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WOUND CARE AND HEALING (H LEV-TOV, SECTION EDITOR)

Pyoderma Gangrenosum: What Do We Know Now?

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Abstract
Purpose of Review To summarize the recent literature on the pathophysiology, diagnosis, and treatment of pyoderma gangrenosum.
Recent Findings A complex interplay between both the innate and adaptive immune systems underlies the pathogenesis of pyoderma gangrenosum (PG). Diagnosis remains a challenge, as there is no gold standard test to confirm the presence of the disease. Efforts to establish diagnostic criteria based on clinical findings have recently been proposed. Definitive management strategies are also lacking; however, current trends in treatment have favored the use of immunosuppressive medications, wound care management, and analgesia.
Summary PG is a complex disease that continues to pose a challenge. Current research on PG is focused on improving our understanding of the pathophysiology so that we might improve our diagnostic consistency and identify treatment approaches optimized for each individual patient's specific pathology.

Keywords Pyoderma gangrenosum · Neutrophilic dermatosis · Wounds

Introduction

Pyoderma gangrenosum (PG), a rare autoinflammatory disease considered a prototypic neutrophilic dermatosis, presents as ulcerated lesions most commonly appearing on the lower extremities. It affects approximately three to ten patients per million; however, this might be underestimated due to lack of a diagnostic test and frequent misdiagnosis. The pathogenesis of PG is complex, as it can be idiopathic or present in association with a variety of inflammatory or neoplastic conditions. Occasionally, PG may have extracutaneous manifestations, including sterile neutrophilic infiltration of internal organs, muscle, or bone [1, 2]. Patients with a history of inflammatory bowel disease are especially susceptible to peristomal PG, a subtype that may occur after placement of an ileostomy or colostomy, which comes with its own diagnostic and treatment challenges. Moreover, PG can also occur in the context of autoinflammatory syndromes (PAPA, SAPHO, and PASH).

Classically, patients develop one or more irregularly shaped ulcers with undermined edges that display a characteristic gun-metal gray or violaceous hue. The ulcers typically have differing sizes and depths; frequently, the ulcers extend deeply to expose underlying muscle and tendons. However, non-ulcerative forms have been described including pustular, bullous, and vegetative forms. While systemic corticosteroids or cyclosporine are considered a mainstay of treatment, response to either topical or systemic immunosuppressives can be unpredictable. Recalcitrant cases are not uncommon in clinical practice. Large-scale studies and clinical trials have been limited. Recent studies have focused on gaining a better understanding of the pathogenesis of PG, improving the diagnosis, and finding targeted treatment options. The present review aims to summarize the most recent literature on PG to improve our comprehension of one of the most perplexing diseases in dermatology.

Pathophysiology

PG is currently considered an autoinflammatory ailment that is most likely secondary to aberrant activation of the innate immune system in patients with a genetic predisposition. It

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has also been recently proposed that the adaptive immune system might play a role in the pathogenesis of this condition [3•]. It remains unknown how different external triggers (e.g., pathergy, the process through which minor skin trauma leads to ulceration) interact with a patient's intrinsic genetic factors to cause the varying morphologic presentations of PG. Additionally, it is poorly understood how the interface of these factors then goes on to affect clinical outcomes for patients. We strongly believe that understanding of the pathophysiology of PG is the cornerstone to revealing further diagnostic and therapeutic clues. The current knowledge on the pathogenesis has been summarized in Fig. 1 [3•, 4–10, 11••, 12–15, 16•, 17–20, 21••, 22–28]. Of note, as indicated in Fig. 1, there is a synergistic interplay between the innate and adaptive immune systems that likely contributes to the pathogenesis of PG. Furthermore, the current understanding of PG places a strong emphasis on the role of IL-1β. Studies have found elevated levels of IL-1β in PG lesions, and several case reports have documented successful treatment with therapies that interfere with IL-1 activity [11••, 16•, 23, 29–34]. Additionally, genetic abnormalities documented in syndromic PG also support IL-1 as a potential causative factor. Mutations in the proline-serine-threonine phosphatase-interacting protein 1 (PSTPIP1) gene on chromosome 15 have been described in pyogenic arthritis, PG, and acne (PAPA) syndrome and pyogenic arthritis, PG, acne, and hidradenitis suppurativa (PAPASH) syndrome, where decreased inhibition of inflammasomes results in increased IL-1β and IL-18, and subsequently, neutrophilic infiltration [9, 26, 35]. Similarly, increased CCTG microsatellite repeats have been observed in the promoter region of the

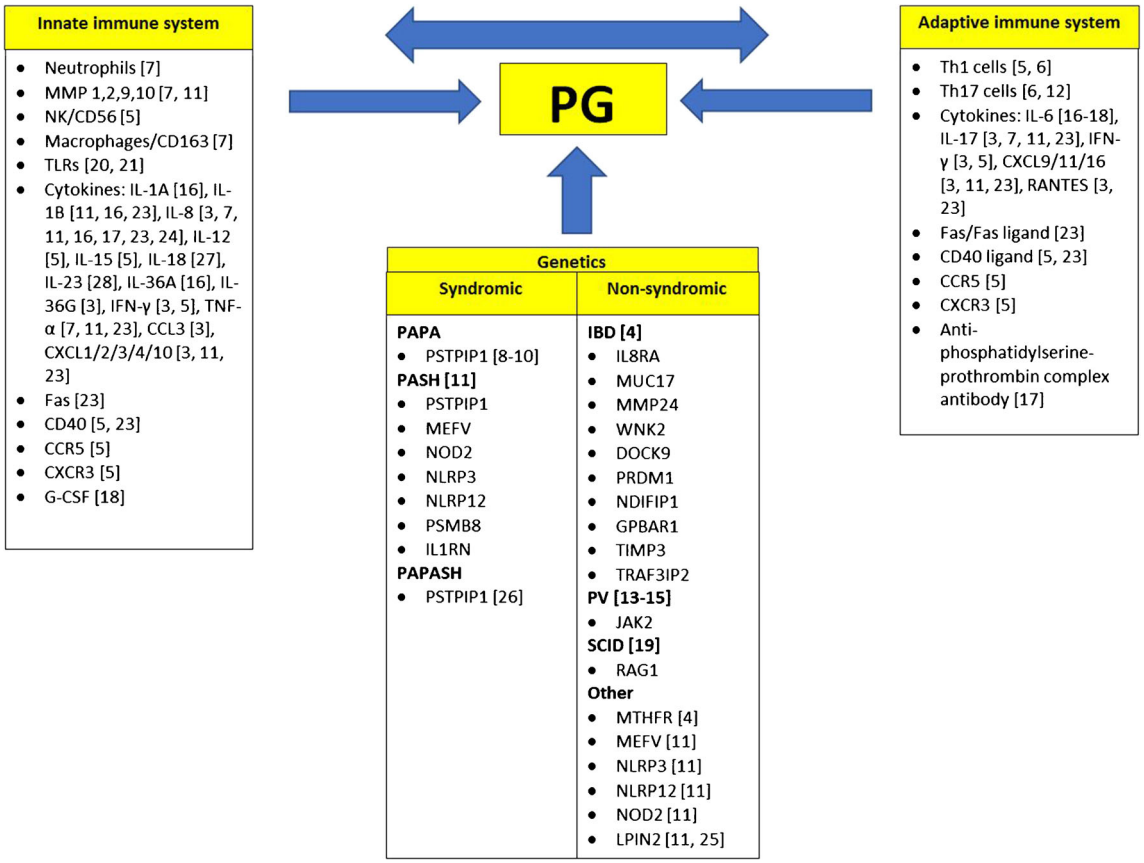

Fig. 1 Pathogenesis of pyoderma gangrenosum. This schematic diagram addresses the complexity of the pathogenesis of PG. It depicts the influence and interactions of several innate and adaptive genes, as well as a variety of molecules in the immune system that may predispose patients to develop PG lesions. *CD*, cluster of differentiation; *DOCK*, dedicator of cytokinesis; *G-CSF*, granulocyte colony-stimulating factor; *GPBAR*, G protein-coupled bile acid receptor; *IBD*, inflammatory bowel disease; *IFN*, interferon; *IL*, interleukin; *IL-1RN*, gene for interleukin 1 receptor antagonist; *IL-8RA*, gene for interleukin 8 receptor alpha; *JAK*, Janus kinase; *LPIN2*, gene for lipin 2; *MEFV*, gene for Mediterranean fever; *MMP*, matrix metalloproteinase; *MTHFR*, methylene tetrahydrofolate reductase; *MUC17*, gene for mucin 17; *NK*, natural killer; *NLRP*, NOD-like receptor protein; *NOD*, nucleotide-binding oligomerization domain-containing protein; *PAPA*, pyogenic arthritis, pyoderma gangrenosum, acne; *PAPASH*, pyogenic arthritis, pyoderma gangrenosum, acne, and suppurative hidradenitis; *PASH*, pyoderma gangrenosum, acne, and suppurative hidradenitis; *PSMB*, proteasome subunit beta; *PSTPIP*, proline-serine-threonine phosphatase-interacting protein; *PV*, polycythemia vera; *RAG*, recombination activating gene; *RANTES*, regulated on activation, normal T cell expressed and secreted; *TIMP*, tissue inhibitor of metalloproteinase; *TLR*, Toll-like receptor; *TNF*, tumor necrosis factor; *SCID*, severe combined immunodeficiency; *TRAF3IP2*, TNF receptor-associated factor 3-interacting protein 2; *WNK*, human gene for WNK lysine-deficient protein kinase

PSTPIP1 gene in cases of PG, acne, and suppurative hidradenitis (PASH) syndrome [10]. Just as the IL-1 antagonists anakinra and canakinumab have led to improvement in PG, biologics targeting other inflammatory markers (i.e., TNF-α, IL-12/23, IL-6, a4b7 integrin) have also led to ulcer resolution [28, 36–38]. It is possible that different etiologies and potentially different phenotypes could be determined based upon responsiveness to blocking certain inflammatory pathways.

Diagnosis

Misdiagnosing PG is not uncommon in clinical practice. Previous reports have demonstrated a misdiagnosis rate of 10–20% [39]. PG has primarily been a diagnosis of exclusion, and the lack of validated diagnostic criteria [40] has made it difficult to conduct clinical studies on patients with PG. In response to these challenges, several attempts have been made to create formal diagnostic criteria to better distinguish PG from similar ulcerative skin conditions. A recent panel of dermatology experts convened to develop diagnostic criteria utilizing a Delphi approach [41••]. Nine criteria—one major and eight minor—were suggested to assist with diagnosis of PG (Table 1). The presence of the one major criterion and at least four of the eight minor criteria are required for a diagnosis of PG to be made. The selected criteria were validated against 113 case reports of ulcerative PG ($n = 65$) and PG mimickers ($n = 48$), which yielded a sensitivity and specificity of 86 and 90%, respectively.

Most recently, a group of European dermatology experts developed a diagnostic tool for PG titled the PARACELSUS score [42••]. The components of this score are based on a combination of criteria that have been previously reported in the literature [40, 43, 44], as well as the findings from a retrospective chart review evaluating the clinical history and images of 60 patients with PG. The astutely named PARACELSUS score consists of ten criteria that are then sub-classified into major, minor, and additional criteria (Table 1). The percentage of patients who presented with each of the key findings was then used to define what constitutes a major, minor, and additional classification; major criteria were defined as being present in > 95% of patients, minor criteria were present in 60–94% of patients, and additional criteria were present in less than 60% of patients. A scoring system was then developed assigning 3 points to major criteria, 2 points to minor criteria, and 1 point to additional criteria. Using the PARACELSUS score, two teams of experts reviewed the clinical history and images of 60 patients with confirmed PG and 50 patients with venous leg ulcers. Compared to the group of patients with venous leg ulcers, all patients with confirmed PG scored ≥ 10 points. Patients with venous leg ulcers all scored ≤ 7 points. To further validate the criteria, alternative definitions of major, minor, and

Table 1 Two recently proposed diagnostic approaches for PG

Delphi Consensus PG Diagnostic Criteria (Maverakis et al.)

Criteria	Designation
Biopsy with neutrophilic infiltrate	Major
Exclusion of infection on histology	Minor
Pathergy	Minor
Personal history of IBD or inflammatory arthritis	Minor
Papule, pustule, or vesicle that rapidly ulcerates	Minor
Peripheral erythema, undermining border, and tenderness at site of ulceration	Minor
Multiple ulcerations (at least one occurring on an anterior lower leg)	Minor
Cribriform or wrinkled paper scars at healed ulcer sites	Minor
Decrease in ulcer size after immunosuppressive treatment	Minor

The Delphi criteria were validated using 65 case reports of ulcerative PG and 48 mimickers (including vasculitis, venous ulcers, and calciphylaxis), all identified using PubMed. These criteria have a sensitivity and specificity of 86% and 90%, respectively.

*Shaded items represent overlapping criteria.

PARACELSUS Score (Jöckenhofer et al.)

Criteria	Designation	Value
(Rapidly) Progressing disease	Major	3 points
Assessment (Absence) of relevant differential diagnoses	Major	3 points
Reddish-violaceous wound margin	Major	3 points
Amelioration (Alleviation) by immunosuppressant drugs	Minor	2 points
Characteristically irregular (bizarre) ulcer shape	Minor	2 points
Extreme pain >4/10 on visual analogue scale	Minor	2 points
Localized pathergy phenomenon	Minor	2 points
Suppurative inflammation in histopathology	Additional	1 point
Undermined wound border	Additional	1 point
Systemic disease associated	Additional	1 point

The PARACELSUS score was validated by two panels of experts who applied the criteria to 30 PG cases and a control group of 50 venous leg ulcers. Cases were selected from patients previously treated in the authors' home departments.

alternative criteria as well as various scoring scales were tested, all of which resulted in comparable findings with PG cases having significantly higher scores than controls.

Both of these newly proposed diagnostic schemes advance the current effort to improve the accuracy and consistency of PG diagnoses. Despite the overlap in several of the proposed criteria (Table 1), the role of skin biopsy was inconsistent between the two diagnostic tools. Importantly, assessing for and excluding other similar appearing ulcerating conditions of the skin are a key step in both approaches. Exclusion of infection by microbiological cultures (via tissue culture or superficial swab), a relevant differential diagnosis to consider, is not explicitly included in the newly proposed criteria for PG diagnosis. Waiting for culture results, which can take upwards of 2 days or more, can postpone initiation of immunosuppression and ultimately lead to untimely, ineffective care. Not infrequently, patients with PG will have endured numerous unsuccessful courses of antibiotics and mechanical debridements and had negative cultures by the time a dermatologist is consulted. As diagnostic molecular microbiology continues to evolve, new techniques to improve the diagnosis of infections in a more expeditious and effective manner might be incorporated in the workup of patients with PG.

Future prospective studies evaluating the utility of the proposed diagnostic criteria should aim to clarify their accuracy and feasibility in the clinical practice setting. Only time will determine how the medical community will apply these criteria in their clinical and research practices; however, we foresee challenges asking non-dermatologists (primary care providers, emergency medicine physicians, surgeons) to use diagnostic criteria/tools, as they do not receive training to recognize the appearance of PG ulcers and they are not as familiar with the diagnosis of atypical ulcers such as PG. A gold standard diagnostic test might fulfill this need but is still lacking.

Treatment

There is no gold standard treatment for PG. However, it is widely accepted that the mainstay treatment requires topical or systemic immunosuppression combined with wound care and pain management (Fig. 2). The authors' proposed algorithm is also depicted below (Fig. 3).

Immunosuppression

Systemic corticosteroids and cyclosporine are often the first-line therapy; however, intralesional and topical applications have also been successful in patients with small and/or smoldering ulcerations (based on our experience, small ulcers are < 2 cm). Peristomal PG is also particularly responsive to topical corticosteroids and calcineurin inhibitors, with one review citing complete healing in 62 and 56%, respectively, of patients using these treatments [45]. In 2015, the randomized control trial titled STOP GAP found no significant difference in outcomes among patients who received oral cyclosporine compared to prednisolone. By 6 months, almost 50% of PG ulcers had healed, irrespective of whether patients received oral cyclosporine or prednisolone [46••]. This study also suggested patients with diabetes, osteoporosis, and/or peptic ulceration should avoid systemic corticosteroids, while patients with hypertension or renal insufficiency should not use cyclosporine.

The addition of topical or systemic antimicrobials and anti-neutrophilic agents (e.g., dapsone, colchicine) has been based on physician's preference. Based on the authors' experience, our group advocates for the use of adjuvant dapsone in addition to immunosuppression for acute treatment of PG. Dapsone has a dual effect in patients with PG; it has anti-inflammatory actions to inhibit chemotaxis of neutrophils [41••] and provides prophylaxis against *Pneumocystis jiroveci* (PJP) while the patient is receiving chronic immunosuppression [47].

Recent investigations into alternative treatment options for PG have focused on biologics. With the increasing knowledge of the role of cytokines and other inflammatory molecules in the pathogenesis of PG, the ability to target specific mediators of the disease process has become an increasingly favorable approach. TNF-α inhibitors have been studied in several small samples yielding mixed results [48–63]. These therapies offer a two-pronged approach to treatment, as about half of patients presenting with PG have a comorbid condition that is also responsive to treatment with these medications. Specifically, infliximab has shown a strong benefit among patients with and without IBD in a randomized clinical trial [36]. Almost half of the patients reported improvement after 2 weeks, and two thirds reported improvement by week 6. The remainder of the patients had no response to treatment. Only a couple of patients developed serious adverse events, which included congestive heart failure (1/29 patients) and MRSA soft tissue infection complicated with sepsis (1/29).

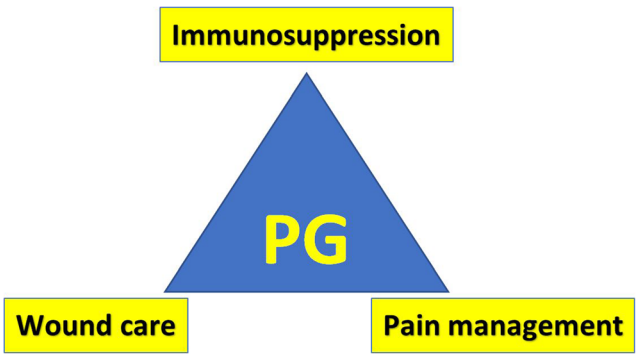

Fig. 2 Treatment approach for patients with PG

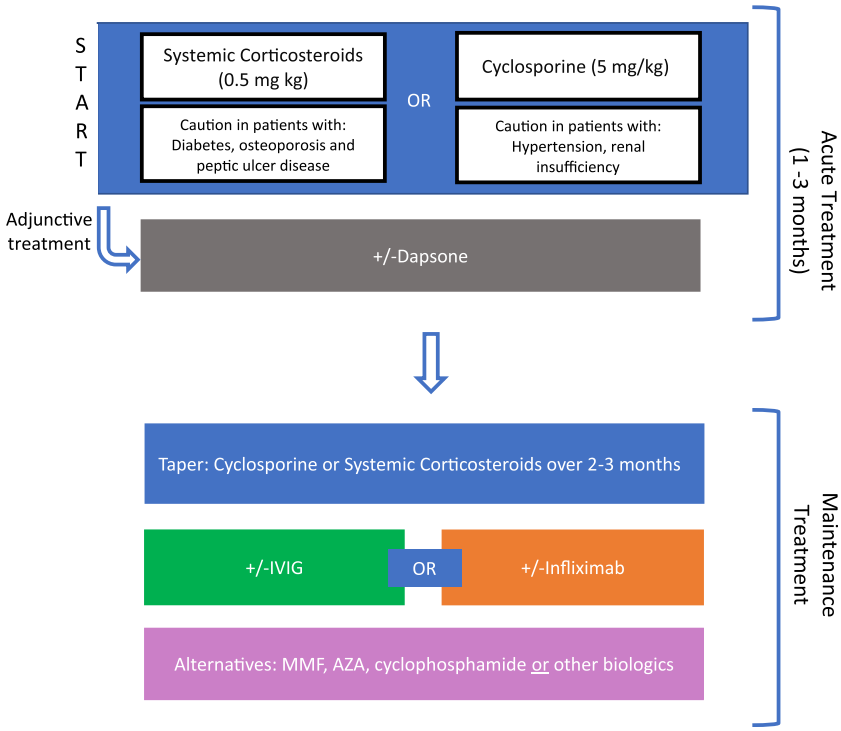

Fig. 3 PG treatment algorithm. Management of PG frequently requires concurrent use of a variety of immunosuppressive and immunomodulating medications. This figure shows the authors' preference in regard to combining these medications. Medications in different colored boxes can be safely combined for treatment of PG

Case reports and small case series have also described high rates of complete healing or significant clinical improvement in patients with syndromic and non-syndromic PG using other TNF inhibitors such as adalimumab [64–73], certolizumab [74, 75], and etanercept [76–81]. Conversely, reports of golimumab therapy have described failure of improvement in severe recalcitrant PG [82] and drug-associated PG in the setting of RA [83]. Another viable alternative to TNF-α inhibitors has been ustekinumab [28, 38, 82, 84], an IL-12/23 antibody, which has been especially effective at higher doses [84]. Tocilizumab, an IL-6 inhibitor, has also led to ulcer resolution in a patient with RA and interstitial lung disease, a contraindication for TNF-α inhibitors [37]. Other beneficial therapies in patients with comorbid IBD include vedolizumab, which interferes with gastrointestinal T cells [38], and visilizumab, an anti-CD3 antibody [85].

There are also some case reports supporting the inhibition of IL-1 as another viable treatment option in patients with PG. Anakinra, an IL-1 receptor antagonist, has been successfully utilized in the treatment of some patients with syndromic and non-syndromic PG [32–34, 86–88]. On the other hand, there are some cases reporting failure of this approach [89]. Additionally, canakinumab, an IL-1β antagonist, has had success in treating patients with steroid-refractory PG [16•, 29, 30]. In one report, five out of six patients had either a complete or a partial response, and only one patient did not respond to treatment [16•]. Additional case reports have documented treatment failure with canakinumab as well [90].

While there is favorable case-based evidence to support the use of biologics in the treatment of PG, further study with larger sample sizes is warranted before any conclusions can be drawn on their overall effectiveness in patients with syndromic and non-syndromic PG. Notably, their use might be advantageous when patients present with underlying systemic conditions (inflammatory bowel disease, rheumatoid arthritis) or associated skin conditions (hidradenitis suppurativa, psoriasis) that are also responsive to these medications.

More recently, small-molecule drugs have also been considered as potential therapies for patients with PG, including Janus kinase (JAK) inhibitors (e.g., ruxolitinib) [14, 15, 91] and PDE4 inhibitors (apremilast) [92].

Based on the authors' experience, high doses of intravenous immunoglobulin (IVIG), with 2 g/kg administered over 2 to 3 consecutive days once a month for 6 months, have been another useful alternative. This is particularly helpful in recalcitrant cases and in cases with repetitive superinfection of PG ulcers. It has been proposed that the effect of IVIG is likely due to its anti-inflammatory activity, which involves decreasing the half-life of IgG antibodies by binding the neonatal Fc receptor (FcRn), inhibition of Fc receptor activation, and prevention of tissue destruction by complement [93, 94]. Additionally, if a patient has contraindications to the aforementioned medications due to comorbidities and immunosuppression, IVIG seems to have a relatively safe profile [94].

Wound Care Management

Wound care is another key component of PG management that should be used in conjunction with immunosuppressive therapy. Creating an appropriate environment that will foster revascularization and re-epithelialization is crucial for the healing of PG ulcers. Dressings are especially important in preventing potential superinfections. Several types of dressings have been reported in the treatment of PG ulcers including hydrogels and films, non-adherent povidone-iodine (Inadine™; Systagenix) [95]; alginate [95]; acellular bovine collagen-glycosamine complex/silicone (Integra™ Matrix Wound Dressing) [96]; flexible polyester mesh impregnated with hydrocolloid and petroleum jelly particles (UrgoTul®; Urgo Medical) [97]; sodium carboxymethylcellulose (NaCMC) containing 1.2% silver (Aquacel® Silver) [97]; antimicrobial foam (Mepilex® Ag; Mölnlycke) [97]; sulfamylon [98]; 45% oxidized regenerated cellulose and 55% collagen composite (PROMOGRAN™ Matrix; Acelity) [99]; nanocrystalline silver alginate (Acticoat Absorbent®; Smith & Nephew) [99]; and lyophilized type I bovine collagen matrix (SkinTemp®; Biocore Inc.) [100]. The dressing selected depends on the ulcer's characteristics, which includes the amount of drainage, the presence of fibrin/slough, and the presence of non-viable tissue. Sharp debridement is not usually recommended in PG ulcers; however, if the presence of non-viable tissue is impairing healing and the patient is currently receiving immunosuppression, debridement becomes another alternative to improve the ulcer environment. Moreover, there is some evidence for the use of negative-pressure wound therapy in conjunction with systemic immunosuppression [101, 102], which might represent another alternative to promote healing. Some cases have reported successful use of adjuvant hyperbaric oxygen [103–106]. Biologic dressings might represent an alternative to accelerate the healing process [107, 108], but this is still an unexplored area of research. Finally, wireless microcurrent stimulation has also been reported as beneficial in a small number of PG patients [109].

Surgery has traditionally been considered counterproductive to PG treatment, as the trauma introduced to the wound may lead to a pathergy reaction facilitating further ulceration. However, based on a systematic review, there may be a role for surgical treatment using negative-pressure wound therapy (NPWT) followed by split-thickness skin graft (STSG) alongside antibiotic prophylaxis and other adjuvant immunosuppressive/immunomodulatory treatment as needed. This approach led to increased healing rates in the majority of patients studied [110]. Despite the favorable outcomes observed, it must be noted that STSG does confer a risk of relapse or pathergy; however, this risk could be minimized if the patient is receiving concurrent systemic immunosuppression. A proposed lower risk alternative to STSG is epidermal grafting in which grafts are harvested via suction blisters created by heat and negative pressure. One study reports complete healing in three out of five patients and reduction in ulcer size in two others who underwent this procedure; no pathergy was observed [111]. Unfortunately, amputation has also been performed and reported in some patients with severe recalcitrant PG [95, 106, 112].

Pain Management

Pain control is often necessary in conjunction with wound care and typically consists of systemic anti-inflammatories or opioids. Topical morphine has also been used with some success in patients with PG and other chronic ulcers [113, 114]. In addition to opioids, combination therapy with neuropathic medications (gabapentin or pregabalin) or antidepressants has been suggested to address neuropathic pain, which can develop secondary to nerve damage from ulceration [115]. Interestingly, newer evidence suggests opioids are associated with decreased healing rates in venous ulcers; therefore, alternative pain management strategies are being considered [116]. A recent report documents clinically significant pain reduction using topical medical cannabis in three patients whose pain was uncontrolled with opioids and acetaminophen [117].

Additional general therapeutic measurements include minimizing edema with compression garments, smoking cessation, glycemic control in diabetics, and optimizing nutritional status [35].

Conclusion

Pyoderma gangrenosum is a complex autoinflammatory ulcerative skin condition. It is a rare pathology for which the etiology has yet to be fully understood. A number of inflammatory mediators have been identified as playing a role in its pathogenesis, and a growing body of evidence suggests both innate and adaptive immune cells malfunction to initiate the disease process. Indeed, the complex interaction between genetic predisposition and immune dysfunction makes it possible that no single causative pathway exists, but instead, under the right conditions, a number of stimuli may trigger the cascade of inflammation. Furthermore, the incomplete understanding of the pathophysiology has also posed challenges in diagnosis and treatment. No biomarkers exist to detect PG; therefore, diagnosis has traditionally been made on the basis of exclusion. Fortunately, promising diagnostic criteria have recently been proposed to attempt to increase accuracy and consistency in diagnosis among medical providers. Recent attention has also been directed toward developing an outcome instrument to assess severity and response to treatment. Systemic corticosteroids and cyclosporine have traditionally been the first-line therapies; however, biologics that

target the many inflammatory molecules found in PG lesions are now being considered. Moreover, IVIG has been successfully reported in the majority of recalcitrant cases. Collaborations through larger clinical trials are needed before a gold standard treatment protocol is set. In the near future, PG patients will require a precision medicine approach; utilizing genetic inflammatory markers for diagnosis of the different phenotypes to select the appropriate treatment alternatives and to predict outcomes.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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