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Research Article

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Skin Grafting for Orthopedic Surgery Wounds Complicated by Pyoderma Gangrenosum

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Abstract

Orthopedic surgery wounds complicated by pyoderma gangrenosum (PG) present a unique clinical challenge due to the inflammatory nature of PG, its propensity for rapid progression, and the difficulty in achieving wound closure. PG, a rare neutrophilic dermatosis, is often triggered by trauma, including surgical interventions, through pathergy, leading to progressive tissue necrosis, and delayed healing. Traditional wound care strategies alone are often insufficient in this context, necessitating the integration of advanced techniques, such as split-thickness or full-thickness skin grafting. However, the success of skin grafting in PG-complicated wounds depends on meticulous preoperative management, including the suppression of underlying inflammation through systemic corticosteroids, cyclosporine, or biologics, such as TNF-α inhibitors. Advanced wound care techniques, including the use of negative pressure wound therapy (NPWT) and bioengineered skin substitutes, provide a supportive environment for graft take and epithelialization by reducing exudate, enhancing angiogenesis, and minimizing shear forces. Interdisciplinary collaboration among dermatologists, orthopedic surgeons, and wound care specialists is critical to optimize outcomes, ensuring that the inflammatory component of PG is controlled, while promoting wound bed preparation and graft survival. Recent case studies have highlighted the importance of personalized care plans, incorporating both systemic immunomodulation and local therapies, in reducing recurrence rates, and improving healing times. Understanding the intersection between orthopedic trauma, PG pathophysiology, and advanced grafting techniques offers a path forward to improve outcomes for this complex and challenging subset of patients, emphasizing the need for tailored, interdisciplinary approaches.

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Introduction

Pyoderma gangrenosum (PG) is a rare neutrophilic dermatosis that is characterized by painful, necrotic ulcers, with an undermined violaceous border [1]. The etiology of PG is still unclear. However, it is speculated that the pathogenesis is related to an immune dysregulation, with a characteristic neutrophilic infiltration on histological examinations [1]. PG presents similarly to many non-healing ulcers and vasculitis, however, bacterial cultures and biopsies are often inconclusive [2]. As stated above, PG is often misdiagnosed as a non-healing ulcer, this can further complicate PG as the excessive neutrophil infiltration can be exacerbated by trauma, a phenomenon known as pathergy. Pathergy is a paradoxical worsening of a lesion following wound debridement and minor surgical interventions, pathergy is thought to be driven by exaggerated inflammatory response [2]. The clinical presentation of PG in its early stages mimics that of a non-healing ulceration or cellulitis, thus presenting a difficult and frequently missed diagnosis [2]. Diagnosing PG is often exclusion based and involves ruling out all other cutaneous ulcers [2]. Another aspect of PG's pathogenesis is the association with systemic diseases, such as diabetes, inflammatory bowel disease, and rheumatoid arthritis [3]. These comorbidities suggest a shared pathway of immune dysregulation, involving neutrophil trafficking and cytokine development. PG often presents on the lower extremities or in postoperative locations [3]. Orthopedic surgical wounds can often be complicated by PG, which represents a particularly challenging subset of cases. This intersection of surgical intervention and trauma along with the inflammatory pathogenesis of PG can create a cascade of complications. Orthopedic wounds complicated by PG exhibit delayed healing, extensive necrosis, and recurrent ulcerations, making postoperative care difficult [4]. Traditional wound management techniques often fail to address the underlying pathogenesis of PG, and can become a worsening problem given frequent wound debridements and surgical interventions which can drive pathergy [4]. As such, treatment and management of PG is often difficult.

Effective management of PG in the context of orthopedic wounds requires a comprehensive and interdisciplinary approach. The typical approach to treating PG involves agents, such corticosteroids, cyclosporine, and biologics like TNF-α inhibitors [5]. These agents allow the mitigating of inflammatory processes to help resolve the dermatosis or prepare the wound bed for further interventions, such as skin grafting [6]. Skin grafting has shown promise in achieving wound closure in PG-complicated wounds [6]. In PG cases, meticulous wound bed preparation is paramount for successful grafting, as an active inflammation can undermine graft viability and lead to recurrence of PG [6]. There are many different skin grafts that can be utilized, such as split or full-thickness, or even bioengineered skin substitutes [6]. Postoperative care is critical to ensuring the survival and long-term success of the graft. Strategies for successful management with consideration of PG can involve systemic therapy to control inflammation with close monitoring for signs of infection, utilization of adjuvant therapies, such as negative pressure wound therapy (NPWT), all aiming to help stabilize the graft site [7]. Interdisciplinary collaboration among orthopedic surgeons, dermatologists, plastic surgeons, and wound care specialists is essential to navigate the complexities of PG and its impact on surgical wounds [7]. By utilizing a tailored approach, clinicians can improve healing outcomes, and reduce recurrence in these challenging patient populations.

This literature review explores the multifaceted approach that is required to manage orthopedic wounds complicated by PG. This review explores integrated systemic therapies, advanced wound care modalities, and interdisciplinary collaborations for PG management. By understanding the intersection of PG pathophysiology, wound management, and grafting techniques, clinicians can manage the challenges posed by this rare dermatosis.

Management of Pyoderma Gangrenosum in Orthopedics

The pathogenesis of pyoderma gangrenosum (PG) is complex and not yet fully understood. It is widely believed to stem from immune system dysregulation in genetically or environmentally predisposed individuals. PG ultimately involves the recruitment and accumulation of neutrophils in the skin in the absence of infection, making the suppression of this autoinflammatory process the primary treatment goal [8]. Currently, there are no standardized guidelines for PG management. Treatment recommendations are primarily informed by systematic reviews, case reports, retrospective chart reviews, and limited clinical trials. Management strategies are typically guided by disease severity, with mild cases often treated using topical corticosteroids or calcineurin inhibitors. In contrast, moderate to severe cases require systemic immunosuppressive or immunomodulatory therapies to control the inflammatory cascade [9]. Adjunctive treatments, including appropriate wound care and pain management, are critical to addressing the condition comprehensively.

Systemic corticosteroids, administered intravenously or orally, are considered first-line treatment for pyoderma gangrenosum. A typical dose of 0.5–1 mg/kg/day of prednisolone has shown clinical efficacy in only 40–50% of patients [10,11]. Hence, in severe or refractory cases, corticosteroids are often combined with another potential first line agent, cyclosporine (3–5 mg/kg/day orally), to improve remission rates and reduce the risk of relapse [11]. To date, only one clinical trial has directly compared the efficacy of these first-line therapies. In a multicenter, randomized controlled trial, Ormerod et al. (2015) found no significant difference in healing rates between prednisolone (0.75 mg/kg/day) and cyclosporine (4 mg/kg/day) at 6 weeks or 6 months [12]. By 6 months, approximately 47% of ulcers in both treatment groups had healed, but adverse events were common in nearly two-thirds of participants [12]. Reported side effects included hypertension, gastrointestinal disturbances, and renal dysfunction with cyclosporine. Prednisolone side effects include hyperglycemia, new-onset diabetes, and severe infections requiring hospitalization [12]. Additionally, about one-third of patients in both groups experienced a recurrence of PG after an average of 582 days [12]. These findings highlight the limitations of current first-line therapies and underscore the need for more effective and safer treatment options for PG.

Biologic therapies have gained increasing recognition for their effectiveness in treating certain types of PG. Tumor necrosis factor-alpha (TNF-α) inhibitors, including infliximab, adalimumab, etanercept, certolizumab pegol, and golimumab, have shown promising results in managing PG [9]. Infliximab, administered intravenously at a dose of 5–10 mg/kg at weeks 0, 2, and 6, followed by maintenance doses every 8 weeks, has been particularly effective [11,13]. Similarly, adalimumab, initiated at 80 mg subcutaneously weekly and tapered to 40 mg weekly and eventually 40 mg every other week, has demonstrated success in PG treatment [11]. A systematic review by Ben Abdallah et al. (2018) analyzed 222 studies involving 365 patients treated with TNF-α inhibitors, including 275 with infliximab and 43 with adalimumab. The review reported an 87% response rate at 12 weeks and a 67% complete response rate at an average of 20.37 weeks, highlighting the significant efficacy of these agents in adult PG patients [14]. TNF-α inhibitors may be considered a first-line treatment option in scenarios where corticosteroids are contraindicated or poorly tolerated.

Local wound care in PG presents significant challenges due to pathergy, a phenomenon where even minor trauma, such as wound debridement, can trigger an exaggerated inflammatory response, and worsen the wound [8]. Pathergy occurs in approximately 30% of PG patients [15]. As a result, standard debridement techniques are generally contraindicated. The role of surgery in PG management remains controversial, as it may exacerbate the condition rather than promote healing [8]. Effective management of PG prioritizes reducing underlying inflammation through systemic therapy and adjunctive measures, preparing the wound for controlled healing. Balancing the need to address necrotic tissue while minimizing trauma requires careful planning, often incorporating non-traumatic methods, such as gentle mechanical and autolytic enzymatic debridement or advanced dressings [16]. A retrospective cohort study, conducted at a tertiary care center, found that debridement was associated with poorer healing outcomes in PG [17]. Specifically, disease progression occurred in 68.42% (n = 26) of patients who underwent debridement compared to only 15.15% (n = 10) in the non-debridement group ($p < 0.001$) [17]. These findings highlight the need for an individualized approach to local wound care in PG, emphasizing strategies that prioritize inflammation control and minimize the risk of pathergy.

Systemic immunosuppressive therapies for PG have shown only modest effectiveness, with response rates of 50-60%, and recurrence rates as high as 30%. Due to the challenges and risks of surgical management in PG, including the potential for pathergy, alternative approaches are needed to improve outcomes. Recent evidence suggests that split-thickness skin grafts, when combined with negative pressure wound therapy and prolonged prior immunosuppressive treatment, may enhance healing [11,18] A systematic review by Morgenstjerne-Schwenck et al. (2021) evaluated 102 studies involving 212 wounds in 153 patients, and reported complete healing in 75.5% of PG and primary vasculitic ulcer wounds. The average time to complete healing was 10.8 weeks (95% CI 6.1–15.6), though pathergy occurred in 5.2% of cases [19]. Despite these promising results, the chronic nature of PG and the risk of recurrence upon tapering immunosuppression remain significant barriers [20]. Skin grafting offers a valuable option for achieving wound closure in PG. Still its success is tempered by the risks of pathergy, recurrence, and progression of the disease, underscoring the need for careful patient selection and comprehensive management strategies.

Skin Grafting with Pyoderma Gangrenosum

Skin grafting plays an essential role in managing PG wounds in orthopedic settings, offering a potential solution for wound closure in cases where traditional wound care strategies prove insufficient [21,22]. Both split-thickness skin grafts (STSG) and full-thickness skin grafts (FTSG) can be employed, each with distinct advantages and challenges. STSGs, composed of the epidermis and a superficial part of the dermis, can be expanded to cover larger areas, making them suitable for extensive PG wounds [22]. The flexibility to expand allows for greater coverage with less donor site morbidity, a crucial consideration in patients with compromised skin integrity or limited donor sites. However, STSGs are prone to contractions and may result in less favorable cosmetic outcomes [23]. Adams & Ramsey (2005) also discuss FTSGs, containing both the full epidermis and dermis, provide better aesthetic results with minimal scarring and contracture, but are limited in size and donor site availability. The primary challenge in utilizing skin grafting for PG wounds lies in the risk of pathergy, where surgical intervention may trigger new or worsening ulcerations. This heightened sensitivity to trauma implies surgical intervention, including skin grafting, can potentially worsen the condition it aims to treat. Romanelli et al. (2018) encourages clinicians to carefully weigh the potential benefits of skin grafting against the risk of triggering an adverse response, which could lead to graft failure, new ulcerations, or expansion of existing wounds [15]. Despite these challenges, the integration of skin grafting with appropriate systemic therapy and advanced wound care techniques offers a promising approach for managing recalcitrant PG wounds in orthopedic patients.

Preoperative considerations are paramount to ensure successful outcomes. Systemic immunosuppression with corticosteroids or other agents is essential to control underlying inflammation and minimize the risk of pathergy [24]. This preoperative management is critical, as it helps stabilize the wound and create a favorable environment for graft take. Wound preparation is equally important and involves meticulous cleaning, debridement of necrotic tissue, and ensuring a well-vascularized wound bed. NPWT can be employed as an adjunct to enhance wound bed preparation, reduce exudate, and promote tissue formation [15]. The use of advanced dressings and topical agents, such as cadexomer iodine, may further optimize the wound environment prior to grafting [25]. Davis et al. (2021) highlights the importance of reducing wound microbes to prevent suboptimal, delayed or compromised wound healing. Careful consideration must be given to the timing of the grafting procedure, verifying that the wound has stabilized and shows signs of improvement under systemic therapy. Successful STSG are typically only possible after the PG wound has been adequately controlled and prepared [26]. By adhering to these preoperative and wound preparation principles, surgeons can significantly improve the chances of successful skin grafting in PG wounds, ultimately leading to better outcomes for orthopedic patients.

NPWT and bioengineered skin substitutes represent advanced techniques that have shown promise in managing complex wounds, including those complicated by PG following orthopedic surgery. NPWT promotes wound healing by creating a controlled negative pressure environment, which reduces edema, increases blood flow, and stimulates granulation tissue formation [27]. This therapy can be particularly beneficial in preparing the wound bed for subsequent skin grafting or application of bioengineered skin substitutes. Bioengineered skin substitutes serve as temporary or permanent replacements for damaged skin, providing structural support and delivering growth factors crucial for wound healing. These substitutes can be cellular or acellular, with preparations including autologous, allogenic, and synthetic, showing promising results in treating chronic wounds [28]. The combination of NPWT and bioengineered skin substitutes offers several advantages in managing PG-complicated orthopedic wounds. NPWT can enhance the integration and survival of bioengineered skin grafts by improving contact between the substitute and the wound bed, reducing infection risk, and accelerating vascularization [29]. This synergistic approach may be particularly valuable in cases where traditional skin grafting poses a risk of pathergy, a common concern in PG management. Recent studies have demonstrated high success rates in treating complex wounds using artificial dermis combined with NPWT, followed by split-thickness skin grafting [27]. While further research is needed to establish optimal protocols, the integration of NPWT and bioengineered skin substitutes holds significant promise for improving outcomes in the challenging scenario of PG-complicated orthopedic wounds.

Patients with PG in the domain of orthopedic surgery propose a formidable challenge in wound management, requiring a delicate balance between therapeutic intervention and the risk of exacerbating the condition. However, the diagnosis and treatment of PG in orthopedic settings present significant challenges due to its rarity and potential for misdiagnosis. The condition's ability to mimic post-surgical infections, ulcerative disorders, or other wound complications often leads to delayed recognition and inappropriate interventions [30]. Furthermore, the pathergy phenomenon associated with PG poses a unique dilemma, as surgical interventions, including debridement or grafting, may paradoxically exacerbate the condition [31]. This complexity necessitates a high degree of clinical suspicion and expertise to navigate the fine line between necessary interventions and potential harm. Consequently, an interdisciplinary approach involving orthopedic surgeons, dermatologists, and wound care specialists is crucial for optimal management [27].

This collaborative effort ensures a comprehensive evaluation of the patient, accurate diagnosis, and a tailored treatment plan that balances systemic immunosuppression with advanced wound care techniques including NPWT and skin grafting. An interdisciplinary approach improves outcomes by minimizing the risk of complications associated with mismanagement of this challenging condition.

Interdisciplinary Roles in Management of Pyoderma Gangrenosum

The interdisciplinary approach to treating and managing PG is necessary for tending to all facets of the condition. Currently, there is no validated diagnostic criteria clinically or histologically for PG [32]. Skin biopsies, conducted by dermatologists, are essential for supporting the diagnosis, primarily by excluding other conditions in the differential which cause cutaneous ulceration and may prompt incorrect usage of antibiotics. Given that PG often presents as persistent skin lesions, patients are typically referred to dermatologists. Early detection and prompt treatment to control inflammation are vital, along with measures to prevent infection, such as covering open wounds [33]. In a study involving 25 patients with superficial ulcerative and vegetative PG, dermatological interventions, including corticosteroids, minocycline, tetracycline, or sulfa drugs, led to healing in 15 patients [34]. As the condition progresses and becomes more wound-focused rather than on prevention or treatment, wound care specialists are pertinent for managing the healing process effectively, and preventing infection.

Given the high burden of morbidity with PG, optimization of wound care is necessary to produce more positive patient outcomes. Wound care specialists focus on promoting healing by addressing the underlying pathology, reducing inflammation, and managing local pain [35]. Key principles of wound care in PG include gentle cleansing, maintaining a moist wound environment, and performing conservative debridement with the use of hydrogel or collagenases [36]. Surgical debridement often is avoided, as it can trigger pathergy, and worsen the condition [37]. Wound care specialists aim to provide moisture balance, minimize irritation, and incorporate compression therapy [35]. The choice of dressings and treatment modalities should be individualized based on the stage of the disease and the patient's pain level [35]. Current accepted topical treatments include corticosteroid (clobetasol propionate) and calcineurin inhibitors (tacrolimus, pimecrolimus, cyclosporine), with topical timolol and phenytoin as alternative treatments [38]. In addition to treatment, regular monitoring of the wound is necessary to identify signs of infection or adjustment to the treatment plan. If more advanced wound care, including surgical intervention and skin grafting, becomes necessary, involving orthopedic and plastic surgeons as part of a multidisciplinary team is critical for addressing the complex tissue damage.

Surgical treatments for PG, such as NPWT and skin grafting, remain controversial due to the risk of exacerbating the condition. However, there are patients with success managing PG using surgical interventions. A study involving 16 patients with PG, or strong histopathological evidence of PG, demonstrated that surgical approaches can be effective through a retrospective study over 18 years [39]. These procedures included necrotomies for all patients, wound conditioning with allografts in seven patients, STSG in ten, a latissimus dorsi muscle free flap in one, and primary or secondary closure in one [39]. Additionally, six patients underwent cycles of vacuum-assisted closure (VAC) therapy to help condition the wounds [39]. Among the patients, 13 were discharged with nearly or fully closed wounds after surgical intervention, three patients died due to underlying conditions [39]. The use of skin grafting is used to prevent secondary infection and is employed to reduce the morbidity associated with infected wounds or high-risk open wounds [40]. Specifically, split-thickness grafts have shown the greatest success in treating PG, along with free flap transfers [18]. An effective management of PG requires an interdisciplinary approach, combining dermatologists, wound care specialists, and surgeons. While dermatologists focus on diagnosis and inflammation control, wound care specialists optimize healing, and surgeons provide critical interventions like debridement and skin grafting, improving outcomes in the most severe cases.

Advanced Wound Care Modalities

PG is a rare, non-infectious skin condition characterized by rapidly progressing painful ulcerative lesions [41]. Postoperative PG (PPG) is a variant, where an exaggerated immune response occurs at surgical sites, making it crucial to include PG in the differential diagnosis for wound ulcerations. Misdiagnosis can worsen the condition, leading to extensive scarring, disfigurement, and psychological distress. NPWT can reduce wound size, minimize inflammation, and accelerate recovery, so NPWT can be a beneficial modality that improves PPG outcomes [41]. Bazalinksi et al. (2020) have also demonstrated the benefits of NPWT in their case study investigation. Namely, NPWT has effectively reduced wound size, eliminated exudate, decreased bacterial load, and promoted angiogenesis, aiding wound healing. In the case study, an 83-year-old man with confirmed PG was treated with NPWT after developing a 5×15 cm wound with purulent discharge [41]. NPWT therapy was initiated, and significant wound healing was observed, with no signs of undermining, with the NPWT stopped after 52 days [41]. NPWT positively impacted the wound by reducing purulent discharge and preventing further wound enlargement. When used with doxycycline, NPWT proved an effective and safe supportive treatment for PG wounds, promising results in nursing care and wound management [41]. For PPG and PG, NPWT offers significant management benefits by promoting a wide range of benefits, including wound healing, reducing purulent discharge, and preventing further wound enlargement. Its positive impact on wound recovery highlights its effectiveness as a supportive treatment in clinical care. In addition to case studies, a systematic review of the use of NPWT for PG treatment revealed that NPWT improved wound healing in 85.1% of patients, with better outcomes when combined with immunosuppressive therapy [42]. Almeida et al. (2021) concluded that NPWT, when used alongside immunosuppression, proves to be a beneficial adjuvant therapy for promoting wound healing, and accelerating recovery. The combination of NPWT and skin grafting is recommended to enhance wound closure in PG treatment [42]. Overall, NPWT is an effective advanced wound care technique that promotes wound healing and offers various benefits, playing a crucial role in the overall management of PG.

Chronic wounds pose a substantial healthcare challenge, leading to increased morbidity and mortality. Bioengineered skin substitutes (SSs) with a dermal component have demonstrated potential in improving healing for diabetic foot and venous leg

ulcers. However, research on their effectiveness for complex wounds such as pyoderma gangrenosum, radiation dermatitis, and sclerotic graft-versus-host disease, remains limited. Cancer patients are particularly susceptible to chronic wounds due to their underlying disease and treatments like surgery, medications, and radiation, which complicate the healing process [43]. Bioengineered skin substitutes hold significant promise for improving healing in complex chronic wounds, particularly for cancer patients and those with conditions like pyoderma gangrenosum, offering a potential solution to challenges in wound management. Due to the risk of pathergy in patients with PG, many clinicians avoid using aggressive surgical debridement and autologous grafts for these nonhealing ulcers. De Imus et al. (2001) suggest that applying an allogeneic cultured human skin equivalent addresses this issue and accelerates the re-epithelialization of the ulcer bed. Additionally, it may improve the cosmetic appearance of the final scar by preventing severe wound contracture [44]. Therefore, due to the risk of worsening wounds from trauma in PG patients, many clinicians avoid aggressive surgical debridement and skin grafts for nonhealing ulcers. However, allogeneic cultured human skin equivalents may offer a promising solution. A retrospective study at Memorial Sloan Kettering Cancer Center (2017-2019) explored the use of SSs in patients with chronic wounds [43]. Thirty-two patients were treated, with the most common wound type being peristomal PG [43]. The results showed a clinical response in 84% of patients, with 50% achieving a complete response and 34% demonstrating a partial response [43]. While peristomal PG patients showed a high response rate, recurrence was seen in 57% of cases [43]. No significant correlations were found between healing outcomes and factors such as SS type, wound location, or concurrent treatments [43]. This highlights the effectiveness of skin substitutes in treating chronic wounds, particularly in PG patients, with a high response rate and potential for complete healing, underscoring their importance as a valuable treatment option despite the risk of recurrence. Furthermore, De Imus et al. (2001) also reported a case of newly diagnosed ulcerative PG, where the use of bioengineered skin, in combination with immunosuppressive therapy with cyclosporine, promoted faster healing and reduced pain in a rapidly expanding leg ulcer. After 2 weeks, the ulcer showed 30% to 40% healing, with 100% re-epithelialization achieved within 6 weeks [43]. Bioengineered skin, combined with cyclosporine therapy, significantly accelerated the healing process and alleviated pain in a patient with ulcerative PG. This approach demonstrated promising results in the management of PG, with substantial wound improvement observed within two weeks and complete re-epithelialization achieved within six weeks [43]. By addressing the unique challenges of PG, such as rapid ulceration and pain, this combined treatment strategy proves to be an effective and innovative option, offering faster healing and reducing the need for more invasive interventions in PG management.

As discussed, surgical interventions are generally avoided due to the risk of exacerbating pathergy, an exaggerated skin reaction triggered by trauma. Chan et al. (2021) presents a case series of three PG patients who underwent different treatments, including surgical debridement and the use of fetal bovine dermis (FBD). Combining FBD with medical therapy provided pain relief wound coverage and promoted granulation tissue formation, leading to long-term stability [45]. Thus, the fetal bovine dermis, a bioengineered skin substitute, played a significant role in healing patients with PG. Bioengineered skin substitutes have emerged as a promising PG treatment, offering significant benefits in wound healing and pain reduction. Studies have shown that SSs, such as Graftskin and fetal bovine dermis, accelerate re-epithelialization, improve wound closure, and reduce the need for invasive interventions, particularly for PG patients. Despite the potential for recurrence, these substitutes provide a valuable solution for managing complex chronic wounds in PG, highlighting their importance in enhancing patient outcomes and minimizing complications.

Other adjunctive therapies can be valuable for patients with PG, offering them additional options, and the opportunity to develop a personalized treatment plan. For example, Araujo et al. (2013) investigated a case study of a 50-year-old male with a large leg ulcer who underwent initial immunosuppressive therapy, which stopped disease progression. An adjunctive hyperbaric oxygen therapy (HBOT) was added to enhance wound healing, resulting in significant improvement after 81 sessions [46]. HBOT effectively reduced pain, prevented infection, and promoted tissue regeneration, making it a valuable adjunct in treating refractory ulcers. After five months of treatment, skin grafting was deemed appropriate and was successfully performed, with continued use of HBOT and immunosuppressive therapy [46]. The decision for skin grafting was made after careful consideration by dermatology and plastic surgery teams, weighing the risks and benefits. This case emphasizes the need for personalized treatment plans in PG, where each decision must be based on the patient's condition, and the potential outcomes of the chosen therapies. Therefore, adjunctive therapies like HBOT provide valuable support in managing PG, offering patients additional treatment options to enhance healing, reduce pain, and promote tissue regeneration [47] also investigated a case report about the successful treatment of PG in a patient with ulcerative colitis (UC) using HBOT. The patient, initially in remission from UC, developed PG lesions after stopping azathioprine [47]. Despite antibiotic treatment and daily dressing, the lesions did not improve [47]. After two months, PG was diagnosed, and the patient underwent surgical debridement and HBOT [47]. After three months of HBOT and topical treatment, the PG lesions completely healed, and the UC remained in remission with mesalazine alone [47]. This is the first reported case of PG associated with UC to successfully be treated with HBOT, suggesting it as a safe and effective alternative, especially for patients who do not require anti-TNF agents. HBOT aids in wound healing by enhancing oxygenation, promoting angiogenesis, and reducing bacterial growth, offering a promising option with minimal side effects [47]. Adjunctive therapies like HBOT provide support in managing PG, enhancing healing, reducing pain, and offering personalized treatment options, while minimizing the need for invasive procedures. De Sousa Magalhães et al. (2021) investigated another case study with a UC 42-year-old woman. They were diagnosed with PG following the development of a persistent ulcerated wound with peripheral erythema on the similar surface of her left leg [48]. The patient's PG became complicated by a Pseudomonas aeruginosa superinfection, which was managed with broad-spectrum antibiotics, daily wound care, NPWT, and physiotherapy rehabilitation [48]. Despite these efforts, the PG remained non-healing, exposing deep muscle and tendon layers [48]. Adding HBOT resulted in full remission of the PG and

restored function to the left foot [48]. HBOT can be a valuable adjunct in the management of PG when standard treatments fail to yield adequate results. By enhancing tissue oxygenation, promoting angiogenesis, and supporting overall wound healing, these therapies provide significant clinical benefits, accelerating recovery and improving patient outcomes in refractory or complicated ulcers.

Outcomes and Future Directions

Recent research has demonstrated that recent research has demonstrated that that STSG with NPWT is an effective treatment for PG when combined with adequate immunosuppression. Factors influencing graft success include immunosuppressive therapy, essential for preventing failure, as grafts performed without immunosuppression tend to fail. STSG combined with NPWT achieves superior graft take and enhances healing outcomes compared to NPWT alone. While various surgical approaches, including xenografts, often have high success rates, PG's chronic nature and potential recurrence require sustained immunosuppression. Additionally, the choice of immunosuppressive treatment is still evolving, with biologics like IL-12/23 or IL-23 antibodies emerging as promising alternatives to TNF-alpha inhibitors [49]. The combination of therapies works synergistically to promote successful recovery. The addition of immunosuppressive therapy plays a key role in enhancing the effectiveness of a skin graft treatment. PG, a rare neutrophilic dermatosis, presents a significant challenge, due to its propensity for painful, non-healing skin ulcers. While immunosuppressive therapy remains the cornerstone of treatment, large ulcers often require years to heal. Surgical interventions, including NPWT and skin grafting, are increasingly considered adjuncts to accelerate recovery. However, these procedures remain controversial due to the pathergy phenomenon, where minor trauma exacerbates PG. A recent report highlighted four cases where skin grafting, performed under immunosuppressive control, led to successful outcomes in most patients, with only one experiencing recurrence after five months [24]. Integrating skin grafting with systemic immunosuppression balances the risk of pathergy while promoting faster healing, underscoring the importance of systemic and local management strategies in optimizing graft success, and long-term outcomes in PG. Furthermore, PG is frequently exacerbated by surgical interventions, such as debridement or closure, which can worsen the injury. Plastic surgeons must know the PP6 presentation to prevent further damage and safely manage related soft tissue defects. Early and accurate diagnosis, prevention of further surgical injury, and timely medical management are essential for improving outcomes [50]. Long-term treatment and monitoring are vital for managing PG, as a history of the condition strongly predicts recurrence. Tailored care and preventive strategies are crucial for minimizing flare-ups and ensuring effective management over time.

While the legs are most commonly affected in PG, other areas of the skin and mucous membranes can also be involved. PG can present as mild or severe, often chronic or relapsing, leading to significant morbidity. PG is frequently associated with underlying conditions, such as inflammatory bowel disease, rheumatologic or hematologic disorders, and malignancies [51]. Treatment of PG remains challenging, and most established treatments include systemic corticosteroids and cyclosporin A, with combinations of steroids and cytotoxic drugs for resistant cases. Steroid-sparing approaches involve combining steroids with sulfa drugs or immunosuppressants. Anti-tumor necrosis factor therapy has shown rapid improvement in PG, particularly in patients with Crohn's disease. In selected cases, skin transplants and bioengineered skin can be adjuncts to immunosuppressive therapies. Topical treatments and modern wound dressings help manage pain and reduce the risk of secondary infections. Despite recent treatment advances, the prognosis of PG remains unpredictable [51]. Given PG's chronic and relapsing nature, long-term treatment and monitoring are essential, as a history of PG can serve as a strong indicator for recurrence. Early detection and proactive management are key in preventing and managing recurrences, with tailored strategies based on the patient's medical history and previous PG episodes. Systemic corticosteroids, immunosuppressive therapies, and adjuncts like skin transplants or bioengineered skin are critical in managing severe or resistant cases. Morgenstjerne-Schwenck et al. (2021) evaluated the safety and efficacy of skin grafting for treating PG and primary vasculitic ulcers (PVU). A comprehensive literature showed that over 70% of wounds healed completely, with an average healing time of about 11 weeks [52]. A significant difference in preoperative and postoperative immunosuppressive therapy use was found between patients with complete healing and those without improvement or worsening [52]. Skin grafting of PG and PVU demonstrates significant benefits in healing times and functional outcomes, with a majority complete healing rate, highlighting its efficacy compared to non-grafting approaches. Preoperative and postoperative immunosuppressive therapy further enhances the success of grafting, making it a valuable treatment option for promoting faster recovery and preventing complications. Suoniemi et al. (2024) examined the role of surgical intervention, specifically skin grafting, in treating vasculitis and PG ulcers. Of 80 patients, 11 patients underwent surgery, typically, those who were older had lower mobility, and had underlying conditions like pulmonary diseases and rheumatoid arthritis [53]. Of 181 ulcers, 27 were treated surgically, with most undergoing a single surgery [53]. The study found that over 90% of both surgically and conservatively treated ulcers healed, with a median healing time of less than 100 days for surgically treated ulcers [53]. The results suggest skin grafting is a safe and effective treatment when surgery is necessary, especially with a multidisciplinary approach [53]. Skin grafting for vasculitic and pyoderma gangrenosum ulcers is a safe, effective option, especially for patients with underlying conditions or limited mobility, while offering faster recovery and improved outcomes when conservative treatments fall short.

Future directions in treating PG focus on targeted therapies, with emerging research exploring biologics, and advanced wound care technologies. Although skin grafts have shown promise in PG treatment, gaps remain in understanding the optimal timing, technique, and patient selection for grafting procedures. Emerging treatments such as Janus Kinase inhibitors, IL-36 inhibitors, and complement inhibitors offer new hope for PG patients. Clinical studies suggest biologics may become integral in PG treatment [54]. These therapies could potentially improve healing rates and reduce the need for surgical interventions, such as skin grafts. Additionally, personalized medicine approaches may be able to complement biologic therapies to optimize treatment outcomes. As these therapies progress, future research should aim to integrate these novel treatments with surgical approaches, including skin grafting, and establish specific

protocols tailored to PG's unique characteristics. Collaborative efforts and multi-center trials will be key to advancing treatment options, and bridging the gaps in current knowledge [54]. As biologic therapies like JAK inhibitors and IL-36 inhibitors show promise, further studies are needed to determine how these treatments can complement surgical interventions, such as skin grafting, and lead to more effective, individualized management strategies for PG. While skin grafts have shown potential, there are concerns about pathergy, where grafting can lead to rejection at both donor and recipient sites, especially during the active phase of PG. The integration of advanced immunomodulatory therapies and advanced wound care technologies is being explored to address these challenges. Emerging treatments, such as biologics targeting interleukin 17 and TNF, and synthetic skin grafts like synthetic human skin fibroblast matrix (SHSFM), offer promising alternatives. SHSFM, a synthetic scaffold that mimics the human extracellular matrix, has successfully accelerated wound healing in refractory PG cases, reducing the inflammatory response and minimizing pathergy risks [55]. This synthetic approach provides a potential solution for managing PG wounds by promoting cellular growth, neovascularization, and minimizing bacterial penetration. Personalized medicine and biologic therapies, in combination with advanced wound care technologies like SHSFM, could lead to more effective and safer treatment protocols. Integrating these new technologies and treatments into PG care could improve outcomes and reduce complications associated with traditional grafting methods [55]. As biologics and synthetic skin grafts show promising potential in minimizing pathergy risks and improving healing, further studies are needed to refine these approaches and integrate them into standardized, effective treatment protocols for PG. A promising alternative for PG patients is minced micrografts, a minimally invasive technique involving autologous grafts [56]. This technique involves harvesting a small amount of skin from the clavicular or inguinal region, mincing it into fine pieces, and suspending the minced tissue in a sterile hydrogel or saline solution [56]. The graft is then applied to the wound bed, and this procedure does not require special equipment or complex surgical techniques, making it a low-cost option to promote ulcer healing by releasing cytokines, chemokines, and growth factors [56]. This process aids in forming granulation tissue and angiogenesis. Cammarata et al. (2021) discussed a case study of a 28-year-old man with PG, the minced micrograft procedure successfully sped up wound healing. After only 7 days, there were signs of re-epithelialization, and the ulcer healed completely within three months [56]. Additionally, biologically active cryopreserved human skin allografts (BSA) have been found to induce wound healing by releasing active compounds and promoting revascularization, offering a safer alternative to traditional grafting methods [57]. This suggests that BSA eliminates the risk of pathergy, as it avoids harvesting from the patient and can be applied multiple times to enhance epithelialization and wound recovery [57]. As a result, biologically active cryopreserved human skin allografts demonstrate promising potential for promoting wound healing in PG patients, offering a safe alternative to traditional grafting methods. This underscores the need for future research to address the gaps in PG-specific grafting protocols, focusing on integrating emerging therapies, such as biologics, advanced wound care technologies, and personalized medicine to optimize treatment outcomes and improve healing for PG patients.

Conclusion

Orthopedic wounds complicated by PG presents a challenge that involves orthopedic specialists, dermatologists, and wound specialists. PG is a challenging pathology given the interplay between, surgical trauma, immune dysregulation, and pathergy. Management of such wounds requires not only the management of the local tissue damage, but also the ability to modulate and dampen the immune response. Skin grafting remains a tool in achieving wound closure in PG complicated cases. With a variety of different skin grafts available to a surgeon's disposal, split-thickness, full-thickness, and bioengineered skin, all with distinct advantages and disadvantages. Interdisciplinary collaboration is valuable in enabling tailored treatment plans that address the inflammatory component of PG. While current research about the etiology of PG is still ongoing, there has been significant progress to address the management of PG complicated wounds. By advancing our understanding and treatment of this rare dermatosis we can improve outcomes and quality of life in affected individuals. In this review we sought to illustrate the multifaceted approach that is required to manage orthopedic and other chronic wounds complicated by PG. This review demonstrated the integrated systemic therapies, advanced wound care modalities, and interdisciplinary collaborations useful for PG management. By understanding such complexities and intersection of PG pathophysiology, wound management, and grafting techniques clinicians can manage the challenges posed by this rare dermatosis.

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