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Pyoderma gangrenosum

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Abstract | Pyoderma gangrenosum (PG) is a rare neutrophilic dermatosis that presents with rapidly developing, painful skin ulcers hallmarked by undermined borders and peripheral erythema. Epidemiological studies indicate that the average age of PG onset is in the mid-40s, with an incidence of a few cases per million person-years. PG is often associated with a variety of other immune-mediated diseases, most commonly inflammatory bowel disease and rheumatoid arthritis. The cause of PG is not well understood, but PG is generally considered an autoinflammatory disorder. Studies have focused on the role of T cells, especially at the wound margin; these cells may support the destructive autoinflammatory response by the innate immune system. PG is difficult to diagnose as several differential diagnoses are possible; in addition to clinical examination, laboratory tests of biopsied wound tissue are required for an accurate diagnosis, and new validated diagnostic criteria will facilitate the process. Treatment of PG typically starts with fast-acting immunosuppressive drugs (corticosteroids and/or cyclosporine) to reduce inflammation followed by the addition of more slowly acting immunosuppressive drugs with superior adverse event profiles, including biologics (in particular, anti-tumour necrosis factor (TNF) agents). Appropriate wound care is also essential. Future research should focus on PG-specific outcome measures and PG quality-of-life studies.

Classic ulcerative pyoderma gangrenosum (PG) is a rare neutrophilic dermatosis (ND) characterized by rapidly evolving painful ulcers, with undermined borders and peripheral erythema (red skin)[1]. Of note, the term 'pyoderma gangrenosum' is a misnomer as PG is neither an infection ('pyoderma' historically refers to a bacterial skin infection that produces pus), nor is it a classic 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 later) 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 "*phagédénisme géométrique*" (geometric phagedena), 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 cause 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 comorbidities, 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 eruptions 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 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

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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 classic ulcerative PG. In fact, genetic variants in classic autoinflammatory genes (for example, *MEFV* and *PSTPIP1*) are common in patients with ND, which led to the hypothesis that NDs are a spectrum of polygenic autoinflammatory conditions[10,15–17].

PG remains one of the most difficult dermatological diseases to diagnose and treat. To date, there are only two published randomized clinical trials, which means that PG treatments are largely based on anecdotal data and small case studies. Although we focus mainly on classic ulcerative PG in this Primer, over the years, several PG subtypes (TABLE 2) and PG-like diseases (BOX 1) have been proposed. Herein, we review all of these topics in detail and provide a PG treatment algorithm to aid in clinical decision-making.

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 more than 31 million adult patients. It reported the prevalence of PG to be 58 cases per million adults[18]. A population-based study conducted in the UK reported the incidence of PG to be approximately six cases per million person-years[19].

Most other studies in European regions have relied on historical data generated from specialist centre 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 of age) across multiple countries/regions[18–20,31–33]. For example, a cohort study involving participants from the UK General Practice Research Database revealed that the median age of patients with PG is 59 years (interquartile range 41–72 years)[19]. Similarly, a cross-sectional US-based study demonstrated that nearly 70% of individuals with PG were aged 50 years or older[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 demonstrated that the average age of PG onset is 44.6 years (s.d. ±19.7 years), with similar estimates from studies from other regions, including Italy and Switzerland[20,31,32]. However, one important caveat to consider when one is 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 increased mortality[19,34]. One population-based study using the UK General Practice Research Database reported that patients with PG have mortality threefold 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 adjustment for age, sex and comorbidity[19]. A study from the USA found

Table 1 | **Pyoderma gangrenosum syndromes**

PG syndrome	Clinical presentation	Genes
PAPA syndrome[49]	Pyoderma gangrenosum, acne and pyogenic sterile arthritis	*PSTPIP1*
PASH syndrome[53,217]	Pyoderma gangrenosum, acne and hidradenitis suppurativa	*MEFV*, *NOD2*, *NLRP3*, *PSMB8*, *NCSTN*
PAPASH syndrome[218]	Pyogenic arthritis, pyoderma gangrenosum, acne and hidradenitis suppurativa	*PSTPIP1*, *IL1RN*, *MEFV*
SAPHO syndrome[219,220]	Synovitis, acne, pustulosis, hyperostosis and osteitis	*PSTPIP2*, *LPIN2*, *NOD2*

PAPA, pyogenic arthritis, pyoderma gangrenosum and acne; PAPASH, pyogenic arthritis, pyoderma gangrenosum, acne and hidradenitis suppurativa; PASH, pyoderma gangrenosum, acne and hidradenitis suppurativa; PG, pyoderma gangrenosum; SAPHO, synovitis, acne, pustulosis, hyperostosis and osteitis.

Table 2 | **Clinical variants of pyoderma gangrenosum**

Variant[1,10,19,92,127,221–227]	Clinical presentation	Common locations	Histopathology	Reported associated systemic diseases
Ulcerative[228]	Tender inflammatory nodules or pustules 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. Biopsy samples taken from the ulcer edge show neutrophils and perivascular lymphocytic infiltrates with dermal oedema, whereas biopsy samples taken from the centre show a predominately neutrophilic infiltrate. Vascular damage with fibrin deposition, thrombosis and red blood cell extravasation is common	IBD, haematological malignancies, rheumatoid arthritis, seronegative arthritis and monoclonal gammopathy
Bullous[221]	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
Pustular[229]	Pustules 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
Vegetative[222]	Less-painful variant, slow-growing, non-purulent, often a 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
Peristomal[230]	Papules that erode into ulcers with undermined borders; often difficult to distinguish from other peristomal erosive lesions[121]	Immediately adjacent to the stoma	Dermal neutrophilic infiltrates with granulation tissue	IBD, enteric malignancy, connective tissue disease and monoclonal gammopathy
Postoperative[231]	Erythema at the surgical site, followed by wound dehiscence or ulcerations that coalesce. Pain out of proportion to examination expectations	At the surgical site	Dermal oedema and neutrophilic infiltrate	Commonly associated with abdominal and breast surgery

IBD, inflammatory bowel disease.

that during inpatient hospitalizations, 3.2% of patients with PG died (with 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 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% (REF.[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) of a patient with IBD developing PG is high (29.2, 95% CI 21.0–40.8), but only an exceedingly 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 (REF.[39]), a cytokine thought to have a major role in PG pathophysiology[40]. Minor trauma to the skin has also been shown to increase

Box 1 | **PG-like diseases**

Drug-induced PG

Certain drugs can induce the formation of tender nodules or pustules that evolve to ulcers. The onset of such pyoderma gangrenosum (PG)-like lesions can occur years after drug initiation. Histological features can be variable but a predominant neutrophilic infiltrate is common. Reported drugs include isotretinoin, alitretinoin, propylthiouracil, tumour necrosis factor (TNF) inhibitors (for example, adalimumab, infliximab and etanercept), secukinumab, levamisole, azacytidine, tyrosine kinase inhibitors (for example, gefitinib, imatinib and sunitinib), ipilimumab, enoxaparin, erythropoietin, granulocyte colony-stimulating factor and interferon-α[232]. Of note, some investigators believe that many cases of drug-induced PG, including levamisole-induced PG, can be attributed to other causes, such as vasculitis or vasculopathy.

Neutrophilic dermatosis of the dorsal hands

Neutrophilic dermatosis of the dorsal hands (NDDH) was initially described as "pustular vasculitis of the hands"[233,234]. NDDH presents with tender erythematous to violaceous pustules, plaques and haemorrhagic bullae on the back of both hands. NDDH's associated systemic symptoms, laboratory abnormalities, histological features and response to treatment have led some to hypothesize that NDDH is a variant of Sweet syndrome or is an atypical PG[234], although whereas lesions associated with typical Sweet syndrome can occur on the palms, classic ulcerative PG lesions tend to avoid non-hair-bearing regions (palms, soles and areolas). Patients with NDDH tend to be responsive to systemic corticosteroids or dapsone.

Necrotizing neutrophilic dermatoses

Patients with necrotizing neutrophilic dermatosis[189] present with painful lesions and fever, leukocytosis, hypovolaemic shock and elevated levels of inflammatory markers. The clinical picture might resemble that of necrotizing fasciitis (a severe bacterial infection of the fascia), although, in contrast to necrotizing fasciitis, crepitus (popping sounds from the presence of air in subcutaneous tissue) is not present, and tissue biopsies and cultures fail to reveal pathogenic organisms. Other distinguishing features of necrotizing neutrophilic dermatosis are its association with pathergy and its response to immunosuppression, which are not seen in necrotizing fasciitis.

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 harbouring pathogenic variants of genes involved in the inflammasome pathway (see later).

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[43,44] (TABLE 1). One protein that seems to be relevant is tyrosine-protein phosphatase non-receptor type 6 (PTPN6 (also known as SHP1); encoded by *PTPN6*). PTPN6 modulates signals transmitted by tyrosine-phosphorylated cell-surface receptors, which include various cytokine receptors, and also modulates signals originating from the T cell receptor[45,46]. Studies in a mouse model homozygous for a loss-of-function *Ptpn6* variant that results in a protein with decreased enzymatic activity (*Ptpn6*$^{meB2/meB2}$ 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 pathogenic variants of *PTPN6* supports the involvement of this pathway in human PG[44].

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

In addition to IL-1β, 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-1α in PG stemmed from studies of *Ptpn6*^{spin} 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 PTPN6) 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 *Ptpn6*^{spin} model has revealed that the *Ptpn6*^{spin} 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 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.

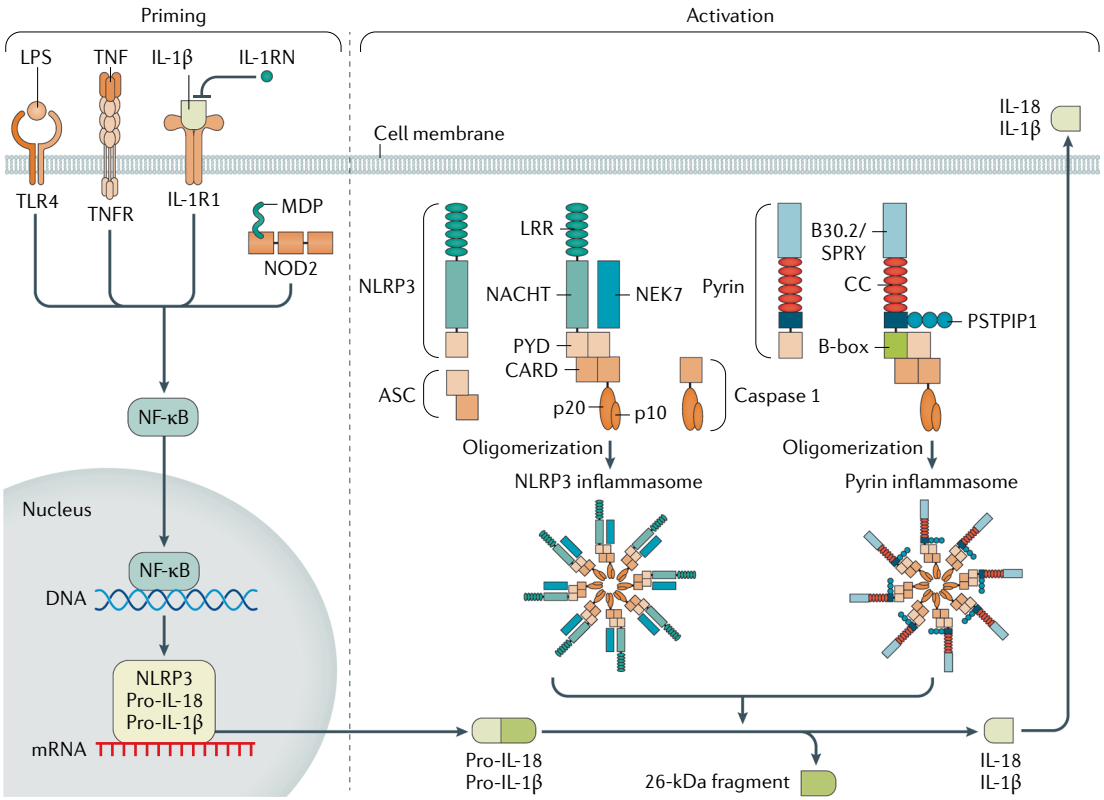


Fig. 1 | **Monogenic autoinflammatory syndromes affecting IL-1β activation.** Examples of autoinflammatory syndromes resulting from monogenic mutations affecting inflammasome proteins are depicted. The NACHT, LRR and PYD domains-containing 3 (NLRP3; also known as cryopyrin) and pyrin inflammasomes are shown. Inflammasome priming occurs following binding of inflammatory cytokines (such as IL-1β and tumour necrosis factor (TNF)) to their cell-surface receptors. Priming can also occur following detection of pathogen-associated molecular patterns (PAMPs), either by cell-surface receptors or by intracellular cytosolic receptors, depending on the type of PAMP detected. For example, the intracellular receptor nucleotide-binding oligomerization domain-containing 2 (NOD2) recognizes the bacterial component muramyl dipeptide (MDP). Cell-surface Toll-like receptor 4 (TLR4) is activated by the Gram-negative bacterial outer-membrane component lipopolysaccharide (LPS). Following PAMP recognition, nuclear factor-κB (NF-κB) translocates to the nucleus and activates expression of *IL1B*, *IL18* and *NLRP3*, among other genes. Inflammasome activation occurs by oligomerization-inducing signals originating from PAMP or damage-associated molecular pattern recognition. Specifically, pyrin is an innate immune sensor that detects bacterial toxin-induced RHO GTPase inactivation. By contrast, NLRP3 can be activated by ATP, pore-forming toxins and particulate matter (such as nigericin, uric acid crystals and amyloid-β fibrils). NEK7, an essential component of NLRP3 inflammasome activation, is a specific K^+ sensor. Cryopyrin-associated autoinflammatory syndromes are a group of illnesses caused by genetic defects in *NLRP3*. Pyogenic arthritis, pyoderma gangrenosum (PG) and acne (PAPA) syndrome is caused by a genetic defect in *PSTPIP1* (encoding proline–serine–threonine phosphatase-interacting protein 1 (PSTPIP1)). Mediterranean fever 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* and *MEFV* that result in their respective monogenic autoinflammatory syndromes all increase activation of IL-1β, a pathway that is thought to be one of the drivers of PG pathophysiology. Variants of *NOD2* have been associated with PG, acne and hidradenitis suppurativa (PASH) syndrome and with synovitis, acne, pustulosis, hyperostosis and osteitis (SAPHO) syndrome. CARD, caspase recruitment domain-containing protein; CC, coiled coil; IL-1R1, IL-1 receptor type 1; IL-1RN, IL-1 receptor antagonist protein; SPRY, Sprouty homologue; TNFR, tumour necrosis factor receptor.

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 (encoded by *CCL5*), C-X-C motif chemokine 9 (CXCL9; encoded by *CXCL9*), CXCL10 (encoded by *CXCL10*), CXCL11 (encoded by *CXCL11*), interferon-γ (encoded by *IFNG*), tumour necrosis factor (TNF; encoded by *TNF*), IL-1α (encoded by *IL1A*), IL-8 (encoded by *CXCL8*), IL-15 (encoded by *IL15*), IL-16 (encoded by *IL16*), IL-17A (encoded by *IL17A*), IL-23 (encoded by *IL23A*), IL-25 (encoded by *IL25*), IL-36α (encoded by *IL36A*) and IL-36γ (encoded by *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 hidradenitis suppurativa[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 cytokine 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 (T_H2) cells[78]. Although IL-25 was initially thought to promote T_H2 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 (REFS[40,56,66,82,83]). Each of these cytokines attracts neutrophils by a different mechanism. For example, IL-8 acts by binding to C-X-C chemokine receptor type 1 (CXCR1) and CXCR2 (REF.[84]). In addition, IL-16 (which is generated by caspase 3 from pro-IL-16) indirectly attracts neutrophils by inducing neutrophil chemoattractant expression[85]. IL-16 is unique in that it does not function through a classic cytokine receptor but rather by 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

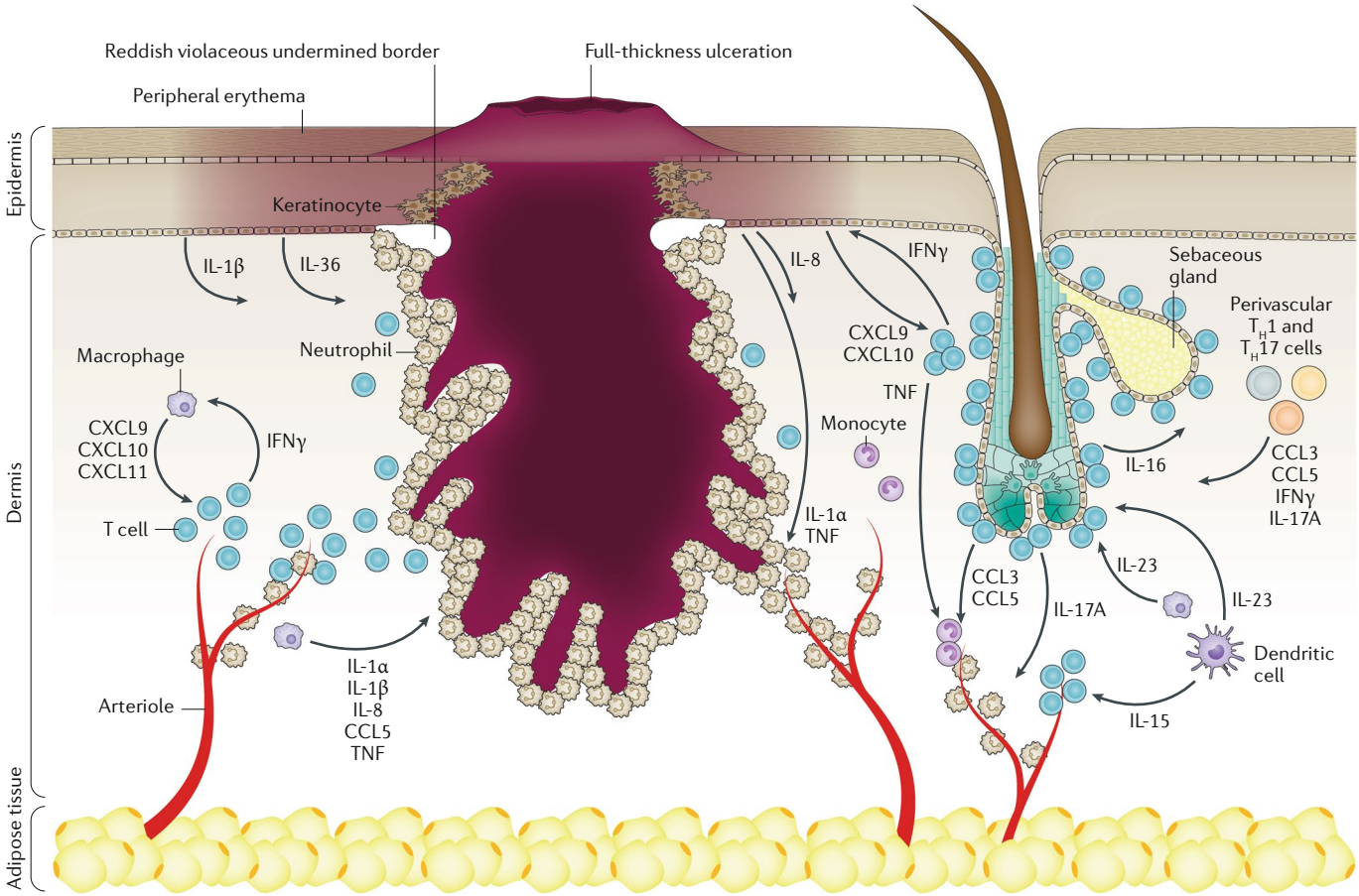


Fig. 2 | **The complex pathophysiology of ulcers in PG.** Clinically, ulcers in pyoderma gangrenosum (PG) have a characteristic undermined border that is created by a dense dermal neutrophilic infiltrate, which destroys the underlying dermis, leaving the overhanging epidermis alive but with a compromised 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 its hallmark reddish-violaceous appearance. The ulcer base is usually highly exudative owing to the dense neutrophilic infiltrate. Peripheral to the undermined border, there is a zone of erythema that, on histology, contains perivascular lymphocytes. Differential expression of numerous genes has been identified in PG, including many of the innate immune system. Keratinocytes are likely a major source of the pro-inflammatory cytokines IL-1α, IL-1β, IL-8, IL-36 and tumour necrosis factor (TNF), all of which promote neutrophil recruitment, especially IL-8, which is a major neutrophil chemotactic factor. Keratinocytes may also be a source of C-X-C motif chemokine 9 (CXCL9), CXCL10 and CXCL11. Macrophages and monocytes are likely a source of IL-1α, IL-1β, IL-8, C-C motif chemokine 5 (CCL5), CXCL9, CXCL10, CXCL11 and TNF. Of these cytokines, CCL5 and CXCL9 attract T cells, which are found perivascularly in the wound periphery or around adnexal structures. T cells in PG are preferentially polarized towards type 1 T helper (T_H1) cell or IL-17-producing T helper (T_H17) cell cytokine secretion profiles and are, thus, a source of IL-17A, CCL3, CCL5 and interferon-γ (IFNγ). IL-17A induces other cells to release various chemokines that support neutrophil and monocyte migration and can also act in concert with TNF and IL-1β to further drive inflammatory pathways. T cell-derived CCL3 attracts macrophages and neutrophils and CCL5 attracts additional T cells. IL-16 secreted by T cells (and possibly keratinocytes) is a chemoattractant for CD4-expressing immune cells.

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 (REFS[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[91] (FIG. 1).

Role of adaptive immunity

Although most 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 outermost 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 antigens 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 type 1 T helper (T_H1) cell-mediated and IL-17-producing T helper (T_H17) cell-mediated immune responses is also predominant. For example, the T_H1 cell-promoting transcription factor genes *STAT1* and *STAT4* are upregulated, whereas the T_H2 cell-promoting transcription factor gene *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[40] (FIG. 2). 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 affect anatomical areas devoid of pilosebaceous units, such as palms, soles and 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 hidradenitis suppurativa[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 T_H17 cell–regulatory T (T_{reg}) cell imbalance, hallmarked by a reduction in T_{reg} cells and concurrent overexpression of T_H17 cell-associated cytokines[40,100]. These cytokines may be one of the early drivers of the PG autoinflammatory response. Thus, a T_H17 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]), 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 T_H17 cells by initiating signalling cascades involving the Janus kinase 2 (JAK2) and signal transducer and activator of transcription 3 (STAT3) pathways[102]. These signalling 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 biologic agents that target these cytokines are readily available to be tested in PG clinical trials. Finally, data suggest that other cell types, such as neutrophils, $CD8^+$ T cells and γδ T cells, can be potential sources of IL-17 (REF.[104]). 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 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 earlier[40]. Among these, IL-10 can block nuclear factor-κB activity, inhibit expression of T_H1 cell-associated cytokines and downregulate major histocompatibility complex expression[106]. The T_{reg} cell transcription factor FOXP3 is also upregulated 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 workup

Clinical presentation. Evaluation of a suspected PG lesion should start with a thorough medical history to assess the patients 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 disease. On physical examination, the location of the lesions, the characteristics of the ulcer border and the presence and

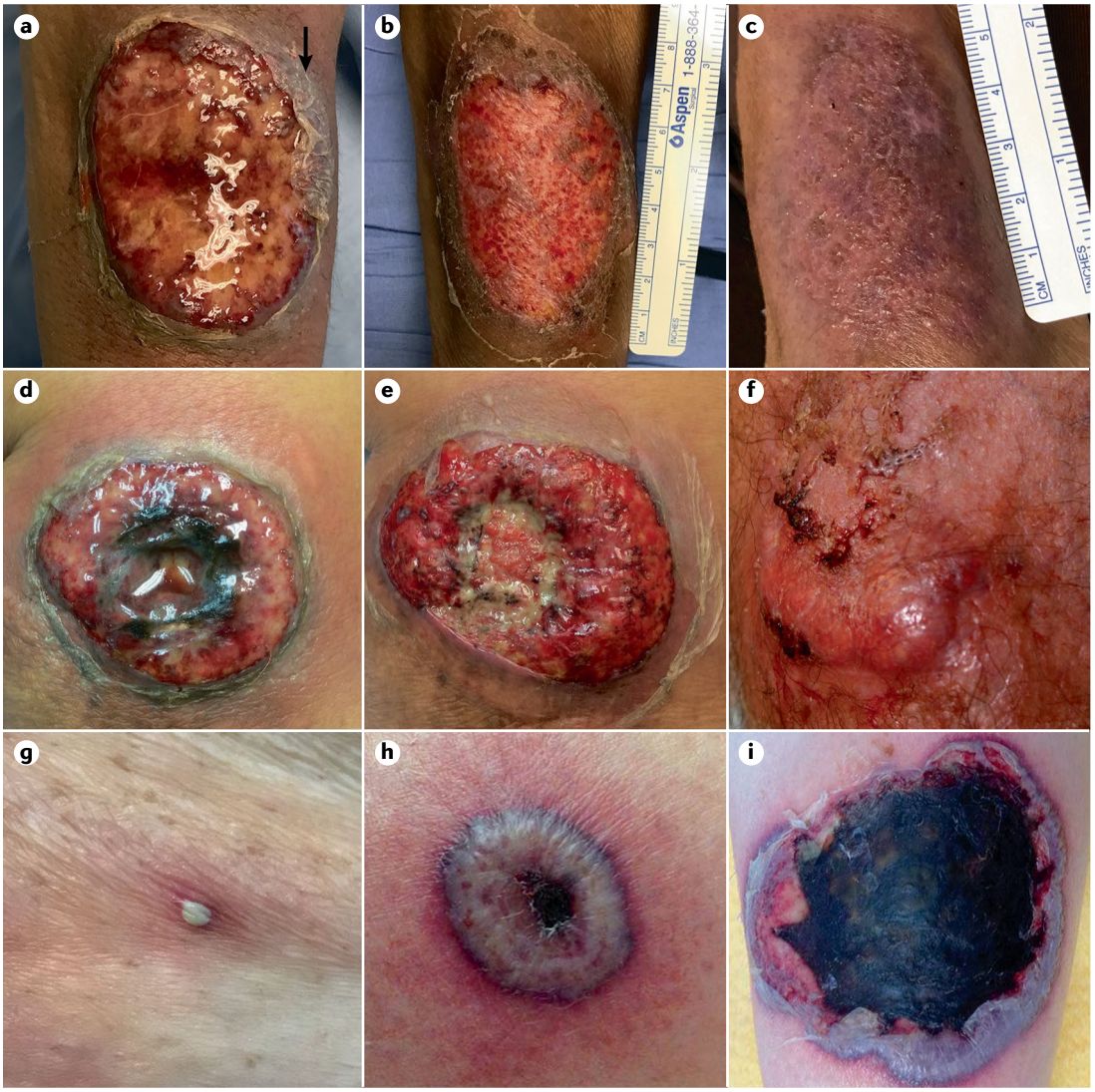


Fig. 3 | **Morphological variation in PG lesions.** Ulcers in patients with pyoderma gangrenosum (PG) form rapidly and, therefore, are often well developed at initial clinical evaluation. In a 2-week-old ulcer of an upper extremity (part **a**), the highly exudative wound base is surrounded by an undermined border (arrow, where the epidermis appears wrinkled and detached from the underlying dermis) and peripheral erythema. As is the case here, surrounding erythema can be difficult to appreciate in patients with darker skin colour. PG ulcers can also extend to various depths: some are more superficial (part **a**) than others. The same ulcer a few weeks after initiation of immunosuppression (part **b**) is the same size but the wound bed is no longer exudative and the peripheral erythema and undermined border have resolved. The healed ulcer formed a cribriform scar (part **c**), with characteristic small indentations that give the scar a pebbly appearance. A 1-week-old PG ulcer (part **d**). Initially, the ulcer is highly exudative and surrounded by an undermined border (part **d**) but with more apparent peripheral erythema and extending deeper than the ulcer in part **a**. The same ulcer approximately 2 weeks after the initiation of immunosuppression (part **e**) is still the same size but is no longer highly exudative, the peripheral erythema has resolved and the undermined border is flaking away. The base of the wound also has exuberant granulation tissue (a common finding in PG), which will resolve as the ulcer begins to heal. A subepidermal bulla in a patient with a long-standing history of PG (part **f**); the bulla does not extend into the superiorly located cribriform scar as PG ulcers do not seem to form in areas of scarring. An early-stage sterile PG pustule (part **g**). PG pustules can be unremarkable or can have significant peripheral erythema and/or a reddish-violaceous appearance. A classic early-stage PG ulcer with very distinctive reddish-violaceous appearance, thick undermined border and peripheral erythema (part **h**). A larger ulcer from the same patient as in part **h**, with a reddish-violaceous undermined border and peripheral erythema (part **i**) but in this case with a large eschar (dead tissue) in the centre of the ulcer. PG ulcers often have adherent eschars.

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 look wrinkled (cigarette paper-like). A PG ulcer border is typically undermined with a characteristic violet colour. 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 results 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 ulcers; although, to date, 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 colour 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 they can extend through the appearance of new peripherally located pustules. In severe cases, ulcers can appear without a 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 differ, depending on how long they have been present and whether the patient is receiving immunosuppression for 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 causes.

Laboratory tests. A PG diagnostic workup 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 the patients for these alternative diagnoses, laboratory diagnostic tests could include a rapid plasma reagin (RPR) or Venereal Disease Research Laboratory (VDRL) test (for syphilis), perinuclear antineutrophil cytoplasmic antibody (pANCA) or cytoplasmic antineutrophil cytoplasmic antibody (cANCA) tests (for autoimmune diseases, in particular vasculitis), complete blood count and peripheral blood smear, anti-*Saccharomyces cerevisiae* test (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 workup may include radiological imaging of the affected joints and/or a colonoscopy to rule out inflammatory arthritis and ulcerative colitis, respectively.

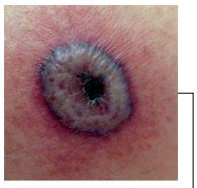
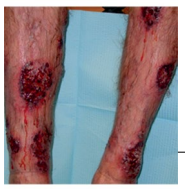
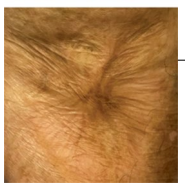
PG can also present as a paraneoplastic phenomenon, frequently observed in patients with myelodysplastic syndromes, multiple myeloma, polycythaemia vera, paraproteinaemia (also known as monoclonal gammopathy) and leukaemia[36,110–112]. These patients can have an atypical presentation with vesiculobullous lesions or more-superficial ulcerations with a blue-grey 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 of ulcers initially attributed to PG that were subsequently reclassified under an alternative diagnosis after additional information about the case emerged; for example, identification of a malignancy, infection or a vascular or nutritional disorder[109,114–119]. Such errors can pose substantial risk to the patient, as therapeutic agents 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 causes 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 for 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 points, two points and one point, respectively. The assignment of a parameter into one of these three categories is based on 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 more than 95% of patients with PG. Patients who receive a PARACLELSUS score of 10 or more 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 RAND Corporation 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. Mathematical calculations outlined in the RAND–UCLA protocol were then applied to determine the degree of appropriateness of each statement and the level of

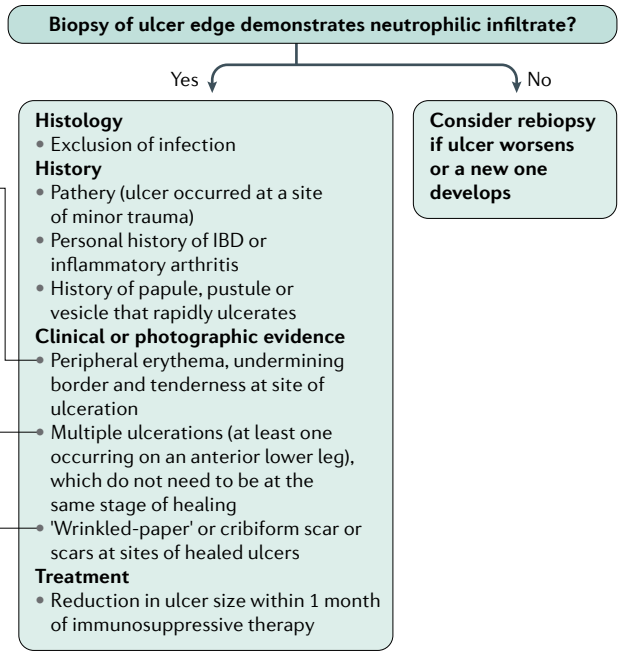


Fig. 4 | **International consensus diagnostic criteria for ulcerative PG.** Three diagnostic tools for pyoderma gangrenosum (PG) have been developed, including one that establishes a PG diagnosis by exclusion of other conditions[120], and the PARACELSUS tool[123], which has major and minor categories based on the prevalence of diagnostic criteria among patients with PG. A third set of international consensus-driven PG diagnostic criteria[12] are depicted here and were established by a Delphi consensus exercise and fine-tuned and cross-validated against published conditions that mimic PG. In addition to a biopsy demonstrating a neutrophilic infiltrate, patients must have at least four minor criteria to meet the PG diagnostic threshold. Minor criteria are divided into histology, history, clinical examination and treatment categories. Medical history establishes whether patients have pathergy and/or autoimmune inflammatory conditions. Clinical examination defines the characteristics of ulcers, including physical aspects (typically painful, with an undermined border and peripheral erythema; top image) and their number and distribution, as well as the appearance of any healed lesions (scars). Patients with PG can have single or multiple ulcers that can occur at any body site, although they occur more frequently on the anterior aspects of the lower extremities (middle image). Furthermore, scars have a 'wrinkled-paper' (lower image) or cribriform appearance, the wrinkled appearance being due to the absence of structural elements in the underlying dermis and not necessarily due to the scar being atrophic. Each feature that is present is assigned a single point, and a total score of greater than 5 supports a PG diagnosis. If the histological features suggest infection, a point can still be awarded if special stains and/or cultures are negative. Culture results due to bacterial colonization would not prevent a point from being awarded. IBD, inflammatory bowel disease.

expert agreement. Preliminary criteria established by the Delphi method 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 reapply 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 they do, which ones 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 offer only 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 the cause, 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 one is 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. Last, 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 for whom future surgical procedures are planned.

Treatment approaches

On the basis mainly of expert opinion, a few investigators have attempted to develop algorithm approaches to treat PG[7,126,129]. An approach agreed on by the authors of this Primer 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 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 most biologics, are slow-acting agents that demonstrate maximum effectiveness between 1 month and 4 months[130,131]. Thus, a reasonable strategy is to add a steroid-sparing agent to the therapy as soon as possible (see the section entitled Systemic agents) to enable the down titration of the fast-acting agents 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 comprises finger-like projections of new epithelium extending towards the ulcer's centre[132], and pain cessation or reduction.

Additionally, physicians need to consider the presence of coexisting diseases when selecting the treatment strategy. For example, if the patient has concurrent IBD, agents approved for treatment of IBD, such as the anti-TNF agents adalimumab, certolizumab pegol and infliximab, are reasonable treatment options[133–135]. 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, increased effectiveness may result either from the ability of methotrexate to enhance the activity of the primary agent or from its ability to reduce the antigenicity of the primary agent[136–138]. Treating patients with PG and haematological malignancies poses a particular challenge, as some immunosuppressants will be contraindicated depending on the type of cancer.

Topical and intralesional therapies

Several topical immunosuppressive agents have been used as monotherapy to treat PG but none has been formally studied in randomized trials[139]. Thus, there is

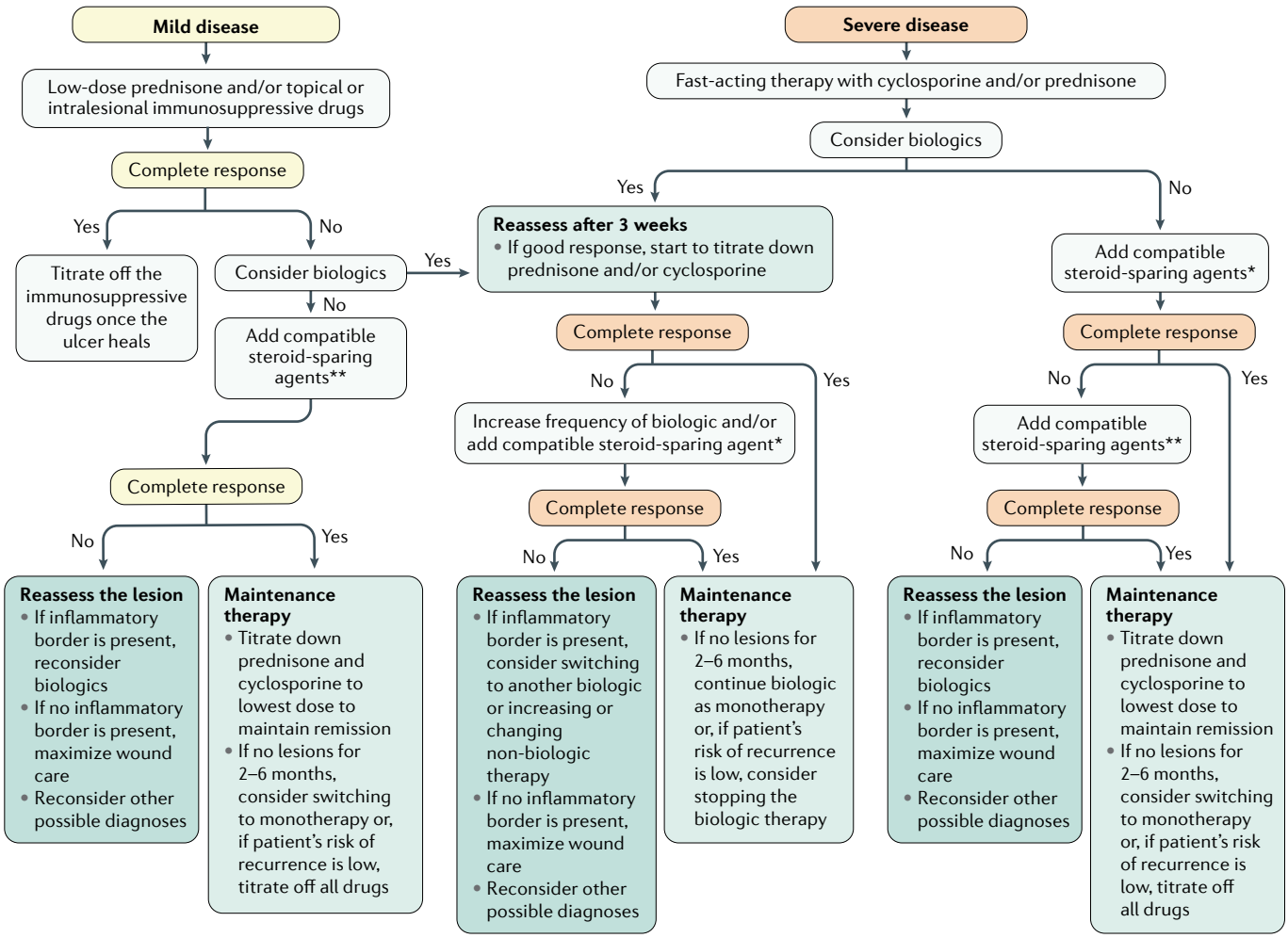


Fig. 5 | **Proposed algorithm for treatment of PG.** Patients should be assessed as having severe or mild disease on the basis of the number, size and location of their pyoderma gangrenosum (PG) ulcers. For the purpose of this algorithm, severe PG is defined as a patient having multiple ulcers, or a single ulcer of 3 cm or greater, or involvement of the face. Patients with mild disease are initially treated with a low-dose immunosuppressive agent (for example, prednisone monotherapy) and/or localized (topical or intralesional) therapy. If complete resolution is not achieved, the physician can consider the use of a biologic agent. By contrast, in patients with severe disease, treatment with a fast-acting immunosuppressive agent (prednisone, cyclosporine or a combination of the two) is begun immediately. The physician can then consider use of a biologic agent (such as an anti-tumour necrosis factor (TNF) agent or ustekinumab) on the basis of patient comorbidities. For example, ustekinumab does not seem to be an effective treatment for rheumatoid arthritis and, therefore, should not be considered in patients with PG who have concomitant rheumatoid arthritis. After treatment with a biologic agent has started, the dose or frequency of administration of the initial fast-acting agents should be tapered slowly. For patients who do not respond completely to biologic therapy, administration frequency can 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 substantial inflammation persists, then the dose of the non-biologic agent may be increased or the non-biologic agent can be changed. Alternatively, another biologic agent can also be considered. For patients who are not treated with biologic agents, compatible non-biologic medications are sequentially added. One triple-drug regimen that may be considered for severe refractory PG is prednisone, cyclosporine and mycophenolate mofetil. If a complete response is not achieved with triple-drug therapy, the clinician should reassess the wound and reconsider starting biologic therapy. *Mycophenolate or another non-steroidal medication. **Cyclosporine can be combined with prednisone and/or mycophenolate to manage severe cases. Biologic agents can be used in combination with methotrexate.

minimal information available to help guide the physician when selecting an appropriate topical medication, its strength, its 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 antihistaminic agent), 5-aminosalicylic acid (an anti-inflammatory agent) and nicotine (usually in a patch formulation, presumably to lower inflammatory leukotriene production)[140–142]. Perhaps in the future, topical JAK inhibitors may also be used, as this drug class is being tested systemically[143–145].

In addition to topical therapy, intralesional therapy has also been reported as an effective local treatment. Most commonly, intralesionally administered triamcinolone (a glucocorticosteroid agent) is used but intralesionally administered cyclosporine and intralesionally administered methotrexate have also been reported to have an effect[146–148]. In our opinion, it may be best to consider topical and intralesional management strategies as adjuvant therapies in conjunction with systemic agents[149].

Systemic therapies

Historically, PG has been managed with systemic corticosteroids. However, the results of a large randomized controlled trial revealed that cyclosporine may be equally efficacious but with fewer serious adverse events (that is, those that lead to hospitalization or death) than prednisolone. 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 of 59 patients) or prednisolone (25 of 53 patients). The rate of disease recurrence with therapy was similar, at 30% and 28%, respectively, and in both arms approximately two-thirds of patients experienced adverse events. However, in this study, serious adverse events, primarily infections, were more common in the patients treated with prednisolone than in those who received cyclosporine[150].

The other randomized controlled trial compared infliximab 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 forwards 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 21% (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 various shortcomings, most importantly a lack of a validated PG outcome measure[151]. 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 enrolment of a uniform population of individuals with PG in a clinical trial difficult.

Multidrug 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, biologic agents and traditional steroid-sparing immunosuppressive agents, such as mycophenolate mofetil, take 2–4 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 dose, combined with a long duration of therapy to achieve ulcer healing, increases the risk of drug-related adverse events, as nearly everyone receiving high-dose cyclosporine or systemic corticosteroids will experience some adverse event during their therapy[150]. Thus, steroid-sparing agents have been studied, including immunosuppressive antibiotics (for example, dapsone, sulfasalazine and minocycline)[152,153]; traditional immunosuppressive agents (for example, azathioprine, mycophenolate mofetil and methotrexate)[154–157]; alkylating agents (for example, chlorambucil and cyclophosphamide)[158]; biologics, including anti-TNF agents (for example, infliximab, adalimumab, golimumab and certolizumab)[159–165], an anti-IL-12–IL-23 agent (ustekinumab)[68,166], an anti-IL-23 agent (tildrakizumab)[167], an anti-IL-17 agent (secukinumab)[168], an IL-1 receptor antagonist (anakinra)[169], anti-IL-1β agents (canakinumab and gevokizumab)[170,171], and an anti-IL-6 receptor agent (tocilizumab)[172]; intravenous immunoglobulin (IVIG; an immune modulator)[173–175]; a phosphodiesterase 4 inhibitor (apremilast)[176]; and JAK–STAT inhibitors (for example, tofacitinib and ruxolitinib)[143–145]. However, the data on the success of all these drugs 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[171].

Wound care

As in other ulcerative diseases, bacterial colonization, oedema and several other factors can impede PG wound 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 use 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 replaced by wound soaks. Providers may use warm tap water or sterile solutions as per regional preferences as there is no evidence for superiority[177]. The effectiveness of cleansing agents has not been extensively studied (for example, povidone-iodine versus benzoyl peroxide 5% soap)[178,179], and some experts argue against the use of soaps altogether as they may damage fragile cells in the wound bed[180]. Dilute vinegar (0.5% acetic acid) soaks have significant antimicrobial effects and may be beneficial in other ulcerative diseases[181,182] 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 with immunosuppression suggest infection. In such cases, cultures of wound tissue may help to guide antibiotic therapy.

With regard 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[183]. In less exudative wounds, providers can consider decreasing bacterial colonization with topical antimicrobials, such as silver sulfadiazine, Iodosorb, Hydrofera Blue and Xeroform. 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 characteristics of the wound as it evolves. Generally, it is wise to avoid overly drying out the wound base. The use of topical analgesics, particularly the use of topical medical cannabis on wounds as recently reported[184], is intriguing, but existing data are insufficient to make 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 PG wounds are 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 who 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 effects[185]. Impaired wound healing by immunosuppressive medications should be considered as a possible factor when patients are slow to heal despite receiving 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 in most circumstances. Unfortunately, it is not uncommon for patients with PG to present to dermatology clinics with rapidly progressing disease after receiving surgical debridement[186,187]. In such cases, the PG ulcers were originally attributed to another cause before 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 postsurgical PG also have accompanying signs and symptoms of fever, sepsis and leukocytosis, their PG might be misdiagnosed as necrotizing fasciitis or another severe infection. Aggressive wound debridement in this setting can have devastating outcomes, including amputation[115,188]. The necrotizing nature of some PG wounds has prompted investigators to prefer the term 'necrotizing neutrophilic dermatosis' in such severe cases[189]. Indeed, pathergy makes management of PG ulcers very difficult. However, it is also controversial whether all patients with PG demonstrate pathergy. One study estimated that pathergy occurs in only ~32% of patients with PG[128], although it is difficult to know the actual percentage because ulcers of other causes are often misdiagnosed as PG[109,190–197]. 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 similarly to ulcers of other causes, which would include the use of skin grafting and wound debridement[22,198].

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 (QOL) 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 odour 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 on whether 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, before therapy is discontinued, 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 them if their disease relapses. This precaution is especially important for patients who plan to undergo a surgical procedure or any other pathergy-inducing stimulus[199]. A small retrospective study revealed that 15.1% of patients with a history of PG develop a recurrence if they undergo a surgical procedure, a finding that does not seem to depend on the time elapsed since the original PG diagnosis or the location of the surgical procedure[199,200]. It is unclear whether prophylactic immunosuppressive agents are beneficial in these situations[200]. Ideally, patients and their surgeons should be well educated on the potential for pathergy.

Quality of life

QOL research for PG has not yet received the same attention as for other dermatological diseases. The lack of a validated PG-specific QOL measure may be one reason why PG has lagged behind other skin diseases in QOL research[201]. Currently, patients with PG have been included in the development and validation of only one non-disease-specific wound-QOL questionnaire[202]. In the absence of a PG-specific patient reported outcome measure, the prospective PG QOL studies that do exist have used standard dermatological questionnaires, mostly the Dermatology Life Quality Index (DLQI)[86,142,203] and/or the European Quality of Life 5 Dimensions (EQ-5D) instruments[86,142,150]. Although 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[142,203]. This score is higher than that for other dermatological diseases, such as non-melanoma skin cancer (2.25), Behçet disease (5.70) and acne vulgaris (7.45)[204]. 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[205,206].

There are many ways PG can negatively affect a patient's QOL. For example, PG is a severely painful skin disease[150,207], and pain is one of the major factors that negatively affect the health-related QOL of a patient with PG[203,208]. When DLQI components are analysed separately, pain-related questions account for 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[203]. When assessed on a separate validated scale, patients with PG had an average pain score of 7.5 out of 10 (REF.[206]). As 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[203]. These findings were recapitulated in a retrospective case series, which revealed that 14% of patients ($n = 103$) with PG have concomitant major depressive disorder[128]. Finally, there is some evidence that treatment can successfully improve a patient's QOL. One prospective cohort study clearly demonstrated improved PG-related QOL with treatment according to both skin-specific (DLQI) and general health status (EQ-5D-3L) questionnaires[142]. However, which therapy has the greatest effect on QOL in patients with PG 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[209]. Taken together, these studies clearly demonstrate that PG has a severe physical and psychosocial burden that considerably reduces QOL.

Outlook

Development of PG outcome measures

Outcome measures can be broadly classified as physical examination-based, laboratory-based or patient-reported measures. 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 treatment of 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[150,207,210]. Although these attempts at scoring PG severity represent a step in the right direction, the development of validated PG-specific outcome measures will hopefully increase 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). Multianalyte classifiers can be determined through molecular modelling techniques that combine two or more individual single-analyte biomarkers to form a composite classifier with superior accuracy to 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 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 to the most appropriate initial therapy and its duration. Classifiers could also help to identify which patients will be most at risk of 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[211]. However, such studies are gaining attention in IBD and rheumatoid arthritis, which are the most common PG-associated diseases[212,213]. 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 achieved 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-1β-targeting agents are of particular interest, including gevokizumab, described earlier, and canakinumab, which has been tested in steroid-refractory PG[170]. A phase II open-label study (NCT01965613) of bermekimab, a monoclonal antibody to IL-1α, has been registered as complete; however, the data have not yet been publicly communicated. C5a is another possible treatment target for PG[214,215] owing to its neutrophil-attracting capacity and its potential to initiate neutrophil-mediated autoinflammation. IFX-1, a monoclonal antibody specific for C5a, is currently under investigation (NCT03971643). A single-arm study is currently recruiting 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[216]. As additional case reports and retrospective case series emerge, we will have a better idea of the most appropriate agents to move forwards to larger randomized controlled clinical trials.

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1. Wang, E. A. & Maverakis, E. The rapidly evolving lesions of ulcerative pyoderma gangrenosum: a timeline. *Int. J. Dermatol.* **57**, 983–984 (2018). **This is the first photographic documentation of the temporal evolution of a PG ulcer.**
2. Hurwitz, R. M. & Haseman, J. H. The evolution of pyoderma gangrenosum. A clinicopathologic correlation. *Am. J. Dermatopathol.* **15**, 28–33 (1993).
3. Brunsting, L. A., Goeckerman, W. H. & O'Leary, P. A. Pyoderma (echthyma) gangrenosum - clinical and experimental observations in five cases occurring in adults. *Arch. Dermatol. Syphilol.* **22**, 655–680 (1930). **This manuscript is the first well-documented description of PG, introducing concepts such as disease associations and ulcers occuring at sites of trauma.**
4. Perry, H. O. & Brunsting, L. A. Pyoderma gangrenosum; a clinical study of nineteen cases. *AMA Arch. Derm.* **75**, 380–386 (1957).
5. Brocq, L. & Simon, C. L. Contribution à l'étude du phagédénisme. *Bull. Soc Med. Hôp. Paris* **25**, 290–307 (1908). **Some experts consider this article to be the first report of PG.**
6. Hobbs, M. M. & Ortega-Loayza, A. G. Pyoderma gangrenosum: from historical perspectives to emerging investigations. *Int. Wound J.* https://doi.org/10.1111/iwj.13389 (2020).
7. Patel, F. et al. Effective strategies for the management of pyoderma gangrenosum: a comprehensive review. *Acta Derm. Venereol.* **95**, 525–531 (2015).
8. Borda, L. J., Wong, L. L., Marzano, A. V. & Ortega-Loayza, A. G. Extracutaneous involvement of pyoderma gangrenosum. *Arch. Dermatol. Res.* **311**, 425–434 (2019).
9. Wallach, D. & Vignon-Pennamen, M. D. From acute febrile neutrophilic dermatosis to neutrophilic disease: forty years of clinical research. *J. Am. Acad. Dermatol.* **55**, 1066–1071 (2006).
10. Marzano, A. V., Borghi, A., Wallach, D. & Cugno, M. A comprehensive review of neutrophilic diseases. *Clin. Rev. Allergy Immunol.* **54**, 114–130 (2018).
11. Marzano, A. V. et al. Role of inflammatory cells, cytokines and matrix metalloproteinases in neutrophil-mediated skin diseases. *Clin. Exp. Immunol.* **162**, 100–107 (2010).
12. Maverakis, E. et al. Diagnostic criteria of ulcerative pyoderma gangrenosum: a Delphi consensus of international experts. *JAMA Dermatol.* **154**, 461–466 (2018). **This article establishes validated PG diagnostic criteria.**
13. Kastner, D. L., Aksentijevich, I. & Goldbach-Mansky, R. Autoinflammatory disease reloaded: a clinical perspective. *Cell* **140**, 784–790 (2010).
14. Farasat, S., Aksentijevich, I. & Toro, J. R. Autoinflammatory diseases: clinical and genetic advances. *Arch. Dermatol.* **144**, 392–402 (2008).
15. Satoh, T. K., Mellett, M., Contassot, E. & French, L. E. Are neutrophilic dermatoses autoinflammatory disorders? *Br. J. Dermatol.* **178**, 603–613 (2018).
16. Cugno, M., Borghi, A. & Marzano, A. V. PAPA, PASH and PAPASH syndromes: pathophysiology, presentation and treatment. *Am. J. Clin. Dermatol.* **18**, 555–562 (2017).
17. Marzano, A. V. et al. Mechanisms of inflammation in neutrophil-mediated skin diseases. *Front. Immunol.* **10**, 1059 (2019).
18. Xu, A., Balgobind, A., Strunk, A., Garg, A. & Alloo, A. Prevalence estimates for pyoderma gangrenosum in the United States: an age- and sex-adjusted population analysis. *J. Am. Acad. Dermatol.* https://doi.org/10.1016/j.jaad.2019.08.001 (2019).
19. Langan, S. M., Groves, R. W., Card, T. R. & Gulliford, M. C. Incidence, mortality, and disease associations of pyoderma gangrenosum in the United Kingdom: a retrospective cohort study. *J. Invest. Dermatol.* **132**, 2166–2170 (2012). **This is one of the largest studies on PG disease associations, mortality and incidence.**
20. Monari, P. et al. Epidemiology of pyoderma gangrenosum: results from an Italian prospective multicentre study. *Int. Wound J.* **15**, 875–879 (2018).

21. Vavricka, S. R. et al. Frequency and risk factors for extraintestinal manifestations in the Swiss inflammatory bowel disease cohort. *Am. J. Gastroenterol.* **106**, 110–119 (2011).
22. Sharon, V. et al. Multimodal therapy of idiopathic pyoderma gangrenosum. *Dermatol. Online J.* **20**, 6 (2014).
23. Bromeo, A. J. & Suller, A. Pyoderma gangrenosum of the upper eyelid. *BMJ Case Rep.* https://doi.org/10.1136/bcr-2019-230645 (2019).
24. Kechichian, E. et al. Pediatric pyoderma gangrenosum: a systematic review and update. *Int. J. Dermatol.* **56**, 486–495 (2017).
25. Schoch, J. J., Tolkachjov, S. N., Cappel, J. A., Gibson, L. E. & Davis, D. M. Pediatric pyoderma gangrenosum: a retrospective review of clinical features, etiologic associations, and treatment. *Pediatr. Dermatol.* **34**, 39–45 (2017).
26. Gilman, A. L., Cohen, B. A., Urbach, A. H. & Blatt, J. Pyoderma gangrenosum as a manifestation of leukemia in childhood. *Pediatrics* **81**, 846–848 (1988).
27. Paller, A. S., Sahn, E. E., Garen, P. D., Dobson, R. L. & Chadwick, E. G. Pyoderma gangrenosum in pediatric acquired immunodeficiency syndrome. *J. Pediatr.* **117**, 63–66 (1990).
28. Hayani, A., Steuber, C. P., Mahoney, D. H. Jr. & Levy, M. L. Pyoderma gangrenosum in childhood leukemia. *Pediatr. Dermatol.* **7**, 296–298 (1990).
29. Omidi, C. J. & Siegfried, E. C. Chronic recurrent multifocal osteomyelitis preceding pyoderma gangrenosum and occult ulcerative colitis in a pediatric patient. *Pediatr. Dermatol.* **15**, 435–438 (1998).
30. Ashchyan, H. J. et al. The association of age with clinical presentation and comorbidities of pyoderma gangrenosum. *JAMA Dermatol.* **154**, 409–413 (2018).
31. Bennett, M. L. et al. Pyoderma gangrenosum. A comparison of typical and atypical forms with an emphasis on time to remission. Case review of 86 patients from 2 institutions. *Medicine* **79**, 37–46 (2000).
This retrospective study from two university-affiliated programmes distinguishes the differences between classic ulcerative PG and atypical PG in terms of the location of lesions and associated diseases.
32. Kolios, A. G. A. et al. Clinical disease patterns in a regional swiss cohort of 34 pyoderma gangrenosum patients. *Dermatology* **233**, 268–276 (2017).
33. Al Ghazal, P. et al. Associated factors and comorbidities in patients with pyoderma gangrenosum in Germany: a retrospective multicentric analysis in 259 patients. *Orphanet J. Rare Dis.* **8**, 136 (2013).
34. Kaffenberger, B. H., Hinton, A. & Krishna, S. G. The impact of underlying disease state on outcomes in patients with pyoderma gangrenosum: a national survey. *J. Am. Acad. Dermatol.* **79**, 659–663 e652 (2018).
35. Sasor, S. E. et al. Pyoderma gangrenosum demographics, treatments, and outcomes: an analysis of 2,273 cases. *J. Wound Care* **27**, S4–S8 (2018).
36. Gupta, A. S. & Ortega-Loayza, A. G. Pyoderma gangrenosum: a too often overlooked facultative paraneoplastic disease. *Ann. Hematol.* **98**, 2247–2248 (2019).
37. Kridin, K., Cohen, A. D. & Amber, K. T. Underlying systemic diseases in pyoderma gangrenosum: a systematic review and meta-analysis. *Am. J. Clin. Dermatol.* **19**, 479–487 (2018).
38. Card, T. R., Langan, S. M. & Chu, T. P. Extra-gastrointestinal manifestations of inflammatory bowel disease may be less common than previously reported. *Dig. Dis. Sci.* **61**, 2619–2626 (2016).
39. Henry, C. M. et al. Neutrophil-derived proteases escalate inflammation through activation of IL-36 family cytokines. *Cell Rep.* **14**, 708–722 (2016).
40. Wang, E. A. et al. Classic ulcerative pyoderma gangrenosum is a T cell-mediated disease targeting follicular adnexal structures: a hypothesis based on molecular and clinicopathologic studies. *Front. Immunol.* **8**, 1980 (2017).
This article proposes PG to be a T cell-mediated disease.
41. Takeuchi, F., Sterilein, R. D. & Hall, R. P. 3rd. Increased E-selectin, IL-8 and IL-10 gene expression in human skin after minimal trauma. *Exp. Dermatol.* **12**, 777–783 (2003).
42. Maverakis, E., van den Elzen, P. & Sercarz, E. E. Self-reactive T cells and degeneracy of T cell recognition: evolving concepts-from sequence homology to shape mimicry and TCR flexibility. *J. Autoimmun.* **16**, 201–209 (2001).
43. Marzano, A. V., Borghi, A., Meroni, P. L. & Cugno, M. Pyoderma gangrenosum and its syndromic forms: evidence for a link with autoinflammation. *Br. J. Dermatol.* **175**, 882–891 (2016).
44. Nesterovitch, A. B. et al. Alteration in the gene encoding protein tyrosine phosphatase nonreceptor type 6 (PTPN6/SHP1) may contribute to neutrophilic dermatoses. *Am. J. Pathol.* **178**, 1434–1441 (2011).
45. Lorenz, U. SHP-1 and SHP-2 in T cells: two phosphatases functioning at many levels. *Immunol. Rev.* **228**, 342–359 (2009).
46. Zhang, J., Somani, A. K. & Siminovitch, K. A. Roles of the SHP-1 tyrosine phosphatase in the negative regulation of cell signalling. *Semin. Immunol.* **12**, 361–378 (2000).
47. Nesterovitch, A. B. et al. Spontaneous insertion of a B2 element in the *Ptpn6* gene drives a systemic autoinflammatory disease in mice resembling neutrophilic dermatosis in humans. *Am. J. Pathol.* **178**, 1701–1714 (2011).
48. Nesterovitch, A. B. et al. Mutations in the PSTPIP1 gene and aberrant splicing variants in patients with pyoderma gangrenosum. *Clin. Exp. Dermatol.* **36**, 889–895 (2011).
49. Wise, C. A. et al. Mutations in CD2BP1 disrupt binding to PTP PEST and are responsible for PAPA syndrome, an autoinflammatory disorder. *Hum. Mol. Genet.* **11**, 961–969 (2002).
50. Smith, E. J. et al. Clinical, molecular, and genetic characteristics of PAPA syndrome: a review. *Curr. Genomics* **11**, 519–527 (2010).
51. Dinarello, C. A. A clinical perspective of IL-1beta as the gatekeeper of inflammation. *Eur. J. Immunol.* **41**, 1203–1217 (2011).
52. Weiss, D. I. et al. IL-1beta induces the rapid secretion of the antimicrobial protein IL-26 from Th17 cells. *J. Immunol.* **203**, 911–921 (2019).
53. Marzano, A. V. et al. Autoinflammation in pyoderma gangrenosum and its syndromic form (pyoderma gangrenosum, acne and suppurative hidradenitis). *Br. J. Dermatol.* **176**, 1588–1598 (2017).
54. Braun-Falco, M., Kovnerystyy, O., Lohse, P. & Ruzicka, T. Pyoderma gangrenosum, acne, and suppurative hidradenitis (PASH)–a new autoinflammatory syndrome distinct from PAPA syndrome. *J. Am. Acad. Dermatol.* **66**, 409–415 (2012).
55. Marzano, A. V., Ishak, R. S., Colombo, A., Caroli, F. & Crosti, C. Pyoderma gangrenosum, acne and suppurative hidradenitis syndrome following bowel bypass surgery. *Dermatology* **225**, 215–219 (2012).
56. Marzano, A. V. et al. Association of pyoderma gangrenosum, acne, and suppurative hidradenitis (PASH) shares genetic and cytokine profiles with other autoinflammatory diseases. *Medicine* **93**, e187 (2014).
57. van der Zee, H. H. & Jemec, G. B. New insights into the diagnosis of hidradenitis suppurativa: clinical presentations and phenotypes. *J. Am. Acad. Dermatol.* **73**, S23–S26 (2015).
58. Tricarico, P. M. et al. An integrated approach to unravel hidradenitis suppurativa etiopathogenesis. *Front. Immunol.* **10**, 892 (2019).
59. Ortega-Loayza, A. G. et al. Dysregulation of inflammatory gene expression in lesional and nonlesional skin of patients with pyoderma gangrenosum. *Br. J. Dermatol.* **178**, e35–e36 (2018).
60. Nesterovitch, A. B., Arbieva, Z., Toth, D. M., Tharp, M. D. & Glant, T. T. A differential gene expression study: Ptpn6 (SHP-1)-insufficiency leads to neutrophilic dermatosis-like disease (NDLD) in mice. *J. Dermatol. Sci.* **83**, 17–25 (2016).
61. Kolios, A. G. A. et al. Comparison of pyoderma gangrenosum and Martorell hypertensive ischaemic leg ulcer in a Swiss cohort. *Br. J. Dermatol.* **178**, e125–e126 (2018).
62. Lukens, J. R. & Kanneganti, T. D. SHP-1 and IL-1alpha conspire to provoke neutrophilic dermatoses. *Rare Dis.* **2**, e27742 (2014).
63. Lukens, J. R. et al. RIP1-driven autoinflammation targets IL-1alpha independently of inflammasomes and RIP3. *Nature* **498**, 224–227 (2013).
This article provides evidence for a potential unique role of IL-1α in autoinflammation.
64. Tartey, S., Gurung, P., Dasari, T. K., Burton, A. & Kanneganti, T. D. ASK1/2 signaling promotes inflammation in a mouse model of neutrophilic dermatosis. *J. Clin. Invest.* **128**, 2042–2047 (2018).
65. Tartey, S., Gurung, P., Samir, P., Burton, A. & Kanneganti, T. D. Cutting edge: dysregulated CARD9 signaling in neutrophils drives inflammation in a mouse model of neutrophilic dermatoses. *J. Immunol.* **201**, 1639–1644 (2018).
66. Marzano, A. V. et al. Expression of cytokines, chemokines and other effector molecules in two prototypic autoinflammatory skin diseases, pyoderma gangrenosum and Sweet's syndrome. *Clin. Exp. Immunol.* **178**, 48–56 (2014).
67. Palanivel, J. A., Macbeth, A. E. & Levell, N. J. Pyoderma gangrenosum in association with Janus kinase 2 (JAK2V617F) mutation. *Clin. Exp. Dermatol.* **38**, 44–46 (2013).
68. Guenova, E. et al. Interleukin 23 expression in pyoderma gangrenosum and targeted therapy with ustekinumab. *Arch. Dermatol.* **147**, 1203–1205 (2011).
This article provides evidence that IL-23 is central to PG pathophysiology.
69. Fletcher, J., Alhusayen, R. & Alavi, A. Recent advances in managing and understanding pyoderma gangrenosum. *F1000ReS* https://doi.org/10.12688/f1000research.19909.1 (2019).
70. Tanaka, N., Fujioka, A., Tajima, S., Ishibashi, A. & Hirose, S. Elafin is induced in epidermis in skin disorders with dermal neutrophilic infiltration: interleukin-1 beta and tumour necrosis factor-alpha stimulate its secretion in vitro. *Brit J. Dermatol.* **143**, 728–732 (2000).
71. Johnston, A. et al. IL-1 and IL-36 are dominant cytokines in generalized pustular psoriasis. *J. Allergy Clin. Immunol.* **140**, 109–120 (2017).
72. Carrier, Y. et al. Inter-regulation of Th17 cytokines and the IL-36 cytokines in vitro and in vivo: implications in psoriasis pathogenesis. *J. Invest. Dermatol.* **131**, 2428–2437 (2011).
73. Bamias, G., Corridoni, D., Pizarro, T. T. & Cominelli, F. New insights into the dichotomous role of innate cytokines in gut homeostasis and inflammation. *Cytokine* **59**, 451–459 (2012).
74. Russell, S. E. et al. IL-36alpha expression is elevated in ulcerative colitis and promotes colonic inflammation. *Mucosal Immunol.* **9**, 1193–1204 (2016).
75. Boutet, M. A. et al. Distinct expression of interleukin (IL)-36alpha, beta and gamma, their antagonist IL-36Ra and IL-38 in psoriasis, rheumatoid arthritis and Crohn's disease. *Clin. Exp. Immunol.* **184**, 159–173 (2016).
76. Hessam, S. et al. Interleukin-36 in hidradenitis suppurativa: evidence for a distinctive proinflammatory role and a key factor in the development of an inflammatory loop. *Br. J. Dermatol.* **178**, 761–767 (2018).
77. Senra, L. et al. IL-17E (IL-25) Enhances innate immune responses during skin inflammation. *J. Invest. Dermatol.* **139**, 1732–1742.e1717 (2019).
78. Pappu, R., Ramirez-Carrozzi, V. & Sambandam, A. The interleukin-17 cytokine family: critical players in host defence and inflammatory diseases. *Immunology* **134**, 8–16 (2011).
79. Hvid, M. et al. IL-25 in atopic dermatitis: a possible link between inflammation and skin barrier dysfunction? *J. Invest. Dermatol.* **131**, 150–157 (2011).
80. Xu, M. & Dong, C. IL-25 in allergic inflammation. *Immunol. Rev.* **278**, 185–191 (2017).
81. Senra, L. et al. Keratinocyte-derived IL-17E contributes to inflammation in psoriasis. *J. Invest. Dermatol.* **136**, 1970–1980 (2016).
82. Yeon, H. B., Lindor, N. M., Seidman, J. G. & Seidman, C. E. Pyogenic arthritis, pyoderma gangrenosum, and acne syndrome maps to chromosome 15q. *Am. J. Hum. Genet.* **66**, 1443–1448 (2000).
83. Oka, M. et al. Interleukin-8 overexpression is present in pyoderma gangrenosum ulcers and leads to ulcer formation in human skin xenografts. *Lab. Invest.* **80**, 595–604 (2000).
84. Baggiolini, M., Dewald, B. & Moser, B. Interleukin-8 and related chemotactic cytokines–CXC and CC chemokines. *Adv. Immunol.* **55**, 97–179 (1994).
85. Smith, S. et al. IL-16/miR-125a axis controls neutrophil recruitment in pristane-induced lung inflammation. *JCI Insight* https://doi.org/10.1172/jci.insight.120798 (2018).
86. Brooklyn, T. N. et al. Infliximab for the treatment of pyoderma gangrenosum: a randomised, double blind, placebo controlled trial. *Gut* **55**, 505–509 (2006).
This is the first randomized controlled trial in PG.
87. Matsushima, K. et al. Molecular cloning of a human monocyte-derived neutrophil chemotactic factor (MDNCF) and the induction of MDNCF mRNA by interleukin 1 and tumor necrosis factor. *J. Exp. Med.* **167**, 1883–1893 (1988).

88. Maverakis, E. et al. Light, including ultraviolet. *J. Autoimmun.* **34**, J247–J257 (2010).
89. Strieter, R. M. et al. Endothelial cell gene expression of a neutrophil chemotactic factor by TNF-alpha, LPS, and IL-1 beta. *Science* **243**, 1467–1469 (1989).
90. Xia, P. et al. Tumor necrosis factor-alpha induces adhesion molecule expression through the sphingosine kinase pathway. *Proc. Natl Acad. Sci. USA* **95**, 14196–14201 (1998).
91. Sharma, D., Malik, A., Guy, C., Vogel, P. & Kanneganti, T. D. TNF/TNFR axis promotes pyrin inflammasome activation and distinctly modulates pyrin inflammasomopathy. *J. Clin. Invest.* **129**, 150–162 (2019).
92. Su, W. P., Schroeter, A. L., Perry, H. O. & Powell, F. C. Histopathologic and immunopathologic study of pyoderma gangrenosum. *J. Cutan. Pathol.* **13**, 323–330 (1986).
This article is one of the first to note a predominance of peripheral lymphocytes in PG.
93. Brooklyn, T. N., Williams, A. M., Dunnill, M. G. & Probert, C. S. T-cell receptor repertoire in pyoderma gangrenosum: evidence for clonal expansions and trafficking. *Br. J. Dermatol.* **157**, 960–966 (2007).
94. Foster, A. M. et al. IL-36 promotes myeloid cell infiltration, activation, and inflammatory activity in skin. *J. Immunol.* **192**, 6053–6061 (2014).
95. Ackerman, A. B. An algorithmic method for histologic diagnosis of inflammatory and neoplastic skin diseases by analysis of their patterns. *Am. J. Dermatopathol.* **7**, 105–107 (1985).
96. Abraham, C. & Cho, J. H. Inflammatory bowel disease. *N. Engl. J. Med.* **361**, 2066–2078 (2009).
97. Chen, W. T. & Chi, C. C. Association of hidradenitis suppurativa with inflammatory bowel disease: a systematic review and meta-analysis. *JAMA Dermatol.* https://doi.org/10.1001/jamadermatol.2019.0891 (2019).
98. Billmeier, U., Dieterich, W., Neurath, M. F. & Atreya, R. Molecular mechanism of action of anti-tumor necrosis factor antibodies in inflammatory bowel diseases. *World J. Gastroenterol.* **22**, 9300–9313 (2016).
99. Antiga, E. et al. T helper type 1-related molecules as well as interleukin-15 are hyperexpressed in the skin lesions of patients with pyoderma gangrenosum. *Clin. Exp. Immunol.* **189**, 383–391 (2017).
100. Caproni, M. et al. The Treg/Th17 cell ratio is reduced in the skin lesions of patients with pyoderma gangrenosum. *Br. J. Dermatol.* **173**, 275–278 (2015).
101. Gooderham, M. J., Papp, K. A. & Lynde, C. W. Shifting the focus - the primary role of IL-23 in psoriasis and other inflammatory disorders. *J. Eur. Acad. Dermatol. Venereol.* **32**, 1111–1119 (2018).
102. Gaffen, S. L., Jain, R., Garg, A. V. & Cua, D. J. The IL-23-IL-17 immune axis: from mechanisms to therapeutic testing. *Nat. Rev. Immunol.* **14**, 585–600 (2014).
103. Langrish, C. L. et al. IL-23 drives a pathogenic T cell population that induces autoimmune inflammation. *J. Exp. Med.* **201**, 233–240 (2005).
104. McGeachy, M. J., Cua, D. J. & Gaffen, S. L. The IL-17 family of cytokines in health and disease. *Immunity* **50**, 892–906 (2019).
105. Barnett, M. H. & Prineas, J. W. Relapsing and remitting multiple sclerosis: pathology of the newly forming lesion. *Ann. Neurol.* **55**, 458–468 (2004).
106. Fiorentino, D. F., Zlotnik, A., Mosmann, T. R., Howard, M. & O'Garra, A. IL-10 inhibits cytokine production by activated macrophages. *J. Immunol.* **147**, 3815–3822 (1991).
107. Horvath, R., Duffy, P. & McCormack, J. G. Necrotic ulceration of the skin and fascia. *Clin. Infect. Dis.* **36**, 925–926 (2003).
108. Thomas, R. H. M., Payne, C. M. E. R. & Black, M. M. Wegener's granulomatosis presenting as pyoderma gangrenosum. *Clin. Exp. Dermatol.* **7**, 523–527 (1982).
109. Weenig, R. H., Davis, M. D. P., Dahl, P. R. & Su, W. P. D. Skin ulcers misdiagnosed as pyoderma gangrenosum. *N. Engl. J. Med.* **347**, 1412–1418 (2002).
110. Duguid, C. M., O'Loughlin, S., Otridge, B. & Powell, F. C. Paraneoplastic pyoderma gangrenosum. *Australas. J. Dermatol.* **34**, 17–22 (1993).
111. Maverakis, E., Goodarzi, H., Wehrli, L. N., Ono, Y. & Garcia, M. S. The etiology of paraneoplastic autoimmunity. *Clin. Rev. Allergy Immunol.* **42**, 135–144 (2012).
112. Montagnon, C. M. et al. Pyoderma gangrenosum in hematologic malignancies: a systematic review. *J. Am. Acad. Dermatol.* **82**, 1346–1359 (2020).
113. Ehst, B. D., Minzer-Conzetti, K., Swerdlin, A. & Devere, T. S. Cutaneous manifestations of internal malignancy. *Curr. Probl. Surg.* **47**, 384–445 (2010).
114. Le, S. T. et al. End stage scurvy in the developed world: a diagnostic conundrum but not to be mistaken for pyoderma gangrenosum. *Int. Wound J.* **16**, 1024–1028 (2019).
115. Haag, C. K. et al. Pyoderma gangrenosum misdiagnosis resulting in amputation: a review. *J. Trauma. Acute Care Surg.* **86**, 307–313 (2019).
116. El-Kehdy, J., Haneke, E. & Karam, P. G. Pyoderma gangrenosum: a misdiagnosis. *J. Drugs Dermatol.* **12**, 228–230 (2013).
117. Conde Montero, E. et al. Factitious ulcer misdiagnosed as pyoderma gangrenosum. *Wounds* **28**, 63–67 (2016).
118. Kumar, L. S., Shanmugasekar, C., Lakshmi, C. & Srinivas, C. R. Herpes misdiagnosed as pyoderma gangrenosum. *Indian J. Sex. Transm. Dis. AIDS* **30**, 106–108 (2009).
119. Bradsher, R. W. Jr. The endemic mimic: blastomycosis an illness often misdiagnosed. *Trans. Am. Clin. Climatol. Assoc.* **125**, 188–202 (2014).
120. Su, W. P., Davis, M. D., Weenig, R. H., Powell, F. C. & Perry, H. O. Pyoderma gangrenosum: clinicopathologic correlation and proposed diagnostic criteria. *Int. J. Dermatol.* **43**, 790–800 (2004).
121. Le, S. T. et al. Peristomal pyoderma gangrenosum: an exceedingly rare and overdiagnosed entity? *J. Am. Acad. Dermatol.* https://doi.org/10.1016/j.jaad.2019.02.026 (2019).
122. Barton, V. R. et al. Peristomal ulcers misdiagnosed as pyoderma gangrenosum: a common error. *J. Eur. Acad. Dermatol. Venereol.* **34**, e108–e110 (2020).
123. Jockenhofer, F., Wollina, U., Salva, K. A., Benson, S. & Dissemond, J. The PARACELSUS score: a novel diagnostic tool for pyoderma gangrenosum. *Br. J. Dermatol.* https://doi.org/10.1111/bjd.16401 (2018).
This article presents a novel PG diagnostic model.
124. Maverakis, E. et al. New validated diagnostic criteria for pyoderma gangrenosum. *J. Am. Acad. Dermatol.* **80**, e87–e88 (2019).
125. Craig, F. F. et al. UK Dermatology Clinical Trials Network's STOP GAP trial (a multicentre trial of prednisolone versus ciclosporin for pyoderma gangrenosum): protocol for a randomised controlled trial. *Trials* **13**, 51 (2012).
126. Goodarzi, H. et al. Effective strategies for the management of pyoderma gangrenosum. *Adv. Wound Care* **1**, 194–199 (2012).
127. Ahronowitz, I., Harp, J. & Shinkai, K. Etiology and management of pyoderma gangrenosum: a comprehensive review. *Am. J. Clin. Dermatol.* **13**, 191–211 (2012).
128. Binus, A. M., Qureshi, A. A., Li, V. W. & Winterfield, L. S. Pyoderma gangrenosum: a retrospective review of patient characteristics, comorbidities and therapy in 103 patients. *Br. J. Dermatol.* **165**, 1244–1250 (2011).
This retrospective analysis demonstrates that pathergy is present in only one-third of patients with PG.
129. Janowska, A. et al. PG-TIME: A practical approach to the clinical management of pyoderma gangrenosum. *Dermatol. Ther.* **33**, e13412 (2020).
130. Woodland, J. et al. Azathioprine in rheumatoid arthritis: double-blind study of full versus half doses versus placebo. *Ann. Rheum. Dis.* **40**, 355–359 (1981).
131. Sandborn, W. J. et al. Adalimumab induces and maintains clinical remission in patients with moderate-to-severe ulcerative colitis. *Gastroenterology* **142**, 257–265 (2012).
132. Landis, E. T., Taheri, A. & Jorizzo, J. L. Gulliver's sign: a recognizable transition from inflammatory to healing stages of pyoderma gangrenosum. *J. Dermatol. Treat.* **26**, 171–172 (2015).
133. Fonder, M. A., Cummins, D. L., Ehst, B. D., Anhalt, G. J. & Meyerle, J. H. Adalimumab therapy for recalcitrant pyoderma gangrenosum. *J. Burn. Wounds* **5**, e8 (2006).
134. Pomerantz, R. G., Husni, M. E., Mody, E. & Qureshi, A. A. Adalimumab for treatment of pyoderma gangrenosum. *Br. J. Dermatol.* **157**, 1274–1275 (2007).
135. Zold, E., Nagy, A., Devenyi, K., Zeher, M. & Barta, Z. Successful use of adalimumab for treating fistulizing Crohn's disease with pyoderma gangrenosum: two birds with one stone. *World J. Gastroenterol.* **15**, 2293–2295 (2009).
136. Breedveld, F. C. et al. The PREMIER study: a multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. *Arthritis Rheum.* **54**, 26–37 (2006).
137. Bartelds, G. M. et al. Clinical response to adalimumab: relationship to anti-adalimumab antibodies and serum adalimumab concentrations in rheumatoid arthritis. *Ann. Rheum. Dis.* **66**, 921–926 (2007).
138. Sivamani, R. K. et al. Biologic therapies in the treatment of psoriasis: a comprehensive evidence-based basic science and clinical review and a practical guide to tuberculosis monitoring. *Clin. Rev. Allergy Immunol.* **44**, 121–140 (2013).
139. Baltazar, D., Haag, C., Gupta, A. S., Marzano, A. M. & Ortega Loayza, A. G. A comprehensive review of local pharmacologic therapy for pyoderma gangrenosum. *Wounds* **31**, 151–157 (2019).
140. Richter-Hintz, D., Schuppe, H. C., Homey, B., Lehmann, P. & Ruzicka, T. Topical tacrolimus (FK 506) is effective in the treatment of pyoderma gangrenosum. *J. Am. Acad. Dermatol.* **42**, 304–305 (2000).
141. Schuppe, H. C., Homey, B., Assmann, T., Martens, R. & Ruzicka, T. Topical tacrolimus for pyoderma gangrenosum. *Lancet* **351**, 832 (1998).
142. Thomas, K. S. et al. Clinical outcomes and response of patients applying topical therapy for pyoderma gangrenosum: a prospective cohort study. *J. Am. Acad. Dermatol.* **75**, 940–949 (2016).
143. Kochar, B. et al. Tofacitinib for the treatment of pyoderma gangrenosum. *Clin. Gastroenterol. Hepatol.* **17**, 991–993 (2019).
144. Gregory, M. H., Ciorba, M. A., Deepak, P. & Christophi, G. P. Successful treatment of pyoderma gangrenosum with concomitant tofacitinib and infliximab. *Inflamm. Bowel Dis.* **25**, e87–e88 (2019).
145. Nasifoglu, S., Heinrich, B. & Welzel, J. Successful therapy for pyoderma gangrenosum with a Janus kinase 2 inhibitor. *Br. J. Dermatol.* **179**, 504–505 (2018).
146. Moschella, S. L. Pyoderma gangrenosum. A patient successfully treated with intralesional injections of steroid. *Arch. Dermatol.* **95**, 121–123 (1967).
147. Jennings, J. L. Pyoderma gangrenosum: successful treatment with intralesional steroids. *J. Am. Acad. Dermatol.* **9**, 575–580 (1983).
148. Mrowietz, U. & Christophers, E. Clearing of pyoderma gangrenosum by intralesional cyclosporin A. *Br. J. Dermatol.* **125**, 499 (1991).
149. He, Y., Maverakis, E., Ramirez-Maverakis, D. & Fitzmaurice, S. Combination therapy with intralesional triamcinolone and oral dapsone for management of palisaded neutrophilic and granulomatous dermatitis. *Dermatol. Online J.* **19**, 17 (2013).
150. Ormerod, A. D. et al. Comparison of the two most commonly used treatments for pyoderma gangrenosum: results of the STOP GAP randomised controlled trial. *BMJ* **350**, h2958 (2015).
This is the largest randomized clinical trial ever conducted in PG.
151. Lu, J. D., Hobbs, M. M., Huang, W. W., Ortega-Loayza, A. G. & Alavi, A. Identification and evaluation of outcome measurement instruments in pyoderma gangrenosum: a systematic review. *Br. J. Dermatol*. (2020).
152. Galun, E., Flugelman, M. Y. & Rachmilewitz, D. Pyoderma gangrenosum complicating ulcerative colitis: successful treatment with methylprednisolone pulse therapy and dapsone. *Am. J. Gastroenterol.* **81**, 988–989 (1986).
153. Shenefelt, P. D. Pyoderma gangrenosum associated with cystic acne and hidradenitis suppurativa controlled by adding minocycline and sulfasalazine to the treatment regimen. *Cutis* **57**, 315–319 (1996).
154. Hohenleutner, U., Mohr, V. D., Michel, S. & Landthaler, M. Mycophenolate mofetil and cyclosporin treatment for recalcitrant pyoderma gangrenosum. *Lancet* **350**, 1748 (1997).
155. Nousari, H. C., Lynch, W., Anhalt, G. J. & Petri, M. The effectiveness of mycophenolate mofetil in refractory pyoderma gangrenosum. *Arch. Dermatol.* **134**, 1509–1511 (1998).
156. Teitel, A. D. Treatment of pyoderma gangrenosum with methotrexate. *Cutis* **57**, 326–328 (1996).
157. Toussi, A. et al. Successful management of anti-TNF-induced psoriasis despite continuation of therapy in a pyoderma gangrenosum patient. *J. Drugs Dermatol.* **19**, 199–201 (2020).

158. Crawford, S. E., Sherman, R. & Favara, B. Pyoderma gangrenosum with response to cyclophosphamide therapy. *J. Pediatr.* **71**, 255–258 (1967).
159. Roy, D. B., Conte, E. T. & Cohen, D. The treatment of pyoderma gangrenosum using etanercept. *J. Am. Acad. Dermatol.* **54**, S128–S134 (2006).
160. Rogge, F. J., Pacifico, M. & Kang, N. Treatment of pyoderma gangrenosum with the anti-TNF alpha drug - Etanercept. *J. Plast. Reconstr. Aesthet. Surg.* **61**, 431–433 (2008).
161. Pastor, N. et al. Pyoderma gangrenosum treated with anti-TNF alpha therapy (etanercept). *Clin. Exp. Dermatol.* **31**, 152–153 (2006).
162. Goldenberg, G. & Jorizzo, J. L. Use of etanercept in treatment of pyoderma gangrenosum in a patient with autoimmune hepatitis. *J. Dermatol. Treat.* **16**, 347–349 (2005).
163. Disla, E., Quayum, B., Cuppari, G. G. & Pancorbo, R. Successful use of etanercept in a patient with pyoderma gangrenosum complicating rheumatoid arthritis. *J Clin. Rheumatol.* **10**, 50–52 (2004).
164. Charles, C. A., Leon, A., Banta, M. R. & Kirsner, R. S. Etanercept for the treatment of refractory pyoderma gangrenosum: a brief series. *Int. J. Dermatol.* **46**, 1095–1099 (2007).
165. Hurabielle, C. et al. Certolizumab pegol - a new therapeutic option for refractory disseminated pyoderma gangrenosum associated with Crohn's disease. *J. Dermatol. Treat.* **27**, 67–69 (2016).
166. Goldminz, A. M., Botto, N. C. & Gottlieb, A. B. Severely recalcitrant pyoderma gangrenosum successfully treated with ustekinumab. *J. Am. Acad. Dermatol.* **67**, e237–e238 (2012).
167. John, J. M. & Sinclair, R. D. Tildrakizumab for treatment of refractory pyoderma gangrenosum of the penis and polymyalgia rheumatica: killing two birds with one stone. *Australas. J. Dermatol.* https://doi.org/10.1111/ajd.13196 (2019).
168. Moreno Garcia, M., Madrid Gonzalez, M. & Prada Lobato, J. M. Secukinumab for pyoderma gangrenosum: a case report. *Med. Clin.* **152**, 246 (2019).
169. Brenner, M., Ruzicka, T., Plewig, G., Thomas, P. & Herzer, P. Targeted treatment of pyoderma gangrenosum in PAPA (pyogenic arthritis, pyoderma gangrenosum and acne) syndrome with the recombinant human interleukin-1 receptor antagonist anakinra. *Br. J. Dermatol.* **161**, 1199–1201 (2009).
170. Kolios, A. G. et al. Canakinumab in adults with steroid-refractory pyoderma gangrenosum. *Br. J. Dermatol.* **173**, 1216–1223 (2015).
171. US National Library of Medicine. *ClinicalTrials.gov* https://clinicaltrials.gov/ct2/show/NCT01882504 (2016).
172. Lee, W. S., Choi, Y. J. & Yoo, W. H. Use of tocilizumab in a patient with pyoderma gangrenosum and rheumatoid arthritis. *J. Eur. Acad. Dermatol. Venereol.* **31**, e75–e77 (2017).
173. Cummins, D. L., Anhalt, G. J., Monahan, T. & Meyerle, J. H. Treatment of pyoderma gangrenosum with intravenous immunoglobulin. *Br. J. Dermatol.* **157**, 1235–1239 (2007).
174. Hagman, J. H., Carrozzo, A. M., Campione, E., Romanelli, P. & Chimenti, S. The use of high-dose immunoglobulin in the treatment of pyoderma gangrenosum. *J. Dermatol. Treat.* **12**, 19–22 (2001).
175. Kreuter, A., Reich-Schupke, S., Stucker, M., Altmeyer, P. & Gambichler, T. Intravenous immunoglobulin for pyoderma gangrenosum. *Br. J. Dermatol.* **158**, 856–857 (2008).
176. Laird, M. E. et al. Novel use of apremilast for adjunctive treatment of recalcitrant pyoderma gangrenosum. *JAAD Case Rep.* **3**, 228–229 (2017).
177. Beam, J. W. Wound cleansing: water or saline? *J. Athl. Train.* **41**, 196–197 (2006).
178. Nguyen, L. Q. & Weiner, J. Treatment of pyoderma gangrenosum with benzoyl peroxide. *Cutis* **19**, 842–844 (1977).
179. Wilkins, R. G. & Unverdorben, M. Wound cleaning and wound healing: a concise review. *Adv. Skin. Wound Care* **26**, 160–163 (2013).
180. Mahoney, E. & Kelly, C. B. in *Orthotics and Prosthetics in Rehabilitation* (Elsevier, 2013).
181. Powers, J. G., Higham, C., Broussard, K. & Phillips, T. J. Wound healing and treating wounds: chronic wound care and management. *J. Am. Acad. Dermatol.* **74**, 607–625 (2016).
182. Lipsky, B. A. & Hoey, C. Topical antimicrobial therapy for treating chronic wounds. *Clin. Infect. Dis.* **49**, 1541–1549 (2009).
183. Lobmann, R., Zemlin, C., Motzkau, M., Reschke, K. & Lehnert, H. Expression of matrix metalloproteinases and growth factors in diabetic foot wounds treated with a protease absorbent dressing. *J. Diabetes Complicat.* **20**, 329–335 (2006).
184. Maida, V. & Corban, J. Topical medical cannabis: a new treatment for wound pain-three cases of pyoderma gangrenosum. *J. Pain Symptom Manage.* **54**, 732–736 (2017).
185. Schwartz, P. M., Barnett, S. K., Atillasoy, E. S. & Milstone, L. M. Methotrexate induces differentiation of human keratinocytes. *Proc. Natl Acad. Sci. USA* **89**, 594–598 (1992).
186. Long, C. C., Jessop, J., Young, M. & Holt, P. J. Minimizing the risk of post-operative pyoderma gangrenosum. *Br. J. Dermatol.* **127**, 45–48 (1992).
187. Zuo, K. J., Fung, E., Tredget, E. E. & Lin, A. N. A systematic review of post-surgical pyoderma gangrenosum: identification of risk factors and proposed management strategy. *J. Plast. Reconstr. Aesthet. Surg.* **68**, 295–303 (2015).
188. Steele, R. B. et al. Pyoderma gangrenosum and pregnancy: an example of abnormal inflammation and challenging treatment. *Br. J. Dermatol.* **174**, 77–87 (2016).
189. Sanchez, I. M. et al. Clinical features of neutrophilic dermatosis variants resembling necrotizing fasciitis. *JAMA Dermatol.* **155**, 79–84 (2019).
190. Crittenden, S. C., Gilbert, J. E. & Callen, J. P. Hydroxyurea-induced leg ulceration in a patient with a homozygous MTHFR polymorphism misdiagnosed as pyoderma gangrenosum. *JAMA Dermatol.* **150**, 780–781 (2014).
191. Delgado-Jimenez, Y. et al. Extranodal NK/T-cell lymphoma nasal type mimicking pyoderma gangrenosum. *Acta Derm. Venereol.* **87**, 176–177 (2007).
192. Ho, K. K., Browne, A., Fitzgibbons, J., Carney, D. & Powell, F. C. Mycosis fungoides bullosa simulating pyoderma gangrenosum. *Br. J. Dermatol.* **142**, 124–127 (2000).
193. Jasch, K. C., Hermes, B., Scheller, U. & Harth, W. Pyoderma gangrenosum-like primary cutaneous cryptococcosis. *Acta Derm. Venereol.* **88**, 76–77 (2008).
194. Kerr, O. A., Bong, C., Wallis, C. & Tidman, M. J. Primary cutaneous mucormycosis masquerading as pyoderma gangrenosum. *Br. J. Dermatol.* **150**, 1212–1213 (2004).
195. Kikuchi, N. et al. Cutaneous cryptococcosis mimicking pyoderma gangrenosum: a report of four cases. *Acta Derm. Venereol.* **96**, 116–117 (2016).
196. Murray, P. R. et al. Pyoderma gangrenosum-like ulcer in a patient with X-linked agammaglobulinemia: identification of Helicobacter bilis by mass spectrometry analysis. *Arch. Dermatol.* **146**, 523–526 (2010).
197. New, D., Eaton, P., Knable, A. & Callen, J. P. The use of B vitamins for cutaneous ulcerations mimicking pyoderma gangrenosum in patients with MTHFR polymorphism. *Arch. Dermatol.* **147**, 450–453 (2011).
198. Eisendle, K., Thuile, T., Deluca, J. & Pichler, M. Surgical treatment of pyoderma gangrenosum with negative pressure wound therapy and skin grafting, including xenografts: personal experience and comprehensive review on 161 cases. *Adv. Wound Care* **9**, 405–425 (2020).
199. Xia, F. D. et al. Risk of developing pyoderma gangrenosum after procedures in patients with a known history of pyoderma gangrenosum-A retrospective analysis. *J. Am. Acad. Dermatol.* **78**, 310–314.e311 (2018).
This article establishes the incidence of PG recurrence following surgical procedures.
200. Haag, C. K. et al. Perioperative management of pyoderma gangrenosum. *J. Am. Acad. Dermatol.* https://doi.org/10.1016/j.jaad.2020.01.002 (2020).
201. Gerard, A. J., Feldman, S. R. & Strowd, L. Quality of life of patients with pyoderma gangrenosum and hidradenitis suppurativa. *J. Cutan. Med. Surg.* **19**, 391–396 (2015).
202. Augustin, M. et al. Validity and feasibility of the wound-QoL questionnaire on health-related quality of life in chronic wounds. *Wound Repair. Regen.* **25**, 852–857 (2017).
203. Ighani, A. et al. Pyoderma gangrenosum and its impact on quality of life: a multicentre, prospective study. *Br. J. Dermatol.* **180**, 672–673 (2019).
204. Basra, M. K., Fenech, R., Gatt, R. M., Salek, M. S. & Finlay, A. Y. The dermatology life quality index 1994–2007: a comprehensive review of validation data and clinical results. *Br. J. Dermatol.* **159**, 997–1035 (2008).
205. Dyer, M. T. D., Goldsmith, K. A., Sharples, L. S. & Buxton, M. J. A review of health utilities using the EQ-5D in studies of cardiovascular disease. *Health Qual. Life Outcomes* **8**, 13 (2010).
206. Huppertz-Hauss, G. et al. Comparison of the multiattribute utility instruments EQ-5D and SF-6D in a Europe-wide population-based cohort of patients with inflammatory bowel disease 10 years after diagnosis. *Gastroenterol. Res. Pract.* **2016**, 5023973 (2016).
207. Beiteke, U., Bigge, S., Reichenberger, C. & Gralow, I. Pain and pain management in dermatology. *J. Dtsch. Dermatol. Ges.* **13**, 967–987 (2015).
208. Wu, X. R. & Shen, B. Diagnosis and management of parastomal pyoderma gangrenosum. *Gastroenterol. Rep.* **1**, 1–8 (2013).
209. Karimkhani, C. et al. Global skin disease morbidity and mortality: an update from the global burden of disease study 2013. *JAMA Dermatol.* **153**, 406–412 (2017).
210. Thomas, K. S. et al. A programme of research to set priorities and reduce uncertainties for the prevention and treatment of skin disease. *Programme Grants for Applied Research* https://doi.org/10.3310/pgfar04180 (2016).
211. Chimento, S. et al. Evaluation of osteopontin expression in chronic wounds: a potential prognostic and therapeutic biomarker. *J. Wound Care* **26**, S4–S8 (2017).
212. Zhang, H., Zeng, Z., Mukherjee, A. & Shen, B. Molecular diagnosis and classification of inflammatory bowel disease. *Expert. Rev. Mol. Diagn.* **18**, 867–886 (2018).
213. Nakken, B. et al. Biomarkers for rheumatoid arthritis: from molecular processes to diagnostic applications-current concepts and future perspectives. *Immunol. Lett.* **189**, 13–18 (2017).
214. Sadik, C. D., Miyabe, Y., Sezin, T. & Luster, A. D. The critical role of C5a as an initiator of neutrophil-mediated autoimmune inflammation of the joint and skin. *Semin. Immunol.* **37**, 21–29 (2018).
215. Woodruff, T. M., Nandakumar, K. S. & Tedesco, F. Inhibiting the C5-C5a receptor axis. *Mol. Immunol.* **48**, 1631–1642 (2011).
216. Feagan, B. G. et al. Induction therapy with the selective interleukin-23 inhibitor risankizumab in patients with moderate-to-severe Crohn's disease: a randomised, double-blind, placebo-controlled phase 2 study. *Lancet* **389**, 1699–1709 (2017).
217. Duchatelet, S. et al. First nicastrin mutation in PASH (pyoderma gangrenosum, acne and suppurative hidradenitis) syndrome. *Br. J. Dermatol.* **173**, 610–612 (2015).
218. Marzano, A. V. et al. Pyogenic arthritis, pyoderma gangrenosum, acne, and hidradenitis suppurativa (PAPASH): a new autoinflammatory syndrome associated with a novel mutation of the PSTPIP1 gene. *JAMA Dermatol.* **149**, 762–764 (2013).
219. Chamot, A. M. et al. [Acne-pustulosis-hyperostosis-osteitis syndrome. Results of a national survey. 85 cases]. *Rev. Rhum. Mal. Osteoartic.* **54**, 187–196 (1987).
220. Hurtado-Nedelec, M. et al. Genetic susceptibility factors in a cohort of 38 patients with SAPHO syndrome: a study of PSTPIP2, NOD2, and LPIN2 genes. *J. Rheumatol.* **37**, 401–409 (2010).
221. Perry, H. O. & Winkelmann, R. K. Bullous pyoderma gangrenosum and leukemia. *Arch. Dermatol.* **106**, 901–905 (1972).
222. Wilson-Jones, E. & Winkelmann, R. K. Superficial granulomatous pyoderma: a localized vegetative form of pyoderma gangrenosum. *J. Am. Acad. Dermatol.* **18**, 511–521 (1988).
223. Powell, F. C., Su, W. P. & Perry, H. O. Pyoderma gangrenosum: classification and management. *J. Am. Acad. Dermatol.* **34**, 395–409 (1996).
224. Ho, K. K.-L., Otridge, B. W., Vandenberg, E. & Powell, F. C. Pyoderma gangrenosum, polycythemia rubra vera, and the development of leukemia. *J. Am. Acad. Dermatol.* **27**, 804–808 (1992).
225. Callen, J. P. & Woo, T. Y. Vesiculopustular eruption in a patient with ulcerative colitis. Pyoderma gangrenosum. *Arch. Dermatol.* **121**, 399–400 (1985).
226. Quimby, S. R., Gibson, L. E. & Winkelmann, R. K. Superficial granulomatous pyoderma: clinicopathologic spectrum. *Mayo Clin. Proc.* **64**, 37–43 (1989).
227. Ahmadi, S. & Powell, F. C. Pyoderma gangrenosum: uncommon presentations. *Clin. Dermatol.* **23**, 612–620 (2005).

228. Brunsting, L. A., Goeckerman, W. H. & O'Leary, P. A. Pyoderma (echthyma) gangrenosum. *Arch. Derm. Syphilol.* **22**, 655–680 (1930).
229. O'Loughlin, S. & Perry, H. O. A diffuse pustular eruption associated with ulcerative colitis. *Arch. Dermatol.* **114**, 1061–1064 (1978).
230. Hughes, A. P., Jackson, J. M. & Callen, J. P. Clinical features and treatment of peristomal pyoderma grangrenosum. *J. Am. Med. Assoc.* **284**, 1546–1548 (2000).
231. Tolkachjov, S. N. et al. Postoperative pyoderma gangrenosum (PG): the Mayo Clinic experience of 20 years from 1994 through 2014. *J. Am. Acad. Dermatol.* **73**, 615–622 (2015).
232. Wang, J. Y. et al. Gangrenosum: a review. *Am. J. Clin. Dermatol.* **19**, 67–77 (2018).
233. Galaria, N. A., Junkins-Hopkins, J. M., Kligman, D. & James, W. D. Neutrophilic dermatosis of the dorsal hands: pustular vasculitis revisited. *J. Am. Acad. Dermatol.* **43**, 870–874 (2000).
234. Walling, H. W., Snipes, C. J., Gerami, P. & Piette, W. W. The relationship between neutrophilic dermatosis of the dorsal hands and sweet syndrome: report of 9 cases and comparison to atypical pyoderma gangrenosum. *Arch. Dermatol.* **142**, 57–63 (2006).

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Competing interests
J.P.C. has ownership of trusts that own stock in Amgen, Pfizer, 3M, Johnson & Johnson, Merck, Abbott Laboratories, AbbVie, Procter and Gamble and Allergen. J.P.C. is a member of a safety monitoring committee for Principia Biopharma. All other authors declare no competing interests.

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