upstream, mutations in *NOD2* have been associated with PG, Acne and Suppurative Hidradenitis (PASH) and Synovitis, Acne, Pustulosis, Hyperostosis, Osteitis (SAPHO).

**Figure 2. The PG ulcer, complex pathophysiology.** Clinically, the PG ulcer has a characteristic undermined border that is created by a dense dermal neutrophilic infiltrate that destroys the underlying dermis, leaving the overhanging epidermis alive but with a compromised blood supply. As the inflammation expands, the central epidermis dies, revealing the underlying ulcer. The deep location of the inflammatory cells gives the undermined border a reddish-violaceous color, which is a PG hallmark. The ulcer base is usually highly exudative due to the dense neutrophilic infiltrate. Peripheral to the undermined border, there is a zone of erythema. On histology, perivascular lymphocytes are noted in this area. Differential expression of numerous genes has been identified in PG, including many of the innate immune system. Keratinocytes are likely a significant source of the pro-inflammatory cytokines IL-1, IL-36, TNF, IL-1 and IL-8, all of which promote neutrophil recruitment, especially IL-8, which is a major neutrophil chemotactic factor. Keratinocytes may also be sources of and possibly CXCL9, CXCL10, and CXCL11. Macrophages and monocytes are a likely source of IL-8, IL-1, CXCL9, CXCL10, CXCL11, CCL5, IL-1, and TNF. Of these, CXCL9 and CCL5 will attract T cells, which are found perivascularly in the periphery or around adnexal structures. T cells in PG are preferentially polarized towards Th1 or Th17 cytokine secretion profiles and are thus, a source of IL-17A, CCL3, CCL5 and IFN. The secreted IL-17A induces other cells to release a variety of chemokines, which supports neutrophil and monocyte migration. It can also act in concert with TNF and IL-1 to further drive inflammatory pathways. T cell derived CCL3 will attract macrophages and neutrophils, and CCL5 will attract additional T cells. Finally, IL-16 secreted by T cells and possibly keratinocytes is a chemoattractant for CD4-expressing immune cells.

**Figure 3. Common variations in PG lesion morphology.**

Top row- PG ulcers form rapidly and thus are often well-developed at time of their initial clinical evaluation. The top left photo is of an upper extremity PG ulcer 2 weeks in duration. Notice the highly exudative wound base, which is surrounded by an undermined border and peripheral erythema. The undermined border is most apparent in the top right of the photo, where the epidermis appears wrinkled and detached from the underlying dermis. As is the case here, surrounding erythema can be difficult to appreciate in skin of color patients. PG ulcers can also be of various depths. The one depicted here is more superficial than others. The middle photograph is of the same ulcer a few weeks after initiation of immunosuppression. Notice that the ulcer is virtually the same size, but the wound bed is no longer exudative, and the peripheral erythema and undermined border have resolved. Top right is a photo after the same ulcer has healed. This is an example of a cribriform scar. Notice the small indentations, which give the scar a pebbly appearance.

Middle row- the middle left photo is of a PG ulcer 1 week in duration. When compared to the previous example, the peripheral erythema is more apparent in this photo. Again, the newly formed ulcer is highly exudative, and it is surrounded by an undermined border. Note that the ulcer is deeper than the previous example. The middle photo depicts the same ulcer approximately 2 weeks later. Notice again that that the wound is the same size, but its appearance has changed. It is no longer highly exudative. The peripheral erythema has also resolved, and the undermined border is now flaking away. The base of the wound also has exuberant granulation tissue, which is a common PG finding. It will resolve as the ulcer begins to heal. The photograph on the far right is a different patient with long standing history of PG. This lesion is a subepidermal bulla. Notice that the bullae does not extend into the superiorly located cribriform scar. PG ulcers avoid scars.

Bottom row- On the left is an early stage sterile PG pustule. PG pustules can be unremarkable or have significant peripheral erythema and/or a reddish-violaceous appearance. The bottom middle image is a classic early stage PG ulcer. Notice the very distinctive reddish-violaceous appearance, thick undermined border and peripheral erythema. The right photo is a larger ulcer from the same patients. Again, reddish-violaceous undermined border and peripheral erythema are present. Note the large eschar in the center of the lesion. PG ulcers often have adherent eschars.

**Figure 4. International consensus PG Diagnostic Criteria.** PG diagnostic criteria were established by a Delphi exercise and then fine-tuned and cross-validated against published PG “mimickers”. In addition to a biopsy demonstrating a neutrophilic infiltrate, patients must have at least 4 minor criteria to meet the PG diagnostic threshold. Minor criteria are divided into categories, histology, history, clinical examination, and treatment. PG ulcers can be solitary or multiple. Although they can occur at any body site, they more frequently occur on the anterior aspects of the lower extremities (middle photo). The diagnostic criteria awards one point for such lesions. A point is also awarded for healed scars with wrinkled paper or cribriform appearances. Depicted here is a wrinkled paper-like scar. The wrinkled appearance of these lesions is due to the underlying dermis being devoid of structural elements. The scar does not have to be atrophic for it to have this appearance.

\* denotes only histologically indicated stains or tissue cultures.

**Figure 5. Proposed PG Treatment algorithm**.

Patients should be assessed as severe or mild, based on the number, size and location of their PG ulcers. Patients with mild disease are initially treated with a low dose immunosuppressive (e.g. prednisone monotherapy) and/or localized therapy (topical or intralesional). If complete resolution is not achieved, the physician can consider the use of a biologic. In contrast, patients with severe PG are started immediately on a fast-acting agent (either prednisone, cyclosporine or a combination of the two). The physician then can consider use of a biologic (e.g. an anti-TNF agent or ustekinumab). Three weeks after starting a biologic agent, a slow taper of the initial agent(s) is started. For patients that do not respond completely to biologic therapy, the frequency of the biologic may be increased. If a complete response is still not achieved, re-evaluation of the ulcer is indicated to confirm the presence of an inflammatory border. If the inflammation is largely resolved, wound care should be maximized. If significant inflammation persists, then the dose of the non-biologic may be increased, or the non-biologic can be changed. Alternatively, another biologic can also be considered. For patients not treated with biologics, compatible non-biologic medications are sequentially added. One triple drug regimen that that may be considered for severe refractory PG is prednisone, cyclosporine, and mycophenolate mofetil. If a complete response is not achieved on triple drug therapy, the clinician should reassess the wound and reconsider starting a biologic.

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