Am J Clin Dermatol (2017) 18:355–372
DOI 10.1007/s40257-017-0251-7

REVIEW ARTICLE

Pyoderma Gangrenosum: An Update on Pathophysiology, Diagnosis and Treatment

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Published online: 21 February 2017

Abstract Pyoderma gangrenosum (PG) is a rare inflammatory neutrophilic disorder with prototypical clinical presentations. Its pathophysiology is complex and not fully explained. Recent information regarding the genetic basis of PG and the role of auto-inflammation provides a better understanding of the disease and new therapeutic targets. PG equally affects patients of both sexes and of any age. Uncontrolled cutaneous neutrophilic inflammation is the cornerstone in a genetically predisposed individual. Multimodality management is often required to reduce inflammation, optimize wound healing, and treat underlying disease. A gold standard for the management of PG does not exist and high-level evidence is limited. Multiple factors must be taken into account when deciding on the optimum treatment for individual patients: location, number and size of lesion/ulceration(s), extracutaneous involvement, presence of associated disease, cost, and side effects of treatment, as well as patient comorbidities and preferences. Refractory and rapidly progressive cases require early initiation of systemic therapy. Newer targeted therapies represent a promising pathway for the management of PG, and the main focus of this review is the management and evidence supporting the role of new targeted therapies in PG.

Key Points

Pyoderma gangrenosum (PG) encompasses a complex neutrophilic reaction pattern that creates heterogeneous disease presentation and course.

Dermatologists are frequently challenged with the diagnosis of PG. There is a need for an update on a systematic approach to management and new therapeutic strategies for patients with PG.

The current management of PG is based on reducing inflammation through anti-inflammatory and immunosuppressive actions.

1 Introduction

Pyoderma gangrenosum (PG) is a prototypic autoinflammatory neutrophilic dermatosis characterized by a spectrum of clinical presentations with variable courses, and has an increased cytokine and chemokine expression in lesional skin [1, 2]. PG is considered a 'diagnosis of exclusion' due to the lack of definitive laboratory or histopathological diagnostic criteria and is thus frequently misdiagnosed [3]. Several factors contribute to the pathophysiology of PG. The patient's genetic background likely alters the immune response affecting both innate and adaptive immune systems, and the aberrant activation of innate-immune complexes termed

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'inflammasomes' leads to increased levels of cytokines that contribute to neutrophilic tissue infiltration. Evidence-based management of patients with PG is limited by the paucity of randomized controlled trials to support treatment outcomes. Treatment options are therefore largely based on expert opinion and anecdotal data from available case reports, small case studies, and a handful of randomized clinical trials (RCTs) [4, 5]. Emerging evidence, coupled with improved understanding of PG pathophysiology, suggest potential targets for therapy. This review provides an update on the clinical presentation, complex pathophysiology, and diagnosis and management of PG.

2 Pathophysiology

The pathophysiology of PG remains incompletely understood. It represents a complex reaction pattern with either multiple pathways or the convergence of various features that creates a heterogeneous disease presentation and course. Dysregulation of the innate immune system, as well as abnormal chemotaxis, neutrophil migration, phagocytosis, bactericidal ability, and abnormal neutrophil trafficking, have been reported in patients with PG [7, 8]. Table 1 lists different clinical presentations of PG. Factors contributing to the clinical manifestations of PG include neutrophil dysfunction, genetic mutations, and abnormal inflammation.

2.1 Neutrophil Dysfunction

PG is considered one of the rare neutrophilic dermatoses, typified by aseptic neutrophilic infiltration and systemic inflammation [6]. It is also associated with other neutrophilic or inflammatory disorders such as inflammatory bowel disease (IBD), rheumatoid arthritis (RA), seronegative arthritis, autoimmune hepatitis, and hematologic disorders, including paraproteninemia, especially immunoglobulin (Ig) A, and neutrophilic malignancies such as acute myelogenous leukemia (AML). In the study by Magro et al. a clonality of neutrophils unrelated to underlying myeloid dyscrasia is seen in both PG and Sweet syndrome [9]. The presence of clonal T-cell expansion has been reported in lesions of PG, which supports the possibility of an aberrant T-cell response. PG has been described in cases of neutropenia or in the setting of leukocyte adhesion deficiency type 1 [10–12]. Furthermore, the presence of neutropenia or neutrophilia is a paradox with a nebulous significance [13].

2.2 Genetic Influence

Certain genetic similarities exist between IBD and PG. They both have increased mediators of neutrophil migration (*Loci IL-8RA*), PR domain-containing protein, and tissue inhibitor of metalloproteinase 3, which are associated with the development of auto-immune diseases [14]. Inflammasomes are multiprotein oligomers often expressed in myeloid cells and keratinocytes.They may be involved in the recruitment/activation of polymorphonuclear neutrophils (PMN), as exemplified in cases associated with a mutation in the gene *proline–serine–threonine phosphatase-interacting protein 1* (*PSTPIP1*) on chromosome 15. More importantly, tumor necrosis factor receptor-associated factor (TRAF) interacting protein 2 is a genetic locus found to be associated with IBD and increased sensitivity to develop concurrent PG. Braswell et al. [14] suggest the sharing of these genetic loci may reveal a common pathway for the development of IBD and PG, as well as another tumor necrosis factor (TNF)-responsive disease, psoriasis. A defect in methylenetetrahydrofolate reductase, which can lead to a risk of hypercoagulability and ulcers, has been linked to PG-like skin ulcers [14]. A mutation affecting Janus kinase (JAK) 2, a non-receptor tyrosine kinase involved in signaling via several cytokines, including the granulocyte monocyte colony-stimulating factor (GM-CSF) receptor family, is also implicated in the pathogenesis of myeloproliferative disorders and has recently been reported in PG [15, 16]. GM-CSF is thought to have a potential role in neutrophilic dermatoses through its action on adhesion and proliferation of neutrophils [14, 15]. GM-CSF can stimulate macrophages and neutrophils, leading to the production of inflammatory mediators and interleukin (IL)-17 cytokines [15].

The genetic implications in PG are best illustrated in the PG-associated genetic syndromes. PG is part of the pyogenic arthritis, pyoderma gangrenosum, acne (PAPA) syndrome, an autoinflammatory disease with excessive IL-1 production (see Table 2 for a list of the syndromes associated with PG). Pyoderma gangrenosum, acne, suppurativa hidradenitis (PASH) and pyoderma arthritis, pyoderma gangrenosum, acne, suppurativa hidradenitis (PAPASH) all have mutations in the *PSTPIP1* gene, which encodes for CD2-binding protein 1 [17]. Mutated *PSTPIP1* by increased binding to pyrin (Fig. 1) leads to a myriad of effects such as decreased inhibition of inflammasomes with activation of caspase 1, increased IL-1B and IL-18 production, and, ultimately, driving the neutrophilic infiltration associated with the aforementioned syndromes [15, 16, 18].

2.3 Inflammation

Elevated levels of inflammatory mediators have been found in lesions of PG, suggesting a pathological inflammatory process. Histologic features include mature, normal-looking neutrophils in the dermis, but various studies have shown them to be functionally abnormal, while, in certain patients, they have shown to have an increased integrin expression or dysregulated integrin signaling [1].

Table 1 Different variants of pyoderma gangrenosum

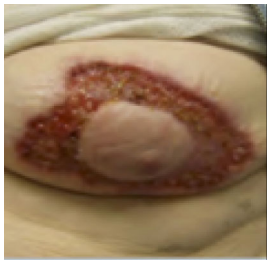
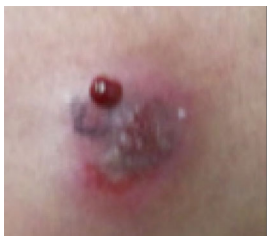
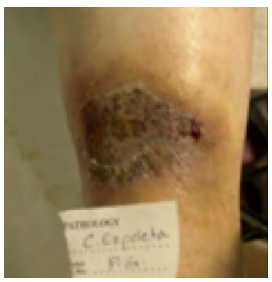
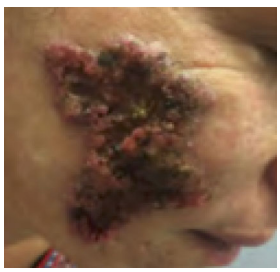
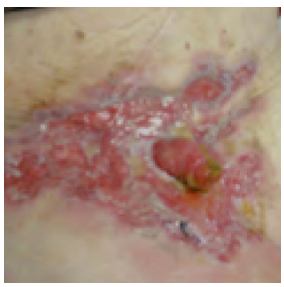
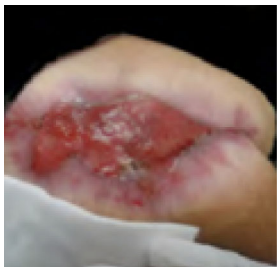
Subtype	Morphology	Common locations	Clinical clues	Associated diseases
Ulcerative		Lower extremities	Rapid progression Violaceous undermined border	IBD Arthritis Myeloproliferative Others
Bullous		Face	Superficial bulla with blue-gray border	Myeloproliferative disease (mainly acute myelogenous leukemia)
Pustular		Legs Upper trunk	Painful pustule with red halo	IBD
Vegetative		Trunk	Superficial ulver No violaceous border	No association
Peristomal		Near ostoma site	Painful ulcer with undermined violaceous border	IBD (0.5% of ulcerative colitis and 0.3% of Crohn's disease) Enteric malignancies

Table 1 continued

Subtype	Morphology	Common locations	Clinical clues	Associated diseases
Post-surgical		Surgery site mainly breast and trunk	Rapid progression, with active border and undermining	Surgical procedures

IBD inflammatory bowel disease

Table 2 Pyoderma gangrenosum-associated syndromes

Associated syndrome		Gene	Treatment
PAPA	Pyogenic arthritis, pyoderma gangrenosum, acne	*PSTPIP1* [105]	IL-1 receptor antagonist [106] TNFα inhibitors [107, 108] Systemic corticosteroids [109]
PASH	Pyoderma gangrenosum, acne, suppurativa hidradenitis	*PSTPIP1* [110, 111] *NCSTN* [100]	IL-1 receptor antagonist [97] Cyclosporine [112] Systemic corticosteroids [111] TNFα inhibitors (infliximab) [113] Cyclosporine [113] Dapsone [113]
PASS	Pyoderma gangrenosum, acne conglobata, suppurativa hidradenitis, seropositive spondyloarthropathies	NA [114]	TNFα inhibitors [115]
PAPASH	Pyogenic arthritis, pyoderma gangrenosum, acne, suppurativa hidradenitis	*PSTPIP1* [17]	IL-1 receptor antagonist [116] TNFα inhibitors [116]
PsAPASH	Psoriatic arthritis, pyoderma gangrenosum, acne, suppurativa hidradenitis	NA [83]	TNFα inhibitors [83]

NA not applicable, *IL* interleukin, *TNF* tumor necrosis factor

T-cell and macrophage involvement occurs at wound edges of PG ulcers, where elevated levels of CD3+ T cells, as well as CD163+ macrophages, have been reported. IL-8 (chemokine [C-X-C motif] ligand 8 [CXCL8]), also known as neutrophil chemotactic factor, has been found in the wound bed [14]; thus, T cells and macrophages likely play a key role in disease pathogenesis through abnormal cytokine signaling [19]. Additionally, Caproni et al. [20] found a decreased ratio of T regulatory to T helper (Th) 17 effector cells in the PG lesions, and proposed anti-IL-17 as an alternative treatment. There is also a distinct abnormality in peripheral blood expression of chemokines supporting lymphocyte polarization towards a Th1/Th17 phenotype with Th2 and T regulatory cells (Treg) downregulation [21].

Proinflammatory cytokine expression, IL1β and its receptor, as well as IL-8 ($p = 0.0001$), Fas, FasL, CD40, CD40L, CXCL 1/2/3, CXCL 16, and regulated upon activation normal T-cell expressed and secreted (RANTES) have been found to be significantly increased in PG lesions [7, 22, 23]. IL-23, a cytokine that plays an important role in driving IL-17-mediated and neutrophil-rich inflammation, has recently been shown to be upregulated at the gene expression and protein level in PG lesions [24]. Elevated levels of IL-23 are found in IBD and psoriasis, similar to lesions of recalcitrant PG, suggesting certain pathogenic characteristics between the diseases that may influence disease progression [16]. Finally, mutations in JAK-2, a non-receptor tyrosine kinase implicated in signaling by members of the type II cytokine receptor family, such as interferon receptors and the GM-CSF receptor, and associated with myeloproliferative disorders, have been reported in single cases of bullous PG [16, 25].

3 Clinical Presentations

PG presents itself clinically in varied ways, and thus diagnosing can be challenging. PG affects individuals of all ages, with a peak incidence between 20 and 50 years of age, and affects men and women almost equally [1]. Legs

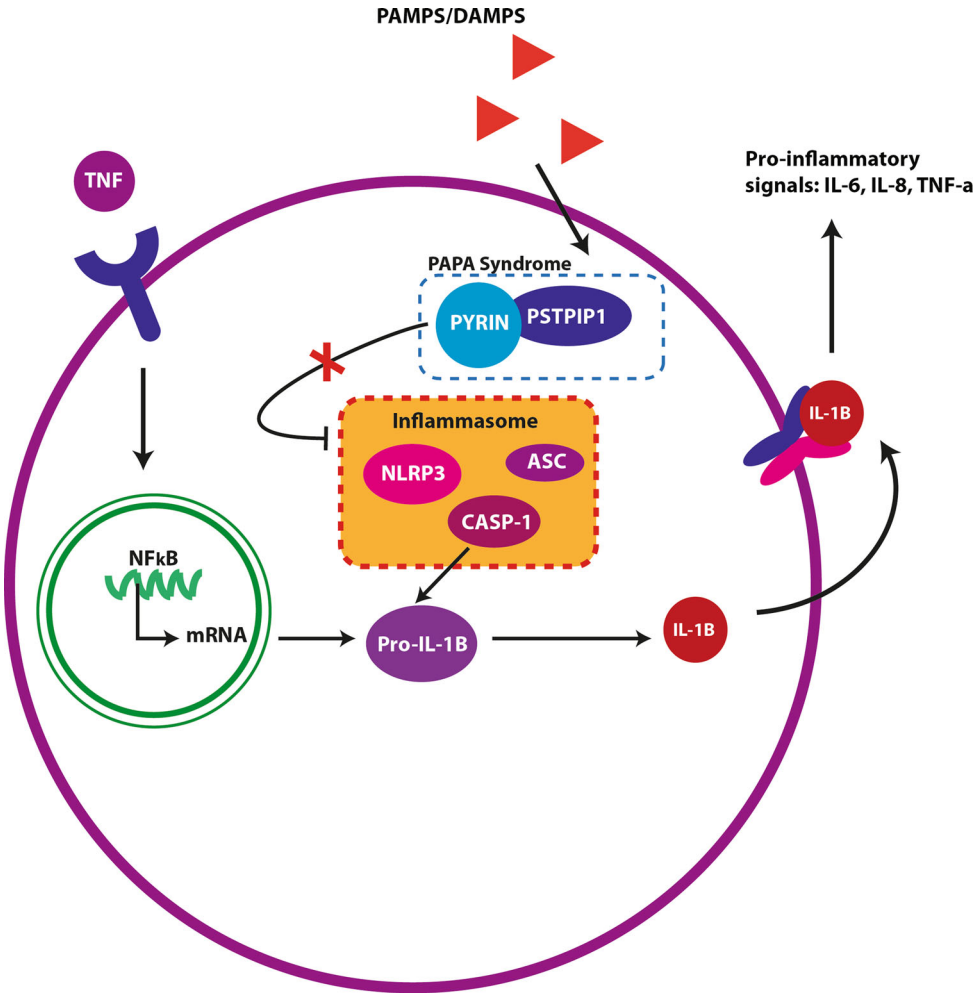


Fig. 1 Mutations in a protein called proline serine threonine phosphatase-interacting protein 1 (*PSTPIP1*) are linked to several auto-inflammatory pyoderma gangrenosum syndromes such as PAPA and PASH. Normally, pyrin inhibits inflammasome activation, however the *PSTPIP1* mutant inhibits the anti-inflammatory effect of pyrin, which leads to the release of pro-inflammatory cytokines such as IL-1β, IL-6, IL-8, and TNFα, which further amplify the inflammatory response. *DAMP* damage-associated molecular pattern, *PAMP* pathogen-associated molecular pattern, *TNF* tumor necrosis factor, *IL* interleukin, *NFkB* nuclear factor kappa B, *mRNA* messenger ribosomal nuclear acid, *NLRP3* NOD-like receptor protein 3, *ASC* apoptosis-associated speck-like protein containing a CARD, *CASP 1* caspase 1, *PAPA* pyogenic arthritis, pyoderma gangrenosum, acne, *PASH* pyoderma gangrenosum, acne, suppurativa hidradenitis

are most commonly affected but head and neck involvement is not uncommon in children, while involvement of the genital and perianal area has been reported in infants [26]. The currently recognized clinical variants of PG are classic, bullous, pustular, vegetative, drug-induced, post-surgical, and peristomal [1, 27]. Pathergy, an exaggeration of a skin injury occurring after minor trauma, is seen in one-third of patients with PG and can contribute to the pathogenesis of peristomal and post-surgical PG (PSPG). PSPG occurs at the site of surgery, most commonly reported after breast, chest, or cardiothoracic surgery.

The course of PG can vary greatly, from relatively indolent (Fig. 2) to aggressive or fulminant (Fig. 3) [28]. Table 1 summarizes the different PG variants and commonly associated conditions [1]. Although it is not common, PG has been reported in association with pregnancy, a condition known to be associated with progressive neutrophilia, which culminates in a major inflammatory event to help drive labor [15].

Classic ulcerative PG has two distinct stages—the ulcerative and healing stages. The ulcerative stage presents as a rapidly progressive wound with a peripheral red halo with raised, red-purple, undermined edges. The centers consist of non-specific necrosis with a purulent or granulomatous base, but the borders are active [29]. Severe pain often accompanies lesion development, especially when rapid progression occurs. In the healing stage, the wound edge has projections of epithelium extending into the ulcer, known as Gulliver's sign, and heals with distinctive 'cigarette paper-like' or cribriform scars (perforating or sieve-like) [7].

Bullous PG often begins at atypical sites, such as the face, dorsum of the hands, or extensor surfaces of the arms; other known disease entities, such as neutrophilic dermatosis of the hands, may represent a spectrum of disease [1]. Bullous PG is significantly associated with underlying hematological malignancy, particularly AML [30]. Pustular PG presents with sterile pustules, with a red halo, and with these lesions most frequently occurring on the trunk and extensor surfaces of limbs. Among PG subtypes, pustular PG is most commonly associated with IBD [7]. Vegetative PG generally presents as an isolated, erythematous warty

eroded and ulcerated plaque, lacking the erythematous border observed in classic PG, is the most uncommon and benign subtype, and is least frequently associated with underlying systemic disorders [1]. Peristomal PG (PPG), a form of pathergy, appears in patients with stomas, as in patients with IBD, and may also occur in patients with urostomies [30]. PSPG, another form of pathergy, is characterized by the development of PG at the site of surgery, either immediately after surgery or within 7–11 days of the procedure [29, 31–33], with the majority of cases occurring following breast, chest, or cardiothoracic surgery [31, 32]. Only one in six patients have a previous history of PG [33]. In case of breast involvement, the nipple is commonly spared [33].

Drug-induced PG is scarce but recently there have been more reported cases in the literature, particularly in relation to new targeted therapies, including gefitinib, imatinib, sunitinib, granulocyte colony-stimulating factor (G-CSF), and biologics (see Table 3 for a list of medications that have been reported in drug-induced PG). Although the pathogenesis of drug-induced PG is unclear, most PG lesions resolve after discontinuation of medication. There are reports of induction after rechallenge with the same drug [34].

4 Associated Conditions and Extracutaneous Manifestations

PG is associated with underlying diseases in up to 75% of cases, most frequently with IBD, inflammatory arthritis, and hematological disorders [35, 36]. In a systematic review of the literature, DeFilippis et al. identified 208 articles describing 823 cases of PG [37]. Overall, when associated conditions were present, IBD was seen in 65.2% (537) of cases, polyarthritis in 16.1% (133), and hematological disorders in

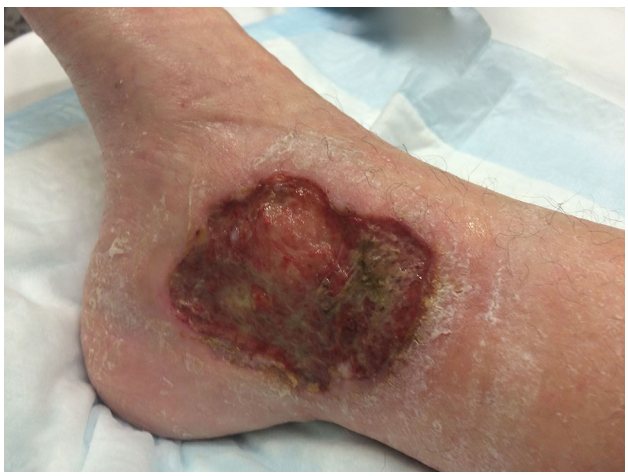


Fig. 2 Classic PG, ulceration with erythematous border on the lower extremity. *PG* pyoderma gangrenosum

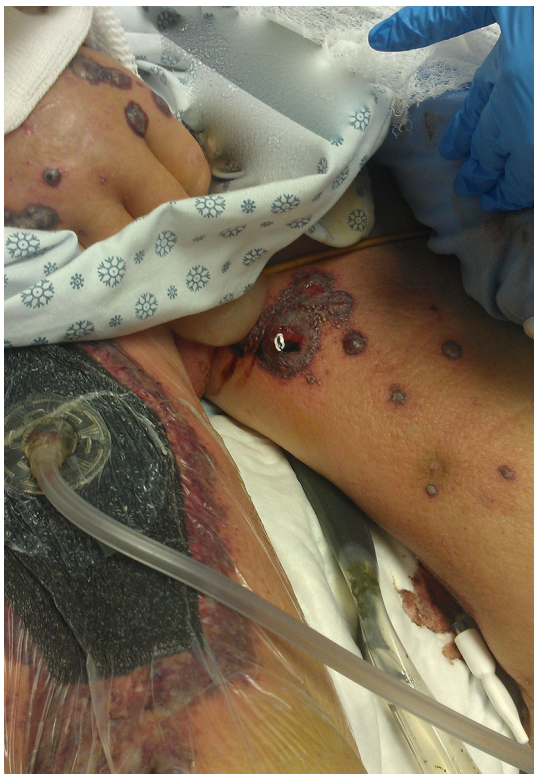


Fig. 3 Aggressive PG with multiple widespread infiltrated plaques and ulcers. *PG* pyoderma gangrenosum

12.5% (103) of patients with PG [37]. In another series by Binus et al., which included 103 patients with PG, 34% had IBD, 20% had hematological disorders, 19% had arthritis, and 27% were idiopathic [38]. PG is the second most common cutaneous manifestation of IBD, with a prevalence of 0.5% in IBD cases, being more common in ulcerative colitis than in Crohn's disease [39]. The overall mortality rate of PG during an 8-year retrospective study was reported to be 16% [38], and, in a case series of 26 patients, 27% died [40].

PG may involve extracutaneous sites, thus affecting the prognosis and choice of treatment. Extracutaneous involvement has been reported for the eyes (scleritis, corneal ulceration), lungs (aseptic pulmonary nodules), spleen, and musculoskeletal system (sterile polyarthrosis, neutrophilic myositis) [1, 41–43]. Although pulmonary involvement is rare in patients with PG, it is more commonly reported in patients with underlying diseases [44]. The reported pulmonary manifestations include nodules with or without cavitation, interstitial lung disease, and pleural effusions [45].

5 Differential Diagnosis

No specific serologic markers exist for PG, and the histopathology is non-specific, as well as variable, depending on the PG subtype and stage of disease

[7, 46, 47]. Therefore, there are many disorders to be considered in the differential diagnoses of PG, which explains the complexity of the PG diagnosis [7, 48]. Table 4 lists common differential diagnoses and relevant investigations. An important part of the diagnostic work-up in PG is to exclude all possible differential diagnoses. Ahronowitz et al. [1] suggested that the minimum evaluation should include a complete history, physical examination, and skin biopsies (a skin biopsy should include the active border of the ulcer and penetrate deep to subcutaneous tissue). Tissue culture to exclude bacterial, atypical mycobacterial, and deep fungal infections is also recommended, however there is no universally accepted diagnostic criterion for PG. In a recent survey-based study from Germany, the erythematous active border, rapid progression of an undermined border, and exclusion of other differential diagnoses were the most important diagnostic clues for PG [49].

5.1 Proposed Diagnostic Criteria

An accepted and validated diagnostic criterion for PG is still lacking. Using a survey-based questioner of 57 patients with PG, researchers from Germany proposed several potential diagnostic criteria, such as erythematous-violaceous undermined borders, rapid progression, exclusion of relevant differential diagnoses, and rapid response to immunosuppressive treatment [50].

Su et al. proposed diagnostic criteria where one [51] of the two major criteria is the exclusion of other causes of cutaneous ulceration, a must if considering a diagnosis of PG [20]. Their proposed criteria for PG include the fulfillment of two major and two minor criteria, as listed in Table 5 [51]. Due to the chronic nature of PG, after healing in some cases, long-term maintenance therapy has to be considered for the prevention of potential relapses [28, 51].

Table 3 Medications reported to cause drug-induced pyoderma gangrenosum

Class	Drugs
Antithyroid medications	Propylthiouracil [117–120]
Retinoids	Isotretinoin [121, 122]
	Alitretinoin [123]
Biologics	Adalimumab [124]
	Infliximab [125]
	Rituximab [126]
Tyrosine kinase inhibitors	Gefitinib [127]
	Sunitinib [128–131]
	Imatinib [34]
Colony-stimulating factor	G-CSF [132–136]
Miscellaneous	Levamisole [137]
	Azacitidine [138]
	Hydroxycarbamide [139]

G-CSF granulocyte colony-stimulating factor

PG is a multifaceted neutrophilic dermatosis that features neutrophilic dysfunction, genetic influence, and a strong link with other inflammatory or neoplastic diseases, most notably IBD, arthritis, and hematological disorders [48]. PG has a major clinical and diagnostic presentation in several mono- or polygenetic diseases, including PAPA, PASH, PAPASH, pyoderma gangrenosum, acne conglobata, suppurativa hidradenitis, seropositive spondyloarthropathies (PASS), and psoriatic arthritis, pyoderma gangrenosum, acne, suppurativa hidradenitis (PsAPASH) syndromes. Shared proinflammatory pathways and/or molecules may underlie common aspects of the pathogenesis of PG, IBD, and psoriasis [7].

6 Management of Pyoderma Gangrenosum

PG is challenging to both diagnose and manage, and treatment is directed towards reducing the associated inflammation that leads to ulceration. The choice of treatment depends on numerous factors, including the location of lesion(s), number, size, extracutaneous involvement, presence of associated diseases, cost, and side effects of treatment, as well as patient comorbidities and preferences. The recognition and treatment of underlying disease such as IBD or arthritis is an important facet of management, although a direct relationship between the severity of associated disease and PG is an issue of debate. The course of PG can vary greatly, from a relatively indolent (limited) course, to an aggressive, occasionally explosive course. In the majority of cases of PG, the lesions are limited to one to three, with less than 5% of body involvement [52]. Optimal management may include the clinically relevant aspects of PG: avoidance of triggers, appropriate wound care, adequate pain management, and topical, systemic and targeted immunomodulatory therapies [53]. Systemic therapy includes high-dose corticosteroids as first-line therapy, while cyclosporine and TNF inhibitors have proved useful as second- and third-line therapies, but are not always successful [4, 54–59]. For patients with or without ulcers with limited disease (e.g. PPG), topical and intralesional therapy may be sufficient to achieve disease control without the need for systemic therapy. A suggested algorithm for treatment based on patient course is illustrated in Fig. 4.

Wound care is an essential part of management. Appropriate dressings and control of edema for limb wounds with compression therapy (in the absence of significant arterial insufficiency) are essential to promote healing. In addition, management of pain is an important aspect of care. Ulcers that develop in patients with PG may

Table 4 Diagnostic algorithm for pyoderma gangrenosum

Complete history, physical examination, biopsy				
Pyoderma gangrenosum work-up guided by history				
Main differential diagnoses				
Infection	*Vasculitis and autoimmune*	*Neutrophilic*	*Vascular*	*Exogenous*
Deep fungal—blastomycosis, sporotrichosis	Behcet's	Sweet syndrome	Martorell ulcer	Factitious
Protozoa—leishmaniasis	Vasculitis		Arterial	Insect bite
Bacterial—ecthyma	Cryoglobulinemia		Venous	
Viral—herpes simplex	Antiphospholipid syndrome			
	Lupus (lupus-associated neutrophilic dermatoses)			
Special stains	ANCA	Clinical	Deep elliptical biopsy	History
Cultures	Blood work		Duplex	Serum bromide and iodide
Chest X-ray	Urinalysis		ABPI or angiography	
	DIF			
	Coagulopathy panel			
	ANA, anti-DNA			

ABPI ankle brachial pressure index, *ANCA* anti-neutrophil cytoplasmic antibody, *ANA* antinuclear antibody, *DIF* direct immunofluorescence

Table 5 Proposed diagnostic criteria for pyoderma gangrenosum [51]

Diagnostic criteria: two major and two out of four minor	
Major criteria	Minor criteria
1. Rapid progression of a painful, necrolytic, cutaneous ulcer with an irregular, violaceous border	1. History suggestive of pathergy or clinical finding of cribriform scarring
2. Exclusion of other causes of cutaneous ulceration	2. Systemic diseases associated with pyoderma gangrenosum
	3. Compatible histopathological findings
	4. Response to treatment

be among the most painful ulcers dermatologists manage. Inadequate treatment of pain may result in stress, anxiety, and depression, which may have a negative impact on quality of life and slows or inhibits healing. Topical agents, as well as systemic acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs), and opiates can be selected to address pain.

The main principles of proper wound care include adequate but gentle cleansing, appropriate use of antibacterial agents in the presence of critical colonization (replicating microbial burden in the wound surface compartment with subtle clinical signs of host injury), and maintenance of a moist wound environment (not overly dry or wet). Wound cleansing is part of standard care, but conservative debridement (enzymatic, autolytic, or blunt surgical) to remove non-viable tissues, while it may reduce bioburden and odor, needs to be carried out cautiously. Aggressive surgical (sharp) debridement, and the use of strong adhesives, should be avoided due to the possibility of inducing pathergy, further exacerbating the ulcerations [32].

6.1 Topical and Intralesional Treatments

Patients with small PG lesions (less than 2 cm square) may respond to topical or intralesional therapy. Topical corticosteroids and intralesional corticosteroids can be used on the active border of PG surrounding the ulcerated areas. In a study of five patients with PG using topical tacrolimus, induced complete remission was achieved in all five patients in a mean time of 6 weeks [52]. Other reported treatments include sodium cromoglycate, nicotine, topical dapsone [60] and 5-aminosalicylic acid [7]. Almost all data on topical therapies in PG are based on case reports or case series with small sample sizes [61].

6.2 Systemic Treatments

Systemic corticosteroids, considered to be first-line therapies for progressive, severe, or disfiguring disease [62], either as oral prednisone (0.5–1 mg/kg/day) or intravenous pulse corticosteroid (1000 mg/day), have been used and the

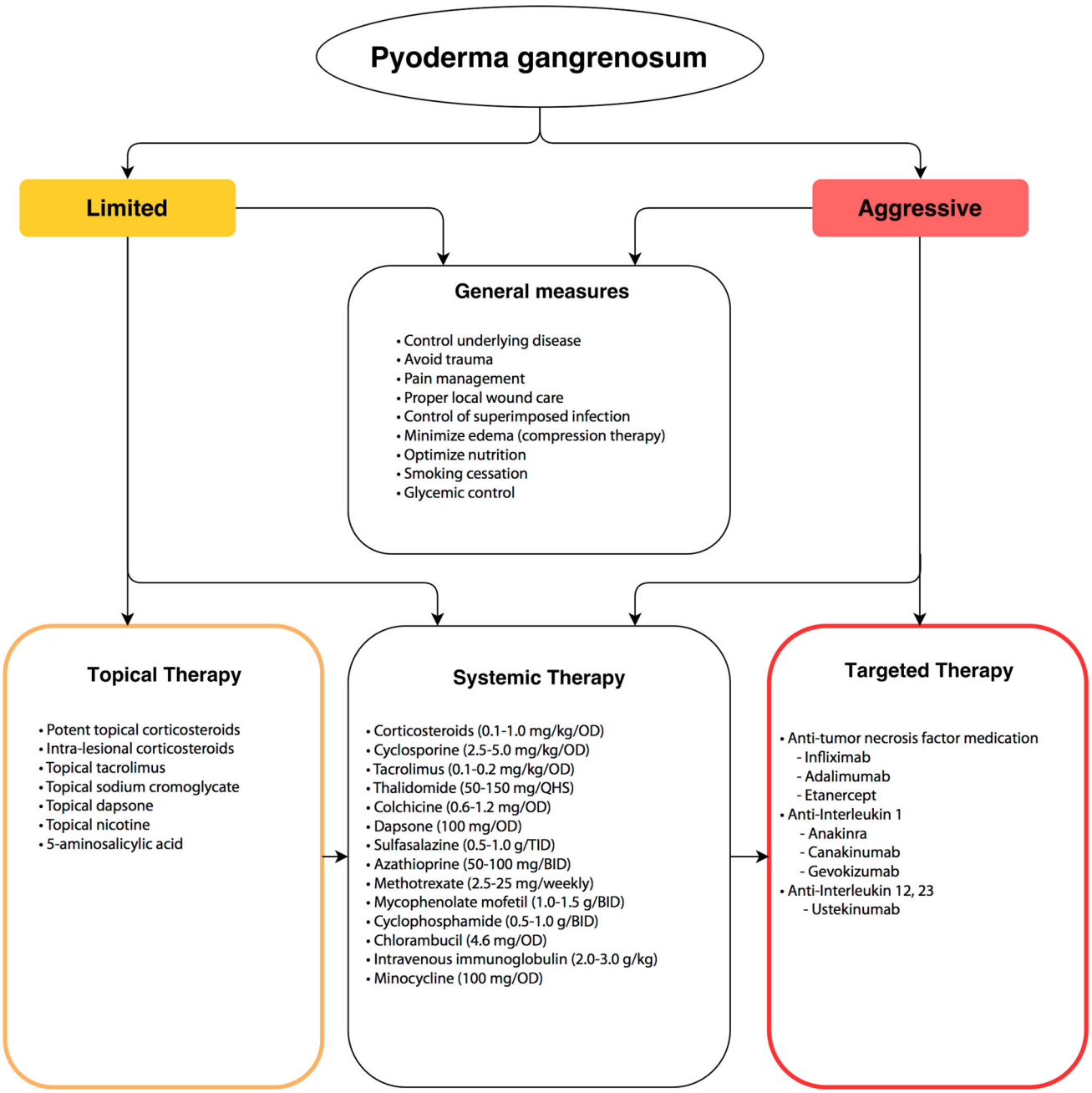


Fig. 4 Algorithm for the management of pyoderma gangrenosum. *BID* twice daily, *OD* once daily, *QHS* every night, *TID* three times daily

response can be seen within 2–3 days [63]. The adverse effects of long-term corticosteroids (including osteopenia, weight gain, glaucoma, cataracts, hyperglycemia, diabetes, Cushing syndrome, immunosuppression, adrenal insufficiency, and corticosteroid psychosis, among others) must be monitored for, and often restrict long-term use of systemic corticosteroids. Cyclosporine (2.5–5 mg/kg/day) is frequently used as second-line treatment and may be effective, especially in corticosteroid-resistant cases. The use of cyclosporine is also limited by side effects, including renal insufficiency and hypertension.

Ormerod et al. [64] performed a study comparing oral prednisolone 0.75 mg/kg/day with cyclosporine 4 mg/kg/day, to a maximum dose of 75 and 400 mg/day, respectively, in 121 patients with PG. Both groups showed the same outcome, with 47% of patients in both the cyclosporine and prednisolone groups completely healing. In those with healed ulcers, eight (30%) receiving cyclosporine and seven (28%) receiving prednisolone had a recurrence.

In 1997, Reynoso-von Drateln et al. [65] performed an open-label study of nine patients with PG with intravenous

cyclophosphamide 500 mg/m^2 body surface area every month until reaching a maximum of six doses, or healing of their ulcers or a lack of response after three doses; seven patients achieved complete healing. The successful use of other common immunosuppressive agents has also been reported in PG, including methotrexate, mycophenolate mofetil, sulfasalazine, and azathioprine [66, 67]. However, taken together there is a lack of controlled trials demonstrating the efficacy of any of these agents (Fig. 5). The use of targeted therapies, such as biologics, has broadened available therapeutic options for the management of PG. In this review, we focus on the value of biologics and the best available evidence supporting their use in the management of PG.

6.3 The Role of Biologics

Targeted therapies are changing the management of many dermatological conditions, including psoriasis and hidradenitis suppurativa. PG has been reported to improve with biologic therapy, most notably with TNF and IL-1β antagonists.

Overactivation of the innate immune system plays an essential role in the pathogenesis of PG. High levels of IL-8, and TNFα are associated with neutrophilic infiltration, characteristic of PG [18, 29]. Recent studies on cytokine expression profile in lesional skin of PG demonstrated the overexpression of IL-1β, a potential proinflammatory cytokine [29]. Additionally, several syndromes associated

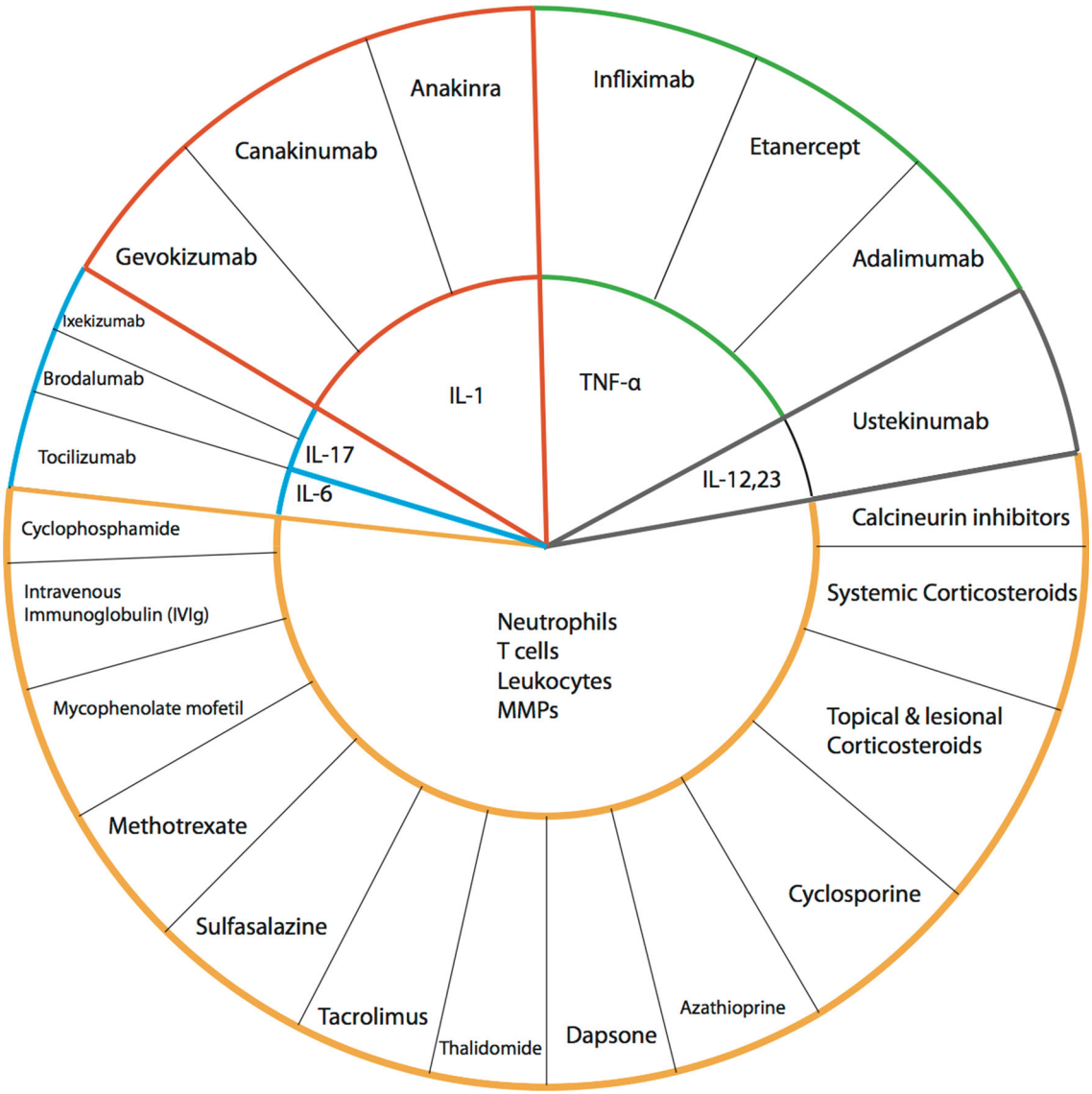


Fig. 5 Targeted and traditional immunosuppressive therapy for pyoderma gangrenosum organized by drug targets. *IL* interleukin, *TNF* tumor necrosis factor, *MMPs* matrix metalloproteinases

with PG have helped shed light on the pathogenesis of the disease. In PAPA syndrome, mutations in proline–serine–threonine phosphatase-interacting protein 1 (*PSTPIP1/CD2BP1*) lead to activation of the cytosolic multimeric inflammasome protein complex, and subsequently maturation of the inflammatory cytokines IL-1β and IL-18 [18, 68].

While evidence for off-label use of biologic response modifiers in PG exists, most is anecdotal and limited [69–71]. A number of small case series describe the use of the TNF antagonists for PG (etanercept, adalimumab, infliximab) [Fig. 5]. The only RCT performed used infliximab, which demonstrated benefit, but this level of evidence does not exist for other TNF antagonists. Table 6 lists the evidence for the use of selected biologics in the management of PG.

6.3.1 Anti-Tumor Necrosis Factor Agents

PG often improves with TNF antagonists and, with the exception of etanercept, TNF antagonists are effective in treating coexisting IBD. The most studied TNF-antagonists are listed here.

6.3.1.1 Infliximab Infliximab, a chimeric monoclonal antibody against TNFα, exerts effects on anergic regulatory T cells to restore their ability to inhibit cytokine production [53, 72–74].

In the RCT led by Brooklyn et al. [72], 30 patients with PG were randomized to receive infliximab or placebo. The infliximab group had a decrease in ulcer size, an increase in healing rate, quality of life improvement, and disease remission compared with placebo. The clinical response to infliximab 5 mg/kg administered intravenously for 6 weeks was 69 versus 21% in the control group [72, 74–76]. While, to date, this is the only RCT for PG, its sample size is small and the results of this small RCT need to be confirmed in larger trials. The results of small retrospective studies and case reports showed favorable results and are listed in Table 6 [77].

6.3.1.2 Adalimumab Several studies examined the treatment of a total of nine patients with PG using adalimumab. All reported patients responded positively to therapy, as defined by decrease in ulcer size, and five patients achieved complete healing with treatment [74, 78–83]. Patel et al. [28] suggested adalimumab is a potential treatment for therapy-resistant PG. This evidence suggests adalimumab (40 mg every 2 weeks) may be useful for the treatment of PG as use in other diseases suggests a good safety profile. The number of cases is limited and more clinical evidence is required [84, 85].

6.3.1.3 Etanercept Etanercept may be useful in the treatment of refractory PG [86] but appears to offer less efficacy compared with infliximab in the management of PG associated with active Crohn's disease [87]. Eleven patients with PG receiving etanercept have been reported, with eight cases associated with complete healing [86, 88–94].

6.3.2 Anti-Interleukin (IL)-12/IL23

Ustekinumab is the only IL-23 inhibitor reported to improve PG. Two patients with PG were successfully treated with ustekinumab [95]; however, more studies are necessary to establish the efficacy of this agent in the treatment of PG [24, 96].

6.3.3 IL-1 Antagonists

The role of IL-1 antagonists in the management of PG is promising but is limited by a paucity of evidence.

6.3.3.1 Canakinumab Canakinumab is a human anti-IL-1β monoclonal antibody (without cross-reactivity against other IL-1 family members) [97]. It is approved for use in cryopyrin-associated periodic syndromes (CAPS) and is also used to treat auto-inflammatory syndromes associated with increased caspase-1 [98]. In a recent study by Kolios et al. [68], five patients with corticosteroid-refractory PG in whom canakinumab was administered subcutaneously at a single dose of 150 mg at weeks 0 and 2, and a dose of 150–300 mg at week 4, were reported. Four of the five patients had a decrease in wound size, an improved Physician Global Assessment (PGA) score, and an improved Dermatology Life Quality Index (DLQI), while three of five patients achieved complete healing at week 16 [68]. Limited by its small sample size, the results are nonetheless promising for PG.

6.3.3.2 Anakinra Anakinra is a recombinant, non-glycosylated form of IL-1 receptor antagonist used to treat RA and cryopyrinopathies.

Three studies of patients with PG with or without associated disease and treated with anakinra have been published [99–101]. In their review, Lipsker and Lenormand [102] suggested anakinra may be less efficacious in managing PG, based on its relative effect in RA or cryopyrinopathies.

6.3.3.3 Gevokizumab As an IL-1β antagonist, gevokizumab has shown efficacy in patients with Behcet's disease, pustular psoriasis, and PAPA syndrome, but has not been reported for the treatment of PG, or PG associated

Table 6 Current evidence for biologic therapy in the treatment of pyoderma gangrenosum

Author, year	Study type (no. of subjects)	Regimen	Outcomes
Infliximab			
Zampeli et al., 2015 [141] Campos-Munoz et al., 2014 [76] Andrisani et al., 2013 [46] Tada et al., 2010 [53] Chan et al., 2010 [75] Akhras et al., 2009 [142] Adisen et al., 2007 [73] Ferkolj et al., 2006 [143] Stichweh et al., 2005 [144] Swale et al., 2005 [145] Mimouni et al., 2003 [146] Batres et al., 2002 [147] Grange et al., 2002 [148] Triantafillidis et al., 2002 [149]	Case reports (16)	Infliximab (5 mg/kg) weeks 0, 2, and 4, then maintenance dose	Complete healing Decrease ulcer size Decrease inflammatory markers Increase healing rate Less recurrence Less pain
Ljung et al., 2002 [150]	Case series (8)	Infliximab (5 mg/kg)	Complete healing Less recurrence
Arguelles-Arias et al., 2013 [151]	Retrospective observational study (67)	Oral corticosteroids vs. infliximab and adalimumab	Complete healing Increase healing rate
Regueiro et al., 2003 [152]	Retrospective study (13)	Infliximab (5 mg/kg) over a 4-year period (ranging from 1 day–4 years)	Increase healing rate Complete healing Less recurrence
Brooklyn et al., 2005 [72]	RCT (30)	13 patients received infliximab vs. 17 patients receiving placebo After week 2, 23 patients did not improve, and all received open-label infliximab	Decrease ulcer size and depth (at week 2) Less undermining of ulcer edge Increase healing rate Improve DLQI
Adalimumab			
Sagami et al., 2015 [84] Saraceno et al., 2015 [83] Hinterberger, 2012 [153] Reddick et al., 2010 [85] Zold et al., 2009 [78] Heffernan et al., 2007 [80] Pomerantz et al., 2007 [81] Fonder et al., 2006 [74] Hubbard et al., 2005 [82]	Case reports (9)	Adalimumab (40–80 mg) every other week. Hubbard et al. used intravenous infliximab (5 mg/kg) at weeks 0, 2, 6 and 16; after recurrence at 16 weeks, 40 mg/week for 3 weeks was administered	Complete healing Increase healing rate Less recurrence Improve DLQI Less pain Less hospitalization Blood marker changes (CRP, ESR)

Table 6 continued

Author, year	Study type (no. of subjects)	Regimen	Outcomes
Etanercept			
Kim et al., 2012 [88] Kleinpenning et al., 2011 [154] Vandevyvere et al., 2007 [54] Pastor et al., 2006 [90] Roy et al., 2006 [91] Rogge et al., 2008 [93] Goldenberg et al., 2005 [92] Disla et al., 2004 [155] McGowan et al., 2004 [86]	Case reports (11)	Etanercept (50 mg once or twice/week), to 50 mg every other week for 6 months	Decrease ulcer size Complete healing Less recurrence Increase healing rate
Charles et al., 2007 [89]	Retrospective analysis (11)	Etanercept (subcutaneous injections 25–50 mg twice/week)	Complete healing Decrease ulcer size Increase healing rate Less recurrence
Ustekinumab			
Goldminz et al., 2012 [96] Guenova et al., 2011 [24]	Case reports (2)	One dose of ustekinumab 90 mg, twice at 4-week intervals, then the same dose every 8 weeks thereafter for 22 weeks, or 45 mg twice at weeks 0 and 4	Increase healing rate Decrease ulcer size Complete healing Less recurrence
Canakinumab			
Geusau et al., 2013 [98]	Case report (1)	150 mg every 8 weeks	Decrease number of lesions
Kolios et al., 2015 [68]	Prospective, open-label study (5)	150 mg weeks 0 and 2, and 150–300 mg week 4 if needed	Increase healing rate Increase healing rate 3/5 complete healing Improve DLQI
Anakinra			
Acquitter et al., 2015 [99] Lin et al., 2011 [101] Brenner et al., 2009 [100]	Case reports (3)	Anakinra (100 mg once/day) from 8 weeks–10 months	Increase granulation rate Increase healing rate Complete healing Less recurrence

RCT randomized controlled trial, *DLQI* Dermatology Life Quality Index, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate

with other inflammatory conditions such as IBD [103, 104]. A proof-of-concept study in six patients with PG has been reported, with five of six patients having a significant response at day 28 [140].

6.3.4 Other Biologics

New targeted therapies, including anti-IL-6 (e.g. tocilizumab) and anti-IL-17 (e.g. brodalumab, ixekizumab) agents, have the potential for future studies.

7 Conclusions

PG is a rare disease that continues to be challenging from a diagnostic and therapeutic point of view. Diagnosis is complicated by the lack of established serological and histological markers, coupled with the abundance of clinical mimickers. Current research suggests that neutrophil dysfunction, inflammation, and genetics play a role in disease progression. Fully understanding pathophysiologic mechanisms remains a challenge, and, possibly as a result of this, treatment requirements vary from patient to patient, and even vary at different times for individual patients. The goals of management are to control inflammation and optimize wound healing. In doing so, all patients should be informed of the importance of ulcer prevention, by avoiding trauma and, if possible, surgery, as well as being informed about the optimal treatment of any underlying disorder. There is no gold standard for treatment. For localized PG, topical and intralesional corticosteroids are often tried initially; for more severe or recalcitrant disease, systemic treatment such as systemic corticosteroids, and immunosuppressive medications such as cyclosporine, may be used. Theoretically, targeted biologic therapies may offer advantages for the treatment of PG but evidence is limited. Among targeted biologic treatments, evidence to date is strongest for the use of infliximab, but adalimumab and etanercept may also be of benefit. IL-1 antagonists and IL-12/23 antagonists represent other theoretically possible therapies. More clinical trials are needed to better define the efficacy of biologicals in PG.

Acknowledgements The authors would like to thank Delaram Farzanfar for her work on the tables and figures in this article.

Compliance with Ethical Standards

Funding No funding was received for the preparation of this review and the paper has not been presented elsewhere.

Conflict of interest Afsaneh Alavi has been a consultant and investigator for Abbvie, Galderma, Janssen, Novartis, Regeneron, Valeant, and Xoma, and received a grant from Abbvie; Lars E. French received study funding from Novartis; Alain Brassard has been a consultant and speaker for AbbVie, Janssen, Celgene, 3M, and Coloplast; and Robert S. Kirsner has been a consultant for Abbvie. Mark Davis has no conflicts of interest to declare.

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