

Special Considerations in Disease Manifestations and Management of Pemphigus in the Elderly

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ABSTRACT Pemphigus, including its main subtypes of pemphigus vulgaris, pemphigus foliaceus and paraneoplastic autoimmune multiorgan syndrome (formally known as paraneoplastic pemphigus), is an autoimmune blistering disease which is characterized by acantholysis resulting from autoantibodies targeting epithelial cell surface antigens. Elderly patients with pemphigus face unique challenges pertaining to diagnostics and therapeutics. This review focuses on the special considerations which relate to the care of this patient group.

KEY WORDS: pemphigus, elderly, disease manifestations, management

INTRODUCTION

As the world continues to experience increasing levels of life expectancy and decreasing fertility levels, people are now living longer lives and the proportion of older persons in the total global population is expected to continue rising. The United Nations World Population 2020 report reflects that globally, there were 727 million persons aged 65 years or over in 2020 and projects that the number of older persons worldwide will more than double, reaching over 1.5 billion in 2050 (1). The proportion of the global population aged 65 years or over has been expected to increase from 9.3% in 2020 to around 16.0 % in 2050 (1). As people advance in age, so does their likelihood of developing cardiovascular disease(2), other metabolic disorders, malignancies, neurological disease and skin diseases (3), among others. Polypharmacy, which has also increased through the years amongst elderly patients (4), interacts with the physical, socioeconomic conditions of each country, resulting in a rise of drug-induced dermatoses as well (5). Recognition of autoimmune blistering diseases (AIBD) from other

inflammatory skin diseases in the elderly is critical because the prognosis and therapeutic options differ greatly depending on the primary disease process, and the implications of these are greater in elderly individuals with potential comorbid conditions and organ dysfunction (6).

Skin changes in the elderly include alterations in the epidermis such as flattening of the epidermis and reduced numbers of Langerhans cells, melanocytes, and melanosomes. Changes in the dermis include a reduction in collagen, elastin, fibroblasts, mast cells and macrophages in addition to dilation of lymphatic channels. In endemic pemphigus foliaceus (fogo selvagem), whole families are found to have the autoantibodies to Desmoglein 1 (Dsg-1) in serum for a long time before one or more of them develop the blistering disease. In non-endemic pemphigus we do not know how long these antibodies have been present before they become pathogenic (7, 8). Whilst elderly individuals appear to have an increased tendency compared to younger individuals overall in

developing blistering disorders, the exact reasons delineated in the current literature are not entirely clear. One hypothesis proposes that this could be partially explained by immunologic dysregulation that occurs with aging (9). Other studies demonstrate that chemical induction of early blisters occurs more readily in elderly skin compared with younger skin (5, 10, 11). The structural changes described above leading to increased fragility in elderly skin could lead to an overall increased tendency of formation of antibodies against exposed epidermal proteins. Senescent keratinocytes also become impervious to apoptosis, leading to slow cellular migration and proliferation and decreased rates of epidermal turnover with consequent delayed re-epithelialization and wound healing (12). In addition, due to distorted skin integrity in aged skin, safety concerns with systemic absorption are increased with the long-term use of any topical medication (11, 13). Chronic low-grade inflammation is a common hallmark of the aging process, with aging leading to increased pro-inflammatory senescent cells that promote compensatory immunosuppression (14) – hence, increased age is itself a known cause of immunosuppression.

Pemphigus is a group of disorders, of which the main subtypes are pemphigus vulgaris (PV) and pemphigus foliaceus (PF). PV is characterized by flaccid blistering with mucocutaneous involvement (Figure 1a, Figure 1b) whilst typical features of PF include flaccid, superficial vesicles and crusted erosions. (Figure 2a, Figure 2b). Paraneoplastic autoimmune multiorgan syndrome (PAMS) is a form of pemphigus which is associated with underlying neoplasia.

Pemphigus, when compared to the pemphigoid group of diseases overall, occurs with higher preva-

lence in the younger age-groups (15). There is an increasing incidence of bullous pemphigoid worldwide in the last 2 decades; such a phenomenon is not yet reported in pemphigus (15). However, with the world's population aging, it is likely that more elderly patients will have active pemphigus or a history of pemphigus. Elderly patients with pemphigus deserve special consideration due to an increased risk of delayed diagnosis owing to confounding comorbidities such as skin oedema from visceral dysfunction, a higher risk of complications from the disease or treatment, and inherent challenges such as mobility or social circumstances which pose barriers to treatment and care. This article will address some specific aspects of disease manifestations and treatment principles in the elderly.

ORAL MANIFESTATIONS

Studies have indicated that there is an association between oral health problems and frailty in older patients (16, 17). Aging causes changes in the oral mucosa: epidermal turnover slows down due to decreased division of keratinocytes and longer migration from the basal layer to the surface. Increased fragility occurs due to atrophy of the epidermis and flattening of the dermo-epidermal junction. Structural changes during ageing also decrease elasticity and superficial microvasculature leading to poorer wound healing and immunity (18).

Diagnosing oral pemphigus can be challenging especially in elderly patients, owing to the heterogeneity of oral PV lesions that may mimic other oral conditions such as lichen planus. This leads to diagnostic delays until cutaneous blistering and/or other mucosal lesions have developed which make pemphigus



Figure 1a: fresh erosions on posterior thigh of elderly patient



Figure 1b: small and large erosions at various stages of re-epithelisation on trunk and proximal anterior thighs of elderly patient

evident (19). Pemphigus patients with oral lesions of desquamative gingivitis have been shown to experience longer diagnostic delays than patients with ulcers and erosions (20).

Oral manifestations in pemphigus vulgaris and PAMS are protean and can range from erythema, to lichenoid, reticular, erosive lesions to diffuse, painful haemorrhagic stomatitis involving the lips, tongue, cheeks, gingivae, or the entire oral cavity. Lesions may extend to the nasal mucosa, pharynx, larynx or oesophagus. Compared to patients with PV, PAMS has more prominent pan-stomatitis and haemorrhagic mucositis. Oral involvement occurs usually early in PAMS and is typically treatment-resistant. In a multi-center retrospective study of incident pemphigus in individuals aged 70 years and older, authors found that 64% (25 out of 39) patients had oral involvement and a third had nose and throat involvement (21). Resultant odynophagia and dysphagia from oral pemphigus further contributes to major malnutrition in elderly patients, and may prompt feeding supplementation through naso-enteric tubes or gastrostomy and nutritional support.

A prospective, observational Iranian study (22) analysing patient and treatment factors that affect the prognosis of oral lesions in PV demonstrated that buccal lesions took the longest to resolve (73 [33.5-105.5] days), and that the likelihood of improvement in buccal and soft palate lesions decreased by 5% and 3% with each additional year of age, respectively. Concomitant herpes simplex virus infection increased the healing time of lesions by 26 days (median of 55 days vs. 29 days, hazard ratio 2.62, 95% CI: 1.04-5.92). The tendency for delayed healing in the elderly may be further exacerbated by the microtrauma from denture use.

The treatment of oral lesions of pemphigus in the elderly is nuanced by the patient's adversity to pain, concomitant comorbid conditions which necessitate the careful use of systemic medications, the compromised immunity due to age and the presence of pre-existing oral interventions such as dentures or implants. Wherever possible, effort should be made to optimise local treatment in conjunction with or before starting systemic treatment.

GENERAL MEASURES FOR ORAL PEMPHIGUS IN THE ELDERLY

All elderly pemphigus patients should attend their dentists for gum cleaning to mitigate plaque-induced gingivitis on top of that caused by pemphigus, especially when immunosuppressed. Knowledgeable dentists can use topical anaesthetic preparations to

reduce or eliminate the pain of gum cleaning. Maintaining good oral hygiene using antiseptic (chlorhexidine) mouthwashes is critical. Use of prophylactic anti-candida therapy (such as nystatin swishes/gargles) for patients on long-term corticosteroid treatments is beneficial (23).

Elderly patients are predisposed to salivary gland hypofunction (either directly from age, or polypharmacy/medicine side effects), and pre-clinical evidence further shows that oral wound healing is impaired in such settings. To ameliorate dry mouth in elderly pemphigus patients, simple measures such as advising patients to chew sugar-free gum or suck on sugar-free hard candies to stimulate the flow of saliva, limiting caffeine intake, smoking cessation can be advised. In addition, patients should be advised to avoid alcohol-containing mouthwashes and avoid using over-the-counter antihistamines and decongestants. There is also literature to suggest a beneficial role of cholinomimetic agents in the treatment of pemphigus (24, 25) (in terms of preventing acantholysis by competing with autoantibodies for acetylcholine receptor occupancy). In an open-label prospective study, De *et al.* assessed the effectiveness of topical pilocarpine 2% eye-drops (as a parasympathetic cholinergic agonist) in the treatment of recalcitrant oral lesions of pemphigus and found that topical pilocarpine could promote re-epithelialization without imparting any immunomodulatory activity (26).

Elderly pemphigus patients should also be advised to undergo regular dental evaluation, including evaluation of existing dentures and prosthetic restorations where applicable. Studies have shown that oral remission in pemphigus patients can be maintained with adequate oral rehabilitation, and regular follow-ups (27). Dental implants such as mandibular acrylic resin-based ones can also cause less friction on mucosae than regular dentures (28).

Diet modifications (such as a soft diet without irritants) may be required in edentulous patients or patients with dental issues. In elderly patients, owing to their comorbid burden, nutrition may already be suboptimal. Hence, the involvement of a multi-disciplinary team of dentists, nutritionists, dieticians and speech therapists is instrumental.

MEDICAL TREATMENT OPTIONS FOR ORAL PEMPHIGUS IN THE ELDERLY

Intralesional injections of corticosteroids (triamcinolone acetonide (20µg/L) (23) or paramethasone can be administered every 7–15 days with careful evaluation of response (23)), intralesional rituximab injections (29) for isolated lesions of oral mucosa,



Table 1 : Dressing types and special considerations for use in elderly patients

Type of dressing*	Dressing	Wound types	Summary of studies providing evidence	Examples	Special considerations for use in elderly patients
Primary	Silicone	Used on low exudating wounds.	1. Duipmans JC, Bolling MC. Wound Care in Autoimmune Bullous Diseases. In: Horváth B, editor. Autoimmune Bullous Diseases: Text and Review. Cham: Springer International Publishing; 2022. p. 193-	<ul style="list-style-type: none"> • DAPTIC TOUCH™ (KCI) • Cardinal Health™ Silicone Contact Layers (Cardinal Health) • ComfiTel™ (DermaRite Industries) • Cuticell® Contact (Essity) • Mepitel® (Mölnlycke Health Care) 	<ul style="list-style-type: none"> • Overall suitable and safe for use in elderly patients. • May dry out if left in place for too long. • In general, it is possible to use dressings such as Mepitel soft silicon mesh as the first wound contact layer for 5-7 days. Further topical treatment can be applied on top of the mesh daily • Avoid overly frequent dressing changes as this can compromise an already re-epithelising and fragile wound.
Primary	Hydrocolloids	Suitable for low to moderately exudating wounds	1. Soares HPL, Brandão EDS, Tonole R. Primary bandages for people with pemphigus vulgaris lesions: an integrative literature review. Rev Gaucha Enferm. 2020;41:e20190259.	<ul style="list-style-type: none"> • Comfeel® (Coloplast Sween, Inc.) • Cutinova® (Smith & Nephew) • Duoderm® (Convatec) 	<ul style="list-style-type: none"> • Not suitable for use on dry/necrotic wounds or highly exudative wounds. • May cause maceration. • Can be left up to 7 days, earlier if there is leakage of fluid • As hydrocolloids have relatively long wear-time, this can be useful to minimise local trauma from dressing changes in the elderly. • To be cautious when removed as can cause stripping from adhesives. • Due to its opaque consistency, there can be difficulties with monitoring wound healing. Moreover, hydrocolloids may produce a brown malodorous exudate that can be mistaken for infection • May cause contact dermatitis
Primary	Hydrogels	Ideal for dry, necrotic wounds, partial thickness wounds, or areas with minimal drainage where the aim is to rehydrate the tissue. When used on a slightly exudative wound, a secondary dressing may be needed to contain any excess fluid.	1. Grada A, Obagi Z, Phillips T. Management of chronic wounds in patients with pemphigus. CHRONIC WOUND CARE MANAGEMENT AND RESEARCH. 2019;6:89-98.	<ul style="list-style-type: none"> • Clearsite® (Conmed Corp.) • Curafil™ (The Kendall Co.) • Elasto-Gel™ (SW Technologies) • Normgel® (SCA Hygiene Products) • 2nd Skin® (Spenco Medical, Ltd.) • Transigel™ (Smith & Nephew) • Vigilon® (CR Bard) 	<ul style="list-style-type: none"> • A hydrogel dressing should typically be changed every 2-3 days, depending on the amount of exudate from the wound (wounds with less drainage can be left with the same dressing for up to 3 days) • Watch for signs like leakage, loosening, displacement, or odor, which can indicate the need for a dressing change. • Not suitable for use on highly exudative wounds or where anaerobic infection is suspected. May cause maceration.

Primary	Alginates	Moderate to highly exudating wounds . Useful for debridement of sloughing wounds	1. Ferraz MP. Wound Dressing Materials: Bridging Material Science and Clinical Practice. Applied Sciences. 2025; 15(4):1725.	<ul style="list-style-type: none"> • Algiderm (Bard) • Algisorb™ (Calgon-Vestal) • Algosteril® (KCI) • Kaltostat® (ConvaTec) 	<ul style="list-style-type: none"> • Not for use on dry/necrotic wounds as there is risk of further desiccating the wound and delaying wound healing • Dressing should be changed daily.
Primary	Wet silver-containing dressing	Suitable for exudating wounds	<p>1. Abedini R et al. Comparison of topical nanocolloidal silver formulation use with eosin 2% solution in management of hard-to-heal ulcers in patients with pemphigus vulgaris. <i>J Wound Care.</i> 2020 Nov 2;29(11):664-8.</p> <p>2. Chen J et al. A preliminary clinical trial comparing wet silver dressings versus wet-to-dry povidone-iodine dressings for wound healing in pemphigus vulgaris patients. <i>Dermatol Ther.</i> 2021 May;34(3):e14906.</p> <p>3. Sinha S et al A. Nanocrystalline Silver Dressings in Extensive Pemphigus Vulgaris: An Underutilized Adjunct. <i>Indian Dermatol Online J.</i> 2021 Jul-Aug;12(4):614-5.</p> <p>4. Masjedi H et al. The healing effect of nano-silver dressings in pemphigus vulgaris. <i>Wounds Middle East.</i> 2015 01/01;2:30-4.</p> <p>5. Etesami I et al. Topical care in pemphigus wounds: A systematic review of the literature. <i>Dermatologic Therapy.</i> 2022 2022/11/01;35(11):e15808.</p>	<ul style="list-style-type: none"> • Aquacel Ag® (ConvaTec) • Acticoat 7 (Smith and nephew) • ACTISORB® Silver 220 (KCI) • Silversorb (medline) Silvercel (KCI) 	<ul style="list-style-type: none"> • Silver containing dressings may cause discoloration of the skin of elderly patients • Rare risk of systemic absorption and silver toxicity. Predictive factors for systemic silver absorption based on an observation study by Brouillard et al were increased size of wound, presence of anaemia and malnutrition. Wound vascularization was postulated to play a role as a higher absorption was observed in cases of wound granulation without arterial components. • Risk of slow elimination of silver from body • Do not use if known sensitivity to silver. • Suggest to discontinue after 2 weeks if no improvement and reevaluate.
Primary	Paraffin embedded tulle net/ Polyester mesh	Flat shallow wounds with low exudates	6. Mutalik SD, Rasal YD. Paraffin-embedded tulle nets as a simple dressing technique for patients with pemphigus. <i>JAAD Int.</i> 2020 Jul;1(1):11-2.	<ul style="list-style-type: none"> • Paraffin embedded tulle net • Jelonet® • Lomatuell® H • Urgotul 	<ul style="list-style-type: none"> • These are low adherent dressings that can be particularly useful for elderly patients with sensitive/fragile skin. These dressings are comfortable and can conform to body contours. • For Jelonet dressings, can be changed every 2-3 days • Urgotul can be left in place for up to 7 days, although might have to be changed more frequently to prevent drying out and infection.
Non-conventional modalities					



Primary	Biobrane	Conventionally used to cover clean burns, donor sites, and meshed skin grafts.	1. Vun YY, Lun K, Stratton G. Use of biosynthetic dressings in paraneoplastic pemphigus. <i>Australas J Dermatol.</i> 2004 May;45(2):133-5. 2. Ehrenreich M, Ruszczak Z. Tissue-engineered temporary wound coverings. Important options for the clinician. <i>Acta Dermatovenerol Alp Pannonica Adriat.</i> 2006 Mar;15(1):5-13. PMID: 16850093.	<ul style="list-style-type: none"> • Biobrane (Mylan Laboratories, Inc) 	<ul style="list-style-type: none"> • High costs may be prohibitive for long term use • Muslim patients may reject the use of Biobrane due to its porcine origins • Due to risk of infection, authors suggest that the Biobrane dressings should be applied within 24–48 hours of the burn injury to reduce infection.
N.A	Platelet gel	N.A	1. Sijan G, Vojvodic A, Milicevic S, et al. Platelet gel in wound treatment in patient with pemphigus vulgaris and type 2 diabetes mellitus: case report. <i>Dermatol Ther.</i> 2019;32(6):e13099.	<ul style="list-style-type: none"> • Homologous platelet gel 	<ul style="list-style-type: none"> • Not conventional treatment; investigate basis • Lack of evidence to encourage widespread use
N.A	Topical insulin	N.A	2. Pawar M. Topical insulin in the treatment of non-healing erosions and ulcers of pemphigus vulgaris. <i>J Am Acad Dermatol.</i> 2021 Nov;85(5):e271-e2.	<ul style="list-style-type: none"> • Human actrapid insulin 40IU/ml® 	<ul style="list-style-type: none"> • Not commonly used- inconsistent dosage and form. • In elderly patients, theoretical side effects of hypoglycemia, hypokalemia, wound infection, bleeding, allergenicity, and pain related to insulin administration could result, although a review by Wang et al of 15 animal studies and 10 clinical studies did not observe these side effects.
N.A	EPIFIBROIN 0039	N.A	3. Sacchelli L, Barisani A, Sgubbi P, Loi C, D'Antuono A, Gaspari V, et al. EPIFIBROIN 0039 dressing and powder as a therapeutic aid for erosive and ulcerated dermatoses of the skin and mucosa: an investigative study. <i>Eur J Dermatol.</i> 2018 Dec 1;28(6):844-5.	<ul style="list-style-type: none"> • EPIFIBROIN 0039 dressing 	<ul style="list-style-type: none"> • Not conventional treatment; investigative basis • Not standardised treatment regimens

*Primary dressings are used directly on the wound surface, whilst secondary dressings serve a therapeutic or protective function or are needed to secure a primary dressing. Some dressings may be used as only a primary or secondary dressing, while some may serve either purposes depending on how it may be used

lips. Topical application of potent corticosteroids (0.05% clobetasol propionate, 0.05% halobetasol where available), less potent corticosteroids (0.1% triamcinolone acetonide in orabase), topical calcineurin inhibitors, topical trichloroacetic acid (30) can also be applied directly to the lesions (23). Topical application of local anaesthetic gel, administration of analgesics such as (paracetamol, non-steroid anti-inflammatory drugs and opioids) may also help.

BLISTERING AND WOUND CARE

Blisters which form in pemphigus are often flaccid lesions with the tendency to easily break down reveal-

ing erosive and exuding areas. This leads to erosions and ulcer formation, which themselves can be hard-to-heal or be complicated by concomitant infections. Erosions are often painful and cause discomfort for patients. The thinned epidermis in elderly patients is more prone to mechanical trauma (shearing and friction). Cutaneous fragility and resultant compromise of the skin barrier in pemphigus also facilitates colonization of the skin by staphylococcal organisms (31), at times rendering individuals refractory to treatment by preventing or further delaying wound healing. Evidence shows that even with the advancement in the effective treatment of pemphigus, infections



Figure 2a: crusted erosions and plaques on posterior trunk of elderly patient



Figure 2b: superficially eroded plaques in healing on buttocks and posterior thighs of elderly patient

and septicemia continue to be the leading cause of morbidity and mortality (32). Therefore, wound care is critical to facilitate healing, reduce infections, and minimise scar formation.

Other considerations in selecting wound care regimens for elderly pemphigus patients include recognition of the patient's ability to comply with the recommended wound dressing regime in view of factors such as cognitive dysfunction, impaired vision, hearing, or mobility as well as socioeconomic factors including the presence of a dedicated caregiver if patients themselves are unable to exhibit self-care). Once again, simple topical regimens specifically for limited or localised sites are preferable in the elderly in order to maximise safety.

Elderly patients with extensive disease, particularly when more than 30% of the body surface area (BSA) is involved, should be considered for transfer of care to a burn care unit, where proper temperature and humidity control can be provided. In patients with less than 30% affected BSA but with extensive wounds, inpatient management should be considered. During hospitalisation, these elderly patients should be considered for single room isolation, preferably in a low flow room, to reduce infection risks.

PAIN MANAGEMENT DURING WOUND DRESSINGS

Optimising analgesia for elderly patients is critical. Measures include both pharmacological and non-pharmacological interventions. Simple analgesia options include paracetamol, non steroidal anti-inflammatory drugs (NSAIDs) and short-acting opioids should be considered, particularly prior to dressing change. Occasionally, anxiolytics may be considered if patients have severe pain and anticipatory anxiety before and during dressing changes.

CLEANSING OF WOUNDS

All erosions and wounds should be cleansed carefully with antiseptics such as Octenidine 0.3% bath wash during showering or bathing as far as the patient can tolerate. If not, water or topical products like wound irrigation solution or gel with polyhexamethylene biguanide (PHMB) can be poured onto the wounds. The room temperature should be ambient, between 20°C and 24°C (68°F and 75°F), and as comfortable as possible for elderly patients.



Table 2: Summary of treatment options with considerations in elderly patients

Treatment options*	Considerations in elderly patients
Treatment of mild pemphigus foliaceus (Options are dapsone OR topical steroids/systemic steroids OR rituximab) Treatment of mild pemphigus vulgaris (Options are systemic steroids OR rituximab)	
Topical steroids/Systemic steroids	<ul style="list-style-type: none"> Risks of osteoporosis, suppression of the hypothalamic-pituitary-adrenal axis, iatrogenic Cushing's syndrome, glaucoma are pertinent especially in elderly patients Other complications of infections with prolonged use, electrolyte derangements (particularly with polypharmacy use), skin atrophy, slower wound healing can further compound problems in elderly pemphigus patients.
Dapsone	<ul style="list-style-type: none"> In elderly patients, the most frequent side-effects such as methemoglobinemia, haemolytic anaemia should be monitored closely for- particularly in G6PD-deficient patients who are more susceptible. Rarer side-effects of dapsone include: agranulocytosis, peripheral neuropathy and dapsone hypersensitivity syndrome
Treatment options for moderate-to-severe pemphigus (Options are steroids + rituximab OR if rituximab is contraindicated or not available, steroid ± azathioprine/mycophenolate mofetil)	
Azathioprine (Aza)	<ul style="list-style-type: none"> Elderly patients with pre-existing liver disease may be at risk of abnormal liver enzymes following azathioprine treatment A study of pemphigus patients (not restricted to elderly) showed that oral candidiasis was the most commonly encountered side effect from Aza use, with less frequent occurrences of infections, bone marrow suppression. (60)
Mycophenolate mofetil (MMF)	<ul style="list-style-type: none"> Elderly patients may be at increased risk of infections, gastrointestinal haemorrhage and pulmonary oedema, compared with younger individuals.(61)
Rituximab	<ul style="list-style-type: none"> The primary concern with using rituximab in elderly patients is the higher likelihood of developing serious infections due to its immunosuppressive effects. Close monitoring for signs of infection is essential during and after rituximab treatment in elderly patients. Lower dose of rituximab might be considered in frail elderly individuals. Low dose rituximab regimens include 2 infusions of 500 mg 2 weeks apart(77)s_ version:"10.0.26100"/"event.category":"DESKTOPA; two 200 mg infusions of RTX 14 days apart(78) (as ultra low dose rituximab)
JAK inhibitors	<ul style="list-style-type: none"> Avoid use in elderly patients who exhibit known hypersensitivity to JAK inhibitors as a class, who have cytopenias (lymphopenia (absolute lymphocyte count <500cells/mm³), neutropenia (ANC <1000cell/mm³) or anaemia (Hb <8g/dL), thrombocytopenia (< 150 x 10³/mm³), a history of malignancy, current or chronic infections. Be careful of severe hepatic or renal impairments that may occur in elderly Use with caution in elderly patients with risk factors for thrombosis (e.g., deep vein thrombosis, pulmonary embolism).

*Conventional adjuvants may be considered as first-line therapy when rituximab is not available, or not permitted as first line, or in patients with contraindications to rituximab.

REMOVAL OF EXISTING DRESSINGS AND RE-APPLICATION OF NEW DRESSINGS

Existing dressings should be carefully removed so that re-epithelializing skin can be left intact. If there are adherent gauzes that are stuck onto the wound bed, gentle soaking with water, saline, paraffin/petroleum jelly ointment or a silicon medical adhesive remover (SMAR) can be used.

FREQUENCY OF DRESSING CHANGE

Frequent dressing changes may compromise wounds that have undergone fragile re-epithelialization. Where wounds clinically clean, dressing changes can be conducted at an approximate frequency of 3 times a week (depending on the longevity of the dressings too). However if there is wound infection,

or if the wound exhibits large amounts of exudate, more frequent dressing changes may be required.

Selecting appropriate wound dressings

Proper dressings will provide a safe environment for the skin wound healing process. Various non-stick dressing materials can be used for wound coverage and enhancement of the healing process (33). These include silicone dressings (34) and conventional film/hydrogel dressings (35). Newer adjuncts to dressings include paraffin-embedded tulle nets, topical insulin, EPIFIBROIN 0039, Platelet gel and Biobrane®. Using similar dressings to those recommended for patients with epidermolysis bullosa is safe as they do not stick to the fragile skin. A summary of available dressings and special considerations for use in elderly patients is provided in Table 1.

TACKLING WOUND INFECTION

Tackling wound infection is crucial in managing healing/re-epithelising wounds in pemphigus patients. This is particularly so for elderly patients who can exhibit reduced inflammatory responses from attenuated T-cell proliferative responses, decreased production of cytokines and number of Langerhans cells. Wound infections delay the overall process of healing and contribute to morbidity and mortality in elderly pemphigus patients. When the elderly experience erosions over large areas, there is increased difficulty in dressing delicate body sites such as the groins, axilla and neck. Extensive wounds can cause the elderly substantial amount of pain, both during dressing changes and daily activities, further complicating care.

In order to prevent infection, patients should be informed not to manipulate blisters (although this can be tricky in elderly patients with cognitive impairment/behavioural issues). Gentle cleansing with normal saline, antibacterial soap/antiseptic twice a day can be considered. Daily shower and frequent cloth changing is typically advised to patients.

Recognising early signs of infection is paramount. Local infection can present with erythema, edema, purulent discharge, or malodor. Systemic signs such as fever and leukocytosis are suggestive of progression to bacteremia requiring early administration of antibiotic therapy. However, the elderly may not always mount a febrile response. This puts them at risk of delayed recognition and management of sepsis (36). Skin swabs should be obtained, where possible, for culture and sensitivity to direct appropriate antibiotic therapy. For superficial skin infections, topical mupirocin can be effective against gram-positive organisms and topical metronidazole can be considered in cases of infection with anaerobic organisms. In severe cases, systematic antibiotics may be required (36).

ASSOCIATION WITH MALIGNANCY

Paraneoplastic autoimmune multiorgan syndrome (PAMS), compared to the other more common forms of pemphigus, occurs largely in individuals aged above 60 years. This coincides with increased rates of malignancy (10, 11). The relationship between PAMS and malignancy is well established, most commonly with haematological malignancies; non-Hodgkin lymphoma is the most frequent, accounting for approximately 40%, followed by Castleman disease (~30%) and chronic lymphocytic leukemia (~10–15%) (37). Unlike PAMS, the association between PV, PF and hematological malignancies is less

distinct. Yet, emerging studies have reported higher incidences of lymphoproliferative disorders in PV and PF patients – these include chronic leukemia, multiple myeloma, and non-Hodgkin lymphoma (38-41). The association between PV and haematological disorders has been postulated to be related to chronic inflammation involving cytokine release and B cell activation, thereby driving the formation of hematological cancers (39, 42).

Solid organ tumors may be found in 14.8-17% of PAMS(43, 44)– and are of epithelial or mesenchymal origin in about 9% and 6% of the cases, respectively (44, 45). Previous studies have reported that there are high rates of gastrointestinal (colon and esophageal) and oropharyngeal (larynx) tumors associated with PV/PF (39, 46). Studies that have indicated that pemphigus can precede or follow the occurrence of laryngeal/esophageal malignancies further postulate that these malignant tumors may induce tissue damage and morphological alterations in the epithelial surface antigens of the laryngeal and oesophageal mucosae, unveiling previously concealed antigens (epitope spreading phenomenon) (47).

In an Israeli study of a PV cohort compared with the national cancer registry, Warshavsky K *et al.* demonstrated higher rates of malignancies (both solid organ and haematological) among patients with PV compared to the general population. In this study, the mean age for PV diagnosis was also found to be higher in the past malignancy and newly diagnosed malignancy groups compared to patients with PV without malignancy (62.2 years vs. 48.9 years and 67.2 years vs. 47.4 years, respectively).

Drawing lessons from this study, PV patients who have concomitant malignancy tend to be older, yet nevertheless with higher rates of malignancy in PV patients (in general) compared to the general population. Although there is no current consensus on cancer screening in patients with pemphigus and treatment algorithms for those with concomitant malignancies, existing S2K guidelines which detail recommended screening approaches for evaluating underlying neoplasms for PAMS can serve as a useful guide (45). Physicians may do so by obtaining a focused medical history of fever, fatigue, night sweats, weight loss, pain and other cancer-related symptoms and performing careful physical examination for lymphadenopathy, organomegaly. Laboratory testing should include: complete blood count (CBC), liver and kidney function tests, tumour markers where appropriate. Relevant imaging studies include a contrasted computed tomography scan of the thorax, abdomen and pelvis, with consideration for endoscopy (oesophagogastroduodenoscopy, colonoscopy)



and/or mammography (age-appropriate screening in the absence of suggestive history/clinical signs) (45). In Asia, screening for nasopharyngeal cancer would be appropriate.

This screening approach is in line with reports that dermatoses in the elderly occur in a higher association with malignancy. In a retrospective cohort study analysing the prevalence of malignancy-associated erythroderma in a single centre where there was concerted effort to systematically offer malignancy screens to all adult erythroderma patients above the age of 65 years, there was a higher observed occurrence of malignancy in association with erythroderma. (48) As delays in evaluation for underlying malignancy could result in potentially deleterious outcomes, it is also prudent to consider systematic screening for malignancy in high-risk populations such as elderly erythroderma patients.

Finally, early diagnosis of the associated malignancies in elderly patients does not only improve the prognosis of cancer but also minimizes the risk of iatrogenic immunosuppression from pemphigus treatment. As pemphigus treatment often requires inductive therapy with corticosteroids or rituximab, followed by long-term immunosuppressants such as cytotoxic immunomodulators (mycophenolate mofetil, azathioprine, methotrexate, cyclosporine) and antimalarial agents, prior cancer screening can avert excessive immunosuppression in malignancy-affected patients.

TREATMENT CONSIDERATIONS

Treatment options of pemphigus in the elderly are detailed below, and further summarised in Table 2. The treatment options are based on the (2020) S2K guidelines on the management of pemphigus vulgaris and foliaceus initiated by the European Academy of Dermatology and Venereology (EADV) (49).

Topical/intralesional therapy

Topical/intralesional corticosteroids

For elderly patients with mild PF, topical corticosteroids: (class III, IV) alone may be possible if there are only very limited lesions. As this treatment option would be most appropriate for limited affected BSA, the risks of systemic absorption of topical steroids would not be considered to be high. The local side effects from topical steroid application in elderly include steroid atrophy, telangiectasias. Prolonged use of topical steroids in the elderly can also lead to systemic side effects such as suppression of the hypothalamic-pituitary-adrenal axis, iatrogenic Cushing's syndrome, glaucoma and elevated risks of osteoporosis.

Topical adjuvant treatment with super-potent corticosteroids (clobetasol propionate or triamcinolone acetonide gel) directly to oral erosions, as well as intralesional corticosteroid injections (to isolated/limited areas on oral mucosa, lips, skin) may be considered in some patients in combination with systemic therapy. However, the risks of systemic absorption must be carefully considered in prolonged use.

SYSTEMIC THERAPY

Systemic corticosteroids

Of the many adverse effects associated with corticosteroid use, those that are especially pertinent for elderly patients include increased risks of infection, psychological/psychiatric side-effects and myopathy.

Elderly patients who experience immobilization/reduced mobilisation find themselves at increased risk for thromboembolic events and pressure ulcers – the latter of which can be secondarily infected leading to widespread sepsis and increased mortality. Concomitant corticosteroid use increases infection risks in general.

Regarding psychological/psychiatric side effects, literature reveals that up to 60% of patients taking systemic corticosteroids exhibit these side effects. When measured using the validated GTI tool prospectively, Liang *et al* identified that 69% of steroid-treated AIBD patients developed neuropsychiatric side effects. (50) Steroid psychosis may not have a uniform presentation, and may present in elderly patients as anxiety, emotional lability, pressured speech, insomnia, mutism, and memory impairment. Patients may present with features that mimic schizophrenia with delusions, visual or auditory hallucinations and disorganized speech and behaviour (51). Kusljic *et al.* observed that psychosis is twice as likely to occur within the first 5 days of treatment (early on in treatment) and that patients on higher doses of steroid therapy (i.e. patients receiving 40 mg/day) were at greater risk of steroid-induced psychosis. Therefore, close monitoring of elderly patients on systemic corticosteroids for identification of changes in mental state and function should be undertaken by family and nursing/care staff.

Myopathy is associated with high doses of prednisolone >40–60 mg/day (52). Individuals may develop myopathy in approximately 2 weeks (cumulative dose >560 mg). Patients who have received steroids for less than 4 weeks rarely develop steroid myopathy, although there are wide variations in the dose and duration of steroid treatment associated with glucocorticoid-induced myopathy. Although the use

of prednisone or equivalent drugs in doses of lower than 10 mg/day are rarely associated with glucocorticoid-induced myopathy; higher glucocorticoid doses result in more rapid onset of clinically significant muscle weakness, which can be observed within 2 weeks after the initiation of corticosteroid therapy; the use of prednisone or equivalent drugs in doses of 40-60 mg/day for at least 1 month results in some degree of muscle weakness (52).

In particular for elderly patients, treatment considerations would include reducing corticosteroid doses or switching to every-other-day treatments, consideration of discontinuing corticosteroids if not required – with evidence showing improved muscle strength in 3–4 weeks upon cessation.

Elderly patients should also be optimised further in a multidisciplinary manner – to increase protein intake and increase physical therapy and mobilisation. In terms of physical therapy for patients with corticosteroid-induced myopathy, both endurance and strength exercise training has been shown to play a preventive role in the development of muscle atrophy, but authors suggest that a combination of both with different frequency, intensity and duration seems to be more effective. Historically, endurance exercise had been found to be an effective against skeletal muscle atrophy that can result from corticosteroid use. Seene *et al.* suggest that since the lack of strength is one of the central reasons in muscle weakness amongst elderly patients, resistance training regimens may be useful. Endurance training, which stimulates mitochondrial biogenesis can also combat the reduced oxidative capacity of skeletal muscle in the elderly, thereby overall improving functional parameters (53).

Dapsone

Dapsone may be useful for treatment of PF patients. As an anti-inflammatory agent with considerably less immunosuppressive properties, it may be considered for use in elderly patients where excessive immunosuppressive may not be desired. Dapsone is usually combined with topical corticosteroids (classes III and IV). In elderly patients, the most frequent side-effects such as methemoglobinemia, haemolytic anaemia should be monitored closely for – particularly in G6PD-deficient patients who are more susceptible. Rarer side-effects of dapsone such as agranulocytosis, peripheral neuropathy and dapsone hypersensitivity syndrome should also be carefully counselled prior to treatment in elderly patients and monitored for.

Rituximab

Elderly patients with pemphigus were considered to be a particularly vulnerable population subgroup during the COVID-19 pandemic, owing to epithelial breakdown from pemphigus activity, and therapy-related immunosuppression. Rituximab, a chimeric CD20 monoclonal antibody, is considered first line therapy based on its well-documented efficacy and safety profile. Joly *et al.* suggest a regimen of rituximab 1g on days 1 and 15, with 2 subsequent infusions of 500 mg rituximab on 12 and 18 months after reaching to a complete remission in patients with pemphigus vulgaris (49). This can be combined with a short-term prednisone regimen (0.5 mg/kg daily for moderate pemphigus and 1 mg/kg daily for severe pemphigus), with initial prednisolone dose maintained for 1 month then tapered after achievement of disease control, with the aim to stop prednisone therapy after 3 months in patients with moderate pemphigus and after 6 months in patients with severe pemphigus.

Kushner *et al.*, when controlling for age and dosing protocol, revealed that older age (65 and older) was significantly associated with achieving complete remission after rituximab therapy. This finding possibly being related to the weakened immune system in elderly patients, making remissions of autoimmune diseases easier to achieve (54).

Observations on the use of rituximab during pandemic times include a more than 5-fold higher risk of COVID-19 infection in patients with AIBD who received Rituximab compared with those who did not (55). Further analysis of 3729 patients with rheumatic diseases revealed that although most traditional immunosuppressive agents were not associated with higher odds of COVID-19-related death, rituximab was (56). To date, data concerning the use of rituximab during the pandemic are still insufficient. Whether its usage is associated with risk of more severe COVID-19 is not yet established. Physicians should consider the risk-benefit ratio of individual cases, and administer rituximab with caution during the periods with high-transmissibility of infections such as during epidemics (57). Long-term follow-up is required for pemphigus patients on rituximab.

Regarding the efficacy of COVID vaccinations in patients who receive rituximab, current literature recommends that patients treated with Rituximab may require an extra vaccine booster to enable reasonable antibody responses following mRNA-based SARS-CoV-2 vaccination (58). However, as no cutoff titre that is most strongly associated with sufficient protection has been defined, the effect of reduced



antibody levels on protection remains unclear (57). Additionally, patients receiving biologics may produce attenuated immune responses, it is not yet clear what the clinical significance of this altered immune response may actually be (57). Long-term follow-up post vaccination is recommended for patients on rituximab.

Based on existing recommendations from literature, for patients with active COVID, it is advisable to postpone the rituximab dose for at least 30 days of infection onset (based on potential length of viral shedding) (59).

Conventional adjuvants may be considered as first-line therapy when rituximab is not available, or not permitted as first line, or in patients with contraindications to rituximab.

Azathioprine

When rituximab is contraindicated, or not available, alternative conventional immunosuppressants that can be considered are azathioprine.(49) Particularly in elderly patients, it is recommended to conduct baseline TPMT and NUDT15 testing to determine metaboliser type, as potential bone marrow suppression may be more risky in an elderly patient with pre-existing conditions such as age-related myelodysplasia. In the first week, a lower dose of 50mg/day can be initiated to detect idiosyncratic reactions (and in case stop immediately), and then subsequently raise to desired dose (49). Elderly patients with high TPMT activity should be treated with normal doses of azathioprine (up to 2.5 mg/kg/day), whilst patients with intermediate or low TPMT activity should receive a lower maintenance dose (up to 0.5 to 1.5 mg/kg/day) depending on level of enzyme activity (49). Patients with lack of TPMT activity should not be treated with azathioprine at all. Studies have shown that between azathioprine and mycophenolate mofetil as adjuvant drugs in pemphigus patients (not limited to elderly patients), recurrence appeared to be higher in those receiving azathioprine (but was not statistically significant) (60). The majority of side effects were minor, including elevated enzymes associated with azathioprine (60). In elderly patients with pre-existing liver disease, closer monitoring may be required if on azathioprine therapy.

Mycophenolate mofetil

Mycophenolate mofetil (MMF) (2 g/day) or mycophenolic acid (1,440 mg/day) can be considered as adjuvant therapy for pemphigus patients (49). Based on guidance from the European Medicines Agency, elderly patients may be at an increased risk of adverse

events such as certain infections (including cytomegalovirus tissue invasive disease) and possibly gastrointestinal haemorrhage and pulmonary oedema, compared with younger individuals (61). Thus for the elderly pemphigus patient, prudence with a starting dose of MMF 1g/day may be utilized instead.

FUTURE POSSIBLE THERAPEUTICS FOR PEMPHIGUS

Janus kinase (JAK) inhibitors

Emerging studies suggest that JAK inhibitors may be potential modalities in the management of refractory pemphigus (62). In elderly patients, JAK inhibitors should be used with caution. Physicians should avoid prescription of JAK inhibitors in elderly patients who exhibit known hypersensitivity to JAK inhibitors as a class, who have cytopenias (lymphopenia (absolute lymphocyte count $<500\text{cells}/\text{mm}^3$), neutropenia (ANC $<1000\text{cell}/\text{mm}^3$) or anaemia (Hb $<8\text{g}/\text{dL}$), thrombocytopenia ($<150 \times 10^3/\text{mm}^3$), a history of malignancy, current or chronic infections. Severe hepatic or renal impairments that may occur in elderly PV patients would also make them unsuitable for JAK inhibitor use. Although large WHO pharmacovigilance studies (63) and systematic reviews show no significant increase in reporting of major cardiovascular events (MACE), JAK inhibitors should still be used with caution in elderly patients with risk factors for thrombosis (e.g., deep vein thrombosis, pulmonary embolism).

BTK inhibitors

Bruton kinase inhibitors are a class of medications that seem to show promise for treatment of pemphigus. Compared to ibrutinib, an irreversible BTK inhibitor that was first suggested to be beneficial to treat PAMS in patients with underlying B cell malignancy, BTK inhibitors like rilzabrutinib and tirabrutinib are reversible and selective oral BTK inhibitors that have been considered for treating pemphigus and have shown acceptable safety and efficacy profiles. Rilzabrutinib was promising in a phase 2 uncontrolled trial in PV as it exhibits reversible covalent binding (and hence self-limited immunomodulatory effects) (64). A phase 3 RCT of rilzabrutinib vs placebo was significant at $p<0.05$ using the original cut off of less than 5mg prednisone but the company requested change to 10mg prednisone showed no difference as 10mg prednisone used long term can be enough to suppress autoantibodies, but results in the latter dose were enough to mask the effect of the BTK (64, 65). Whether or not rilzabrutinib can be considered efficacious for elderly

patients, and can be used under compassionate case basis remains to be seen presently.

FcRN inhibitors

Although previously in the pipeline for pemphigus therapeutics, a recent Phase III ADDRESS study investigating FcRN inhibitor efgartigimod concluded no significant difference in complete remission on minimal steroids (with a changed enforced definition, once again, at 10mg/day instead of 5mg/day) between efgartigimod and placebo in PV patients. The study did not meet its primary endpoint, with 35.5% of subjects achieving complete remission in the efgartigimod arm versus 30.3% in the placebo cohort. This study does not rule out a beneficial effect of efgartigimod in PV as the effect is easily masked by prednisone doses of 10mg/day in the elderly. The consensus definitions allow for any steroid dose below 10mg/day but not zero to be counted as 'minimal' therapy (66).

CAR-T therapy

Early data from phase I open-label trial (NCT04422912) involving DSG3 autoantigen-expressing chimeric antigen receptor (CAR) T-cells (DSG3-CAART) demonstrated that CAR T therapy was well-tolerated with dose-dependent persistence in participants with mucosal-dominant pemphigus vulgaris (67). Studies thus far are only in very mild pemphigus. Drawing from lessons and observations of CAR T therapy utilised for diffuse large-B cell lymphoma treatment in elderly patients, previous literature state that CAR T-cell therapy is associated with favorable event-free survival in older patients, comparable to outcomes in younger patients (68). Further, authors state that CAR T-cell therapy use is low in older patients, demonstrating an unmet need for more accessible, effective, and tolerable therapy (68). However, pemphigus involves more than just T and B cell effects and thus the question of efficacy of this approach remains uncertain at this point.

MONITORING DISEASE PROGRESS OF ELDERLY USING QUALITY OF LIFE (QOL) INSTRUMENTS

The Autoimmune bullous QOL (ABQOL) is a 45-item questionnaire that was first developed as a disease-specific QOL instrument for use in AIBD. (69) Whilst initially formulated and validated in the English language, it has now been validated for use in other languages including Mandarin, Malay, and Greek (70-73). It is able to quantify the effect of a patient's AIBD on their QOL and capture changes in

disease status, which may not be appreciable during routine clinical review. In particular, the ABQOL is able to specifically assess patient concerns for mucosal involvement such as relapse and flares, swelling associated with bullae, and the need to change clothing due to drainage from lesions. Regarding treatment outcomes, Bax et al performed a retrospective study evaluating patients with PV and suggested that even a small amount of disease activity may have a significant impact on QOL (74). Even though apparent disease activity may be low in elderly patients, they may still experience a reduction in QOL. Hence, physicians should consider employing these tools to longitudinally monitor the elderly patient's progress.

ENVIRONMENTAL ADAPTATIONS

Elderly patients are particularly vulnerable to the impact of climate change. They lack the mobility of younger people, who are more able to move out of unsatisfactory or uncomfortable environments and seek more favourable ones compared to homebound, less mobile elderly persons. With respect to pemphigus, it has been shown that humidity, temperature, UV radiation and particulate matter (PM) potentially play important roles in driving disease activity. In an analysis of data from the 2002-2012 National Inpatient Sample in the USA of 68 476 920 children and adults), higher rates of admission primarily for pemphigus were observed to have occurred during the summer and autumn months (June-November) (75). Hospitalization for a primary diagnosis of pemphigus was associated with significantly lower humidity, higher temperature, higher UV index and higher particulate matter of ≤ 2.5 or $\leq 10 \mu\text{m}$ (PM_{2.5} and PM₁₀) (75). Lower humidity causes more disruption to the skin barrier function by increasing trans-epidermal water loss and epidermal proliferation, and by altering distribution of lamellar bodies within the stratum granulosum and corneum. Higher temperatures are thought to result in increased skin moisture evaporation which results in skin dryness. Elevated PM levels induces oxidative stress via production of reactive oxygen species and secretion of pro-inflammatory cytokines (76). With the potential of pemphigus flaring, attention should be paid to reducing the exposure of elderly pemphigus patients to these factors by modifying their ambient surroundings or paying more attention to the application of topical skin-care agents.

CONCLUSION

The management of pemphigus in elderly patients is challenging but fulfilling. Physicians need to bear in mind the multiple co-morbidities arising in the elderly, polypharmacy, and take into account



unique socioeconomic statuses that can directly influence prescription practices. Personalised and tailored treatment plans for elderly patients can help to optimise outcomes.

Statements and Declarations

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Valencia Long, Nisha Suyien Chandran. The first draft of the manuscript was written by Valencia Long, Nisha Suyien Chandran, Dédée F. Murrell, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Conflicts of interest: The authors have no competing interests to declare that are relevant to the content of this article.

Funding: No funding was received for the preparation of this review.

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