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REVIEW

Patient Quality of Life Improvement in Bullous Disease: A Review of Primary Literature and Considerations for the Clinician

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Abstract: Autoimmune and inherited bullous disorders are rare skin diseases that may have a profound negative impact on quality of life (QOL). Common symptoms include pain, pruritus, and scarring, and complications may result in the loss of the ability to perform daily tasks. Diagnosis may have a negative psychological impact, and ongoing management may require a significant allocation of time and resources by both patients and providers. To provide patient-centered care, consideration of these factors is of utmost importance for the dermatologist treating patients with bullous disorders. Herein, we present a review of the primary literature evaluating QOL in autoimmune and inherited bullous disorders, including pemphigus, pemphigoid, epidermolysis bullosa, and Hailey-Hailey disease.

Keywords: bullous disease, autoimmune blistering disease, pemphigus, pemphigoid, epidermolysis bullosa, Hailey-Hailey, quality of life, ABQOL, TABQOL, DLQI

Introduction

Autoimmune and inherited bullous disorders represent rare mucocutaneous diseases that may have a significant negative impact on patients' quality of life (QOL).[1,2] There are various physical, social, and psychiatric factors that contribute to patients' perceived QOL. In order to provide patient-centered care, consideration of these factors is of utmost importance in the treatment of patients with bullous disorders.

In patients with bullous disorders, QOL may be assessed through general medical and dermatology-specific indices, as well as through more specific instruments as evidenced in Table 1. Which QOL assessment best represents patients' experiences remains controversial. For example, Patsatsi et al demonstrated the Autoimmune Bullous Disease Quality of Life (ABQOL) correlated with QOL over time, while Dermatology Life Quality Index (DLQI) assessments did not.[3] In contrast, Ferries et al prospectively assessed the correlation between disease severity scores in pemphigus (Pemphigus Disease Area Index, PDAI), bullous pemphigoid (Bullous Pemphigoid Disease Area Index, BPDAI), and mucous membrane pemphigoid (Mucous Membrane Pemphigoid Disease Area Index, MMPDAI) to ABQOL, Treatment of Autoimmune Bullous Disease Quality of Life (TABQOL), DLQI, and Skindex-29 scores. They concluded that there may be no advantage of the ABQOL over the DLQI or Skindex-29.[4]

An informed understanding of the complexities of how autoimmune and inherited bullous disorders affect QOL is critical to providing patient-centered care. This facilitates shared decision-making between patient and provider and is

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Table 1 A Brief Overview of Frequently Used QOL Assessment Tools

Dermatology Life Quality Index (DLQI)[2,4,7,8,12,13,14,18,20,21,24,30]	The DLQI consists of 10 questions evaluating different aspects of health-related QOL over the preceding week.	Numeric score between 0 and 30. Scores >10 suggest that a patient's life is being severely affected by a skin condition. Higher scores correlate with increased impairment in QOL.
General Health Questionnaire (GHQ-28)[6,18]	The GHQ-28 evaluates general mental health over the last few weeks and is a measure used to detect possible psychiatric disorders. It includes 28 items assessed on a 4-point scale (0–3). The items assess the ability to carry out normal functions and the appearance of new distressing experiences.	Numeric score between 0 and 84. Scores <23 are less concerning for psychiatric stress as compared to scores >24 which should prompt concern for psychiatric distress. Higher scores correlate with increased levels of distress.
Medical Outcome Study 36-item Short-form Survey (SF-36)[6,7,13,19,30,71]	The SF-36 consists of 36 items combined into 8 scored scales. Scales include vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, and mental health.	Numeric score between 0–100. Mean score for the general population is 50. Lower scores correlate with increased levels of disability.
Skindex-29[4,6,7,13,14,30,36]	The Skindex-29 consists of 29 questions that assess the health-related QOL of patients with skin diseases by evaluating 3 domains; degree of symptoms, psychosocial functioning, and emotional status.	Numeric score between 0–100. A score between 0–24 correlates with little impact on QOL, 25–31 with mild, 32–43 with moderate, and 44–100 with severe. Higher scores represent worse QOL.
Autoimmune Bullous Disease Quality of Life (ABQOL)[4,13,14,15] Treatment of Autoimmune Bullous Disease Quality of Life (TABQOL)[4,15]	Both the ABQOL and TABQOL assess QOL on a Likert scale with scores ranging from 0–3. Each questionnaire includes 17 specific questions. ABQOL questions focus on pain, itching, healing, depression, and anxiety while the TABQOL questions focus on the number of medications, financial burdens, fatigue, focus, and fears surrounding relapse.[58] The ABQOL and TABQOL assessments have been validated in various languages including English,[3,59,60] Chinese,[61,62] Arabic,[58] Farsi (ABQOL only),[63] Greek,[3] and Polish.[64]	Both have a numeric score between 0–51. Higher scores represent worse QOL.
The Quality of Life Evaluation in Epidermolysis Bullosa (QOLEB)[24,25,26,28,29,30,31,67,74,75]	The QOLEB includes 17 questions on a Likert scale with scores ranging from 0–3. It is specifically used to assess patients suffering from epidermolysis bullosa (EB).[24] Also validated in Dutch,[26] Farsi,[65] and Portuguese.[25]	Numeric score between 0–51. Higher scores represent worse QOL.
The Infants and Toddlers Dermatology Quality of Life (InTo-DermQoL)[66,67,68,69]	InTo-DermQoL questionnaire is an epidermolysis bullosa-specific tool, which was created and validated by Chernyshov et al[66–68,69] There are 3 versions based on age groups; 10 items for children <1-year-old (max score 30), 12 items for children 1–2 years old (max score 36) and 15 items for children of 3–4 years old (max score 45).[68,69] Includes 17 questions on a Likert scale with scores ranging from 0–3.	Numeric score between 0–45 based on age group. Higher scores represent worse QOL.

essential to develop a long-term therapeutic strategy for these chronic diseases. Herein, we review the primary literature evaluating QOL in autoimmune and inherited bullous disorders, including pemphigus, bullous pemphigoid (BP), epidermolysis bullosa (EB), and Hailey-Hailey disease (HHD).

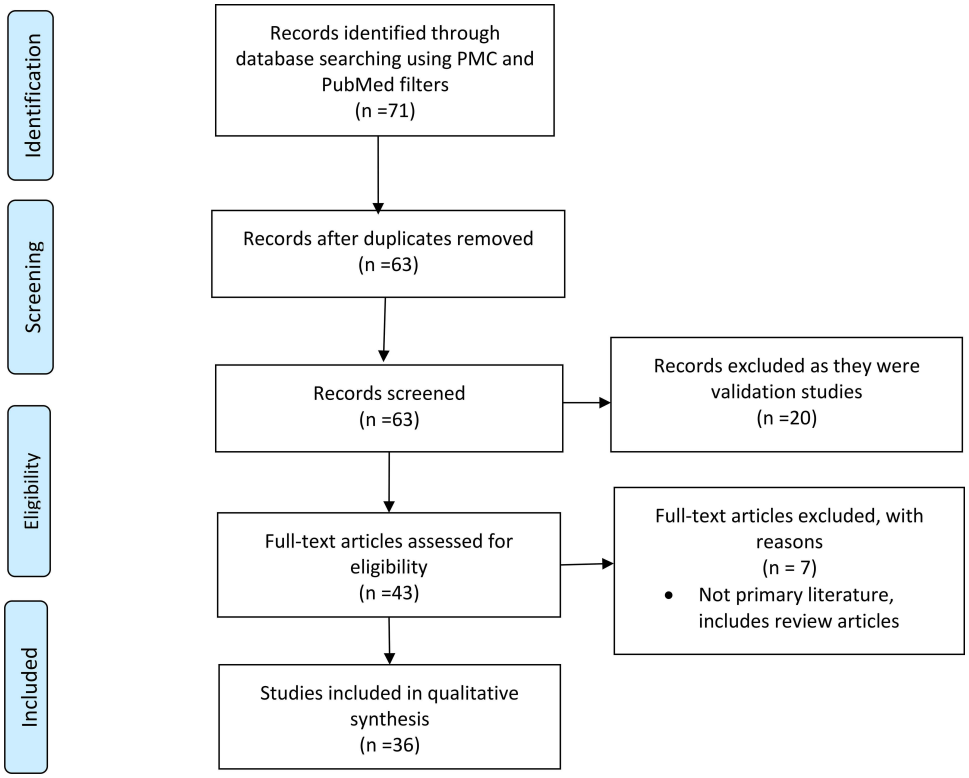

Figure 1 PRISMA flow diagram for the primary literature review detailing the database searches, the number of abstracts screened, and the full texts retrieved.
Notes: Adapted from: Liberati A, Altman D, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. Journal of Clinical Epidemiology. 2009;62(10)e1-e34. Creative Commons.

Methods

A primary literature review was conducted in English using the NCBI database (PMC and PubMed filters) using the keywords "quality of life" AND "bullous," "pemphigus," "pemphigoid," "epidermolysis," "Hailey-Hailey," "blister," OR "blistering." There were no limitations set on date of publication. To be included, articles must have included QOL data specific to a blistering disease. Non-primary literature, such as reviews, meta-analyses, and commentary articles lacking original evidence, were excluded. Two independent authors (JJP and RLS) evaluated titles and abstracts of the articles retrieved during the search. The full article was evaluated if titles and abstracts met the eligibility criteria, or if they did not provide enough information to enable a decision regarding eligibility to be made. Inclusion was be determined once the full text was read. After review, a total of 36 articles were identified (Figure 1).

Given practical considerations among clinicians and patients with blistering diseases during the COVID-19 pandemic, a brief review of additional considerations for the clinician managing this patient population was also included.

Discussion

Autoimmune Bullous Disorders

Autoimmune bullous disorders (AIBD) are acquired diseases resulting from immunologic activity targeting constituents of the skin or mucosa. The spectrum of disease is broad and may range from isolated cutaneous erosions and vesicles to potentially deadly, diffuse sloughing of broad mucocutaneous surfaces. Numerous studies have aimed to assess the impact of AIBD on QOL as outlined in Table 2. For example, a study by Penha et al demonstrated severely impaired QOL in 84 Brazilian patients with various AIBD evidenced by a median DLQI score of 16.0.[2] The greatest impact was noted on symptoms/feelings and daily/leisure activities.[2] This suggests that the impact of AIBD on QOL may be diverse. Historically the emphasis in evaluating QOL was on disease severity but there may be a relationship to disease subtype as well. Here we review studies evaluating QOL in pemphigus, in which QOL has been most studied; BP, the most common AIBD; and other studies which evaluate patients with multiple AIBD subtypes.

Table 2 Review of Literature of QOL in AIBD, PV, and BP

Author	Year	Disease(s)	Study Type	Sample Size	QOL Instrument Used	Conclusions
Pemphigus						
Mayrshofer et al[8]	2005	PV	Cross-sectional	30	DLQI	Overall DLQI score of 10 ± 6.7 in PV patients.
Beissert et al[71]	2011	PV	Randomized controlled trial	94 adults with mild to moderate PV	SF-36	No difference in QOL between mycophenolate mofetil with corticosteroids vs placebo with corticosteroids treatment groups.
Schultz et al[15]	2019	PV	Cross-sectional	235	ABQOL, TABQOL	No difference in QOL using ABQOL and TABQOL in rituximab vs non-rituximab treatment groups.
Bax et al[14]	2021	PV	Cross-sectional	114	ABQOL, DLQI, Skindex-29	PDAI is superior to ABSIS in capturing disease severity.
Segal et al[20]	2021	PV	Cross-sectional	58	DLQI, Revised Illness Perception Questionnaire (IPQ-R), Multidimensional Scale of Perceived Social Support (MSPSS)	IPQ-R was highest for cyclical course and treatment control. Beliefs in cyclical course, emotional influence, psychological cause, and treatment control correlated significantly with QOL.
Calabria et al[19]	2021	OPV	Cross-sectional	30 OPV patients vs 30 healthy controls	SF-36, Pittsburgh Sleep Quality Index (PSQI), Epworth Sleepiness Scale (ESS), Hamilton Rating Scale for Depression (HAM-D), and Hamilton Rating Scale for Anxiety (HAM-A).	Patients with OPV have lower SF-36 scores and higher PSQI, HAM-A, and HAM-D scores. No difference between treatment vs non-treatment groups with OPV.
Tamasi et al[12]	2019	PV, PF	Cross-sectional	109	EQ-5D, DLQI	No difference in EQ-5D scores between patients with PV and PF. Most common EQ-5D dimensions reported: pain/discomfort (50%), mobility (43%), and anxiety/depression (43%).
Paradisi et al[6]	2009	Pemphigus	Cross-sectional	139	SF-36, Skindex-29, 12 item General Health Questionnaire	Impaired QOL in pemphigus patients vs healthy controls on all 3 Skindex-29 scales. GHQ positive in 39.7% suggesting comorbid psychiatric conditions.
Rencz et al[7]	2015	Pemphigus	Systematic review and meta-analysis of 16 HRQoL studies	1465	DLQI, Skindex-29, Skindex-17, Chronic Oral Mucosal Diseases Questionnaire, SF-36, Activities of Daily Living	Highest deterioration in role-physical dimension measured by SF-36. DLQI ranged from 4–13.8 with greatest impairments in symptoms/feelings, daily activities. Skindex-29 showed similar mean scores.

(*Continued*)

Table 2 (Continued).

Author	Year	Disease(s)	Study Type	Sample Size	QOL Instrument Used	Conclusions
Sung et al[18]	2015	Pemphigus	Cross-sectional	66	DLQI, GHQ	Average DLQI score 10.18; 13.45 for patients with active disease, and 5.15 for patients in remission. GHQ positive in 42%.
Krain et al[13]	2019	Pemphigus	Cross-sectional	50	ABQOL, DLQI, Skindex-29, SF-36	Changes in PDAI correlated to changes in ABQOL, Skindex-S, and Skindex-F scales for all patients. ABSIS correlated with Skindex-S for all patients.
Bullous pemphigoid						
Kouris et al[21]	2016	BP	Cross-sectional	57	DLQI, Hospital Anxiety Depression Scale (HADS-scale), Loneliness Scale-Version 3 (UCLA) scale	Mean DLQI score 9.45 ± 3.34. Statistically significant difference in HADS total and depression subscale with no difference in anxiety subscale. Higher scores in UCLA scale in BP group.
Briand et al[22]	2020	BP	Cross-sectional	60	ItchyQoL, 5-D Itch Scale Score	Mean ItchyQOL score was 56.2/110; Mean 5-D Itch Scale Score was 16.5/25. 85% of patients had pruritus daily.
Multiple AIBD subtypes						
Penha et al[2]	2015	AIBD	Cross-sectional	84	DLQI	DLQI median score 16 (9–19) indicating severe impairment specifically on symptoms/feelings, daily and leisure activities.
Heelan et al[1]	2015	AIBD	Cross-sectional	94	DLQI, Work Productivity, and Activity Impairment-Specific Health Problem questionnaires	Severe AIBD impairs QOL more than mild and moderate AIBD which results in more work and activity impairment.
Bilgic et al[23]	2019	AIBD	Cross-sectional	67	Oral Health Impact Profile-14 (OHIP-14)	OHIP-14 scores correlated with pain and severity scores.
Ferries et al[4]	2020	AIBD	Cross-sectional	164	ABQOL, TABQOL, DLQI, Skindex-29	TABQOL was not sensitive to the type of treatment or change in disease. ABQOL is sensitive to change but is poorly correlated with OSS. ABQOL may not have a clear advantage over DLQI or Skindex-29.

Abbreviations: AIBD, autoimmune bullous disease; PV, pemphigus vulgaris; PF, pemphigus foliaceus; BP, bullous pemphigoid; DLQI, Dermatology Life Quality Index; Medical Outcome SF-36, Study 36-item Short-form Survey; ABQOL, Autoimmune Bullous Disease Quality of Life; TABQOL, Treatment of Autoimmune Bullous Disease Quality of Life; WPAI, WorkProductivity and Activity Impairment; SHP, Specific Health Problem Questionnaire; OHIP-14, Oral Health Impact Profile-14; IPQ-R, Revised Illness Perception Questionnaire; MSPSS, Multidimensional Scale of Perceived Social Support; PSQI, Pittsburgh Sleep Quality Index; ESS, Epworth Sleepiness Scale; HAM-D, Hamilton Rating Scale for Depression; HAM-A, Hamilton Rating Scale for Anxiety; GHQ-12, 12 item General Health Questionnaire; COMDQ, Chronic Oral Mucosal Diseases Questionnaire; ADL, activities of daily living; HADS-Scale, Hospital Anxiety Depression Scale; UCLA, Loneliness Scale-Version 3.

Pemphigus

Pemphigus is a family of autoimmune blistering conditions related to loss of adhesion between keratinocytes. In these conditions, acantholysis, caused by autoantibodies targeting intercellular adhesion molecules, leads to intraepithelial blister formation. Pemphigus vulgaris (PV), the most common form of pemphigus, is associated with epidermolysis above the stratum basalis, resulting in flaccid blisters and erosions. In contrast, pemphigus foliaceus (PF) is associated with superficial erosions and crusting due to epidermolysis within the upper stratum spinosum or granulosum. Less common subtypes of pemphigus include pemphigus vegetans, IgA pemphigus, paraneoplastic pemphigus, and drug-induced pemphigus.

SF-36

In 2005, Terrab et al first used the SF-36 in a population of 30 pemphigus patients (PV n=14, seborrheic pemphigus n=10, PF n=4, pemphigus vegetans n=2) and found a significant decrease in all mean scores relative to healthy controls.[5] Most prominent score differences were noted in physical and emotional status suggesting that physical limitations and emotional frustrations may be correlated. These findings also stress the importance of assessing these domains in particular when evaluating patient's QOL. Among a larger population of pemphigus patients (n=139, PV n=112, PF n=10, other n=4), Paradisi et al found SF-36 scores varied by demographic and disease severity.[6] Specifically, investigators observed worse physical and mental component scores as measured by limitations in daily activities and feelings of depression in women as compared to men. Further studies are needed to determine why this disparity exists. They also noted lower average scores in patients with 3–4 years' disease duration and patients >50 years old suggesting that effect on QOL may have a cumulative effect and that there are specific gender- and age-related factors to consider.[6] A meta-analysis of 7 studies using SF-36 in pemphigus patients found the most affected dimensions of SF-36 were role-functioning physical (RP), role-emotional (RE), and vitality (VIT).[7] This study highlights the significant disparities in QOL findings among patients with similar characteristics using the SF-36 and Skindex-29 instruments. This disparity is likely due to lack of pemphigus-specific assessments in these instruments and these patients may benefit from the use of more specific assessment tools. Average SF-36 scores and conclusions across multiple studies are detailed in Table 2.

DLQI

A German study in 2005 examined 36 patients with a new diagnosis of PV across multiple sites and investigators determined that newly diagnosed PV patients had an elevated average DLQI score at 10 ± 6.7 as compared to other skin diseases indicating that PV had a greater impact on QOL.[3] Ghodsi et al found a similar mean DLQI score of 10.9 ± 6.9 in 61 newly diagnosed untreated PV patients in Tehran using the Persian DLQI.[9] The highest subscores were related to symptoms/feelings (2.8) and daily activities (2.2). Investigators found that DLQI score was significantly increased in patients with severe disease, mucosal involvement, positive Nikolsky sign, and itching. Disease severity and extent of symptoms likely affect ability to partake in daily activities and therefore result in lower QOL. A negative correlation between DLQI score and duration of disease was also noted suggesting increased impairment in the initial stages of the disease. This is further supported by Wysocynska et al who reported an average DLQI of 4.0 ± 5.9 in a patient population mainly composed of patients with a >5 years of disease.[10] Patients likely undergo an adjustment period upon initial diagnosis which affects QOL scores early on in disease course. In 2015, a meta-analysis across four studies surrounding QOL in pemphigus patients found a mean DLQI of 12.0 (95% CI 11.1–12.9) with symptoms/feelings and daily activities subscores most consistently affected.[7] A summary of DLQI scores reported in the literature evaluating QOL in pemphigus is noted in Table 2.

Skindex-29

In 2009, Paradisi et al performed the first large study implementing the Skindex-29 among pemphigus patients.[6] They assessed 112 PV patients who had mean scores of 36 in both the symptoms and emotions domains. They also noted 10 PF patients who had the highest mean scores of 52 in both the symptoms and social functioning domains.[6] A meta-analysis of 4 studies found similar mean scores in the symptoms and emotion domains, while slightly lower scores for social functioning.[7] These findings suggest that symptoms and emotional disturbance are most implicated in negative effect on QOL. In a follow-up study, Paradisi et al examined 112 pemphigus patients for treatment-related differences in QOL and found no

significant difference in Skindex-29 scores.[11] It is unlikely that different treatment approaches have significant impact on QOL. These findings suggest that the utility of the Skindex-29, like the SF-36 and DLQI, may be limited by its lack of disease specificity or focus on mucosal involvement. Focused assessment of mucosal involvement may provide a more accurate representation of the effect of disease on QOL in conditions that significantly involve mucous membranes.

EQ-5D

The European Quality of Life Five Dimension (EQ-5D) is a tool that was developed in Europe and used to measure QOL by assessing five dimensions; mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. One study has investigated the role of the EQ-5D in assessing QOL in pemphigus patients. Tamasi et al evaluated 109 patients with either PV or PF using the EQ-5D and found that the top three dimensions affected were pain/discomfort (50%), mobility (43%), and anxiety/depression (43%).[12] There was no significant difference in EQ-5D scores of PF versus PV patients. EQ-5D scores significantly varied by disease severity and the number of comorbidities suggesting that these factors play a role not only in disease-related symptoms but psychosocial factors as well both of which negatively impact QOL. Compared to the Autoimmune Bullous Skin Disorder Intensity Score (ABSIS), EQ-5D scores were better correlated with DLQI scores and average reported pain intensity.[12] This suggests that the EQ-5D may be a valid measure of QOL in pemphigus patients, although comparison studies to disease-specific QOL instruments should be pursued in the future.

ABQOL and TABQOL

The ABQOL and TABQOL are evaluation instruments validated for assessing QOL specifically in patients with AIBD. These tools 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. Assessment of these parameters makes these tools especially useful in assessing bullous disorders. Krain et al examined how the ABQOL, DLQI, Skindex-29, and SF-36 correlate to pemphigus-specific severity indices such as Pemphigus Disease Area Index (PDAI) and ABSIS.[13] After surveying 50 pemphigus patients, the change in PDAI showed a strong correlation (r=0.60–0.79) with changes in the ABQOL, Skindex-S, and Skindex-F subscales for all patients suggesting that each assessment is sensitive to symptom changes.[13] Therefore, any of these tools can be reliably used longitudinally to monitor patient progress. For patients with mucosal involvement (n=24), the change in PDAI showed a strong correlation with changes in the ABQOL and Skindex-S subscale suggesting that these assessments may be particularly useful in evaluating diseases with mucosal involvement.[13] In regards to 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.[14] This suggests that even if disease activity appears to be clinically low, patients may still experience a reduction in QOL.

Effect of Treatment on QOL

Treatment of AIBD often requires travel to treatment facilities often located in urban centers, which may be burdensome for patients living in rural regions, and treatment of the disease itself may carry significant burdens. The TABQOL is a unique tool used to assess treatment burdens on QOL, which have previously been underaddressed. In a study performed by Schultz et al, the ABQOL and TABQOL were used to examine QOL in 235 PV patients treated with rituximab versus non-rituximab modalities. Results demonstrated no difference in QOL among participants treated with rituximab versus those not.[15] This data suggests that ABQOL and TABQOL were either not sensitive enough to discern differences in the examined population or that there is no net benefit between these treatment modalities on QOL in PV patients.[15] In contrast, Joly et al found that the DLQI and Skindex-29 scores showed greater improvements in patients assigned to rituximab plus short-term prednisone as compared with those receiving prednisone alone ($p=0.0411$ and $p=0.0137$, respectively), suggesting that patients receiving rituximab had improved QOL as compared to the non-rituximab modalities.[16] In 2021, Werth et al compared rituximab and mycophenolate mofetil in achievement of remission rates. They noted that the estimated mean change from baseline DLQI score was −8.87 points in the rituximab group and −6.00 points in the mycophenolate mofetil group, and a post hoc analysis revealed that 62% of the patients who received rituximab had a DLQI score of 0 (suggesting no disease-related effects on QOL), while only 25% of patients receiving mycophenolate mofetil reported a DLQI score of 0.[17]

The variations in results suggest the need for further research surrounding the effect of treatment approaches on QOL. Based on current data, we recommend an individualized patient-focused treatment approach specifically taking into account factors such as comorbidities and immunosuppression risk factors, as well as mobility issues, missed work, and commute time. A review of the literature surrounding the use of the ABQOL and TABQOL for assessing QOL is included in Table 2.

Mental Health

Several studies have assessed psychiatric comorbidities in pemphigus patients. Findings to date vary by assessments used and populations examined. One report using the GHQ-28 on 61 patients with newly diagnosed untreated PV found that more than 77% of patients experienced anxiety and depression.[9] Another study of 66 Korean pemphigus patients found that 47% had a positive GHQ indicating likely comorbid psychiatric conditions.[18] The Hamilton Rating Scale for Depression and Anxiety (HAM-D, HAM-A) is a 17 item clinician-administered questionnaire that evaluates symptoms of depression experienced over the preceding week. Using the HAM-D questionnaire, Calabria et al compared 30 patients with oropharyngeal PV (OPV) to healthy controls and showed higher HAM-A and HAM-D scores in patients with OPV.[19] Moreover, significant sleep impairment was observed in the OPV group, as demonstrated by elevated Pittsburgh Sleep Quality Index (PSQI) scores. Paradisi et al demonstrated that psychiatric comorbidity was associated with worse QOL in pemphigus patients based on SF-36, Skindex-29, and the GHQ-12 scores.[11] Segal et al demonstrated that the investigated 58 pemphigus patients had realistic illness perception and high perceived social support.[20] This study also concluded that patients had an improved QOL when they demonstrated understanding of the chronic nature of their condition. This suggests that mental health comorbidities and impaired QOL observed in pemphigus patients may not be as strongly related to the perception of illness or perceived level of social support. Additionally, there is likely benefit to disease education and illness expectation setting at the time of diagnosis.

Pemphigoid

Pemphigoid describes a family of autoimmune blistering diseases characterized by immunoglobulin and complement deposition within the epidermal and/or mucosal basement membrane zone, resulting in subepithelial blisters. BP and mucous membrane pemphigoid (MMP) are most commonly discussed, while pemphigoid gestationis, anti-p200 pemphigoid, and others are less common. BP presents with subepidermal blistering with rare oral involvement. In contrast, MMP more often presents with smooth-bordered mucosal erosions that result in scarring and is less likely to involve cutaneous surfaces.

Bullous Pemphigoid

Two studies have investigated QOL in BP patients. A case-control study examining QOL by DLQI, anxiety, and depression in 57 BP patients compared to healthy controls. The Hospital Anxiety Depression (HADS) is a 14-item assessment tool assessed on a Likert Scale measuring anxiety and depression with higher scores indicating more symptoms. Investigators reported a mean DLQI score of 9.45 ± 3.34, and a significant difference in the total (13.68 ± 5.66 in the BP group and 11.85 ± 3.84 in the control group) and depression subscale (7.77 ± 2.36 in BP group and 6.42 ± 2.09 in the control group) of the HADS assessment.[21] Kouris et al found no difference in the HADS-anxiety subscale between groups. Further studies are needed to explore the effect of BP on the severity of depression and anxiety. BP patients had a higher perceived sense of loneliness as indicated by significantly elevated Loneliness Scale-Version 3 (UCLA) scores compared to controls.[21] Although mixed, these results suggest impaired QOL and increased mental health comorbidities in BP patients. A second study investigated the role pruritus plays in QOL of 60 French BP patients using the 5-D Itch Scale and the ItchyQOL.[22] Results showed that 85% of patients experienced pruritus daily, at a mean severity of 5.2/10. Mean ItchyQOL score was 56.2/100 and 5-D Itchy scale score was 16.5/25 indicating significant QOL impairment due to pruritus which had not been specifically assessed previously. A further review of QOL assessments is outlined in Table 2.

Studies Including Multiple AIBD Subtypes

Larger reviews have evaluated multiple AIBD subtypes and their effect on QOL. Ferries et al demonstrated severely impaired QOL in 164 patients with pemphigus, BP, and MMP across multiple sites in France.[4] Investigators found that the ABQOL correlated with DLQI and Skindex-29 scores, and weakly correlated with

changes in the PDAI, BPDAI, and MMPDAI. This suggests that the use of ABQOL, DLQI and Skindex-29 are useful in assessing QOL in patients with AIBD. The ABQOL and PDAI were more closely correlated in pemphigus and BP patients than in patients with MMP.[4] This was attributed to the smaller number of questions specifically focused on mucosal involvement, which may be required to better assess MMP. Heelan et al found a comparably lower mean DLQI of 6.5 ± 7.3 among 94 patients with AIBD defined as having PV, PF, IgA pemphigus, BP, MMP, epidermolysis bullosa acquisita, or lichen planus pemphigoides, suggesting a moderate effect on QOL.[1] They did, however, determine that patients with a higher DLQI score had greater work and overall activity impairment, providing initial evidence that AIBD may not only affect QOL but also work productivity.

In 2019, Bilgic et al examined 67 BP and PV patients for oral health-related QOL using the Oral Health Impact Profile-14 (OHIP-14). They used ABSIS scores to evaluate disease severity with a score of <17 suggestive of a moderate course and a score >17 suggestive of a significant course. They then used OHIP-14 scores to assess QOL. They found that OHIP-14 scores were higher in active patients with an average score of 42.28 ± 13.66 as compared to inactive patients with average scores of 29.08 ± 12.25.[22] Higher OHIP-14 scores correlated with pain scores.[23] This study may suggest oral health is a significant factor in the QOL of BP and PV patients, but large-scale conclusions were limited by response bias. Close monitoring of oral involvement and inclusion of dentists in the multidisciplinary approach of care should be strongly considered and may result in improved QOL outcomes.

Inherited Bullous Disorders

Epidermolysis Bullosa

Although there are many forms of inherited bullous disorders, much of the current literature focuses on epidermolysis bullosa (EB). EB is an inherited skin fragility disorder characterized by structural disruptions at the dermo-epidermal junction or in the basal epidermis. These disruptions result in increased skin fragility. Although multiple phenotypes exist, the most commonly described are epidermolysis bullosa simplex (EBS), junctional epidermolysis bullosa (JEB), and dystrophic epidermolysis bullosa (DEB). EBS is the most common type of EB, and is characterized by trauma- or friction-induced superficial skin blistering, erosions and crusting, most commonly caused by an autosomal dominant, negative missense mutation in keratinocyte proteins KRT5 and KRT14. Patients may exhibit localized (EBS-l), intermediate, or severe EBS. In contrast, DEB subtypes have a disruption in type VII collagen synthesis, classified by a mutation in COL7A1 gene.

Effect of Disease on QOL

Since the publication of the QOLEB, several studies have analyzed QOL in EBS adult patients, with mean scores ranging from 7.9 ± 5.3/51 to 13.7 ± 8.7/51.[24–26] In children, Zigmond et al found a mean score of 15/30 in the Children's Dermatology Life Quality Index (cDLQI).[27] In a subsequent study, Joen et al evaluated 16 patients using VAS, QOLEB, and total Skindex-29 scores. Mean QOLEB score was 26.62 ± 7.61 and higher scores were observed in female patients, patients with hospitalization greater than 7 days, and severe generalized dystrophic epidermolysis bullosa (RDEB-gen sev).[28] Although these findings were not statistically significant in this study, they suggest that a gender disparity may exist and that increased disease severity as evidenced by prolonged hospitalization likely worsens QOL outcomes. In 2017, Brun et al evaluated 57 patients in France with EBS and found that 73% of patients reported a moderate to severe impact on their QOL using the cDLQI for children and QOLEB for adults.[29] The mean QOLEB score was 6.6 ± 4.9/51.[29] They found that 87% of patients felt frustrated, 27% embarrassed, 17% depressed, 33% uncomfortable, and 40% anxious or worried by their disease.[29] Mean cDLQI score was 8.1 ± 5.1/30 with 76% reporting that QoL was affected by pain, 56% felt sad, and 52% had to decrease or stop any physical activity because of pain.[29] These findings suggest a significant psychosocial and emotional effect of disease on QOL and stress the importance of close screening for psychiatric comorbidities. In 2020, Togo et al performed a systematic review of 12 articles and concluded that women and children suffering from EB require closer monitoring than other groups, suggesting the importance of adjusting monitoring based on the demographic of the group treated.[30] Further studies are needed to assess the differences in QOL disturbance amongst various demographic groups. A further review of QOL assessments is outlined in Table 3.

Effect of Chronic Wounds on QOL

Patients with EB may develop long-lasting, disfiguring wounds, which likely have a significant negative impact on QOL. Eng et al supported this by showing a correlation

Table 3 Review of Literature of QOL in EB, Various EB Subtypes and HHD

Author	Year	Disease(s)	Study Type	Sample Size (n)	QOL Instrument Used	Conclusions
EBS, RDEB, DDEB, JEB						
Horn and Tidman[72]	2002	EBS, RDEB, DEB	Cross-sectional	120 (30 children)	DLQI/ CDLQI	RDEB affects QOL more than EBS and DEB as evidenced by DLQI/ cDLQI scores (mean score of 18 in adults and 22 in children).
Frew et al[24]	2009	EBS, RDEB, DDEB, JEB	Cross-sectional	111	QOLEB	QOLEB is an EB-specific QOL measure with discriminative validity for all subtypes, construct validity, internal consistency and reliability (test-retest reliability) ($p<0.01$).
Tabolli et al[32]	2009	EBS, JEB, DDEB, RDEB	Cross-sectional postal survey	125 (46 children)	SF-36, Skindex-29, GHQ-12, EuroQol 5 dimensions, Family Strain Questionnaire(FSQ)	QOL was decreased and family burden increased with worse patient-perceived disease severity and increased body surface area involvement in patients with RDEB and DDEB. Women have worse QOL based on Skindex-29 and SF-36 scales. GHQ-positive more frequently among women (48%) vs men (16%) ($p=0.003$). GHQ-positivity correlated to worse QOL.
Margari et al[35]	2010	RDEB, EBS	Cross-sectional	25 (14 children)	CBCL, K-SADS-PL, SCL 90, DLQI	No correlation between clinical severity and intensity of psychological disturbance despite high frequency of psychiatric symptoms. Togetherness and affection have a strong and positive influence and result in increased coping. Multidisciplinary treatment approach is recommended.
Yuen et al[26]	2013	EBS, JEB, DDEB, RDEB	Cross-sectional	55 (0 children)	QOLEB	QOLEB scores correlate with Skindex-29 and SF-36. Dutch QOLEB is a reliable and valid QOL instrument.
Kýrová et al[73]	2013	EBS, DDEB, RDEB, JEB	Cross-sectional	43 (27 children)	DLQI/ cDLQI	There is a large to very large impact of disease on QOL with greatest impact noted in RDEB and EBS.
Eismann et al[74]	2014	EBS, RDEB, JEB, DDEB	Cross-sectional	71 children	ABILHAND-Kids, QOLEB	Effect on QOL differs based on type of EB with RDEB having the most effect, followed by JEB, EBS, and DDEB.

(*Continued*)

Table 3 (Continued).

Author	Year	Disease(s)	Study Type	Sample Size (n)	QOL Instrument Used	Conclusions
Cestari et al[25]	2015	EBS, JEB, DEB	Cross-sectional	57 (40 children)	QOLEB	Impact on QOL is correlated to disease severity based on QOLEB, cDLQI and DLQI. Brazilian Portuguese QOLEB is a valid QOL instrument.
Brun et al[29]	2017	EBS-I	Cross-sectional	57 (37 children)	cDLQI, QOLEB	EBS-I has frequent and severe neuropathic-type pain, which may be underrated in effect on QOL.
Danescu et al[75]	2019	EBS, DEB, Kindler syndrome, JEB	Cross-sectional	50 (29 children)	QOLEB, DLQI/ cDLQI	EBDASI scores are strongly correlated with QOL. DEB was associated with higher EBDASI and QOLEB. EBDASI damage disease score was greater in rural areas.
Chernyshov et al[70]	2020	EBS, DEB, JEB, unspecified EB	Cross-sectional	31 children	InToDerm-QoL with EB-specific module	EB-specific modules within the InToDerm-QoL address EB specific issues to better estimate effect on QOL.
RDEB and DDEB						
Jeon et al[28]	2015	RDEB	Cross-sectional	13 (3 patients less than 7 years old who required assistance with surveys)	Skindex-29, QOLEB, Visual Analogue Scale (VAS) on pain and pruritus and questions addressing economic burden of treatment.	RDEB perceived disease severity of "very severe" had worse QOL by Skindex-29 and QOLEB vs "severe" RDEB.
Eng et al[31]	2020	RDEB	Cross-sectional	85	QoLEB	Larger wound size correlated to worse QOL in patients with RDEB.
Fulchand et al[34]	2021	DDEB	Cross-sectional	42	Medical Profile Survey QoLEB	Self-reported severity of disease correlates with severity of pain but not with size of wounds or number of dressing changes. Patients with severe DDEB reported more severe internal disease symptoms and greater analgesic use during dressing changes.
EB						
Angelis et al[76]	2016	EB	Cross-sectional	204 (83 children)	EuroQol 5-domain (EQ-5D)	EB has a negative impact on patient health-related QOL and poses a substantial social/economic burden with high direct non-healthcare costs.

(*Continued*)

Table 3 (Continued).

Author	Year	Disease(s)	Study Type	Sample Size (n)	QOL Instrument Used	Conclusions
Togo et al[30]	2020	EB	Systematic Review	NA (12 articles reviewed)	QOLEB, CDLQI, DLQI, Skindex-29, SF-36	RDEB and JEB have greater impairment of QOL. Women and children may require unique monitoring. Patients may benefit from specific pain management guidelines.
Yazdanshenas et al[67]	2020	EB	Cross-sectional	83	QOLEB	QOLEB and EB severity scores were correlated. QOLEB validated as a QOL assessment tool among Iranian patients.
HHD						
Gisondi et al[36]	2005	HHD	Cross-sectional	20 adults	Skindex-29, GHQ-12	Patients with HHD had higher Skindex-29 scores and higher levels of psychological distress as compared to other cutaneous diseases.

Abbreviations: EBS, epidermolysis bullosa simplex; JEB, junctional epidermolysis bullosa; dystrophic epidermolysis bullosa; severe; RDEB, autosomal recessive dystrophic epidermolysis bullosa; dominant dystrophic epidermolysis bullosa; HHD, Hailey-Hailey disease; DLQI, Dermatology Life Quality Index; CDLQI, Children's Dermatology Life Quality Index; QOLEB, the Quality of Life Evaluation in Epidermolysis Bullosa; SF-36, Medical Outcome Study 36-item Short-form Survey; GHQ-12, 12 item General Health Questionnaire; FSQ, Family Strain Questionnaire; CBCL, Child Behavior Checklist; K-SADS-PL, Kiddie-Sads-Present and Lifetime Version; SCL 90, Symptom Checklist-90; VAS, Visual Analogue Scale; InTo-DermQoL, the Infants and Toddlers Dermatology Quality of Life.

between larger wound size with worsening skin disease severity and worse QOL in 39 participants with RDEB.[31] The mean QOLEB score in their study was 20.0 ± 9 points.[31] Similarly, Tabolli et al found a correlation between increased EB body surface area involvement, worsened QOL, and patient-perceived severity of disease using the SF-36 and Skindex-29 assessments.[32] However, SF-36 mental components scores were similar in patients suffering from EB as those of the normal population.[32,33] This suggests that although wound size has an effect on QOL, wound size does not appear to directly affect mental health comorbidities.

Although RDEB is more commonly studied, Fulchand et al performed Medical Profile and QOLEB surveys in patients with dominant DEB (DDEB) and found that self-reported severity of disease correlated with the severity of pain in the last 12 months (3.4 with mild disease vs 6.8 with severe disease on medical profile, p=0.0002) and a trend toward worse QOLEB score (33.4 vs 24.9 respectively, p=0.09) when compared with mild severity participants. The severity of self-reported disease did not correlate with the size of wounds or the number of dressing changes.[34] Additionally, they noted that patients with severe DDEB had more severe internal disease symptoms, such as difficulty swallowing (62.5%, p=0.01), and greater analgesic use during dressing changes (4.4% mild vs 81.3% severe, p<0.001), as compared with mild DDEB.[34] Increased severity of disease and greater systemic involvement correlate to worsened QOL.

Given the potential psychiatric consequences of inherited bullous disorders, it is important to assess for coexistence of mental health comorbidities, which may affect treatment and overall clinical outcomes. Margari et al used clinical interviews and standardized diagnostic protocols according to age to assess the frequency of psychiatric symptoms. They noted a high frequency of psychiatric symptoms (80%) in patients suffering from EB, but a relatively small percentage (12%) who had undergone psychopharmacological or psychotherapeutic treatments.[35] This disparity between psychiatric symptoms and treatment provides an area of focus that if addressed, could improve patients' QOL substantially.

Hailey-Hailey Disease

HHD, also known as benign familial pemphigus, benign chronic pemphigus, is an autosomal dominant,

intraepidermal blistering disorder that affects keratinocyte adhesion caused by a loss-of-function mutation in the ATP2C1 gene. It is characterized by painful blistering with subsequent erosions and frequent superficial infections of flexural surfaces.

A single study investigated the QOL in patients with HHD (Table 3). The study used the Skindex-29 to assess 20 patients and found that the effect on QOL was substantial, with mean Skindex-29 symptom scores at 57.1 and 60.7 with <4 and >/= 4 sites affected respectively.[36] This study implied that a physician's evaluation may not correlate with a patient's perceived handicap and effect on QOL, therefore aggressive treatments may be warranted even in patients who display seemingly low disease activity.

Considerations of Bullous Diseases During the COVID-19 Pandemic

The ongoing COVID-19 pandemic has resulted in many concerns surrounding the management of blistering disorders. The utility of telemedicine and virtual visits has become increasingly popular, especially for immunosuppressed AIBD patients, and has become a useful strategy to decrease exposure risk.[37–39,40] There remains concern over the use of immunosuppressive and immunomodulating treatment and the risk of acquiring SARS-CoV-2 infection. Joly et al noted a higher risk of COVID-19 infection in patients with AIBD among 59 patients in France.[39] Some providers propose postponing immunosuppressive or immunomodulatory therapies and tapering adjunctive therapies to the lowest effective dose, while other providers state that withdrawal of disease-controlling agents could result in uncontrolled disease activity.[41–43]

Mahmoudi et al found that patients receiving greater than 10 mg/day of prednisolone had a higher risk of COVID-19 and hospitalization.[44] Additionally, they noted that with each passing month after rituximab infusion, the patient's risk of complication decreased.[44] On the contrary, Kridin et al found that the risk of developing COVID-19 (p=0.496), COVID-19-associated hospitalization (p=0.499), and COVID-19-associated mortality (p=0.789), was similar in patients with pemphigus and the age, sex, and ethnicity-matched healthy control group suggesting that the use of systemic corticosteroids and immunosuppressive adjuvant agents was not associated with worse clinical outcomes.[45] However, they found the risk of COVID-19-associated mortality was higher among patients with BP (p=0.023) as compared to the same matched healthy control subjects.[45] Although immunosuppressive and immunomodulating treatments may carry an increased risk of infection, a patient-centered approach advocates for shared decision-making, with a thorough discussion of the risks, benefits, and alternatives to treatment with each patient.[46]

There have been rare reports of flares or new-onset AIBD triggered by the COVID-19 vaccination.[47–49] Although reports are limited, other AIBD may carry a similar risk. This is not unique to the COVID-19 vaccine, as flares of AIBD have been reported from other vaccines.[50–55] In addition, flares and new-onset AIBD have been reported from natural COVID-19 infections.[56–59] Despite the small risk of disease onset or flare with vaccination, individual and public health benefits may outweigh this risk for most patients.

Conclusions

QOL is an important clinical outcome and should be monitored closely especially in patients suffering from blistering disorders such as AIBD, PV, BP, pemphigoid, EB, and HHD. A variety of validated instruments are available for the clinician to monitor QOL. Some of the primary assessment tools used include DLQI, GHQ-28, SF-36, Skindex-29, ABQOL, TABQOL, QOLEB, InTo-DermQOL. Based on the current evidence, it appears that the ABQOL and TABQOL may be more sensitive in assessing patients with AIBD, particularly those with mucocutaneous disease because there are questions specifically addressing mucosal involvement. The TABQOL is a unique assessment tool that assesses QOL burdens related to treatment. Among inherited blistering disorders, the QOLEB and InTo-DermQOL were developed specifically to assess adults and children with EB, respectively.

Although many QOL instruments have been validated in numerous languages, there are important limitations. For example, there may be a disparity between clinical disease severity and perceived QOL, which supports the regular use of both sets of instruments to accurately assess the impact of disease on patients' lives. Frequent monitoring of QOL and ensuring appropriate supports are in place are critical to maintaining patient-centered care. Because bullous disorders affect multiple organ systems and may negatively impact mental health, a multidisciplinary approach including mental health providers, primary care physicians, and when relevant, other specialty providers, should be incorporated to improve patients' overall QOL. In addition, providers should not forget the positive role that many patient support groups have on QOL (eg The

International Pemphigus and Pemphigoid Foundation, The Rare Illness Network, and Dystrophic Epidermolysis Bullosa Research Association "DebRA" International).

Finally, while COVID-19 vaccination, like other forms of vaccination as well as natural infection, may carry a risk of disease flare, we believe that the individual and public health benefits of vaccination typically outweigh potential risks. An informed, individualized discussion should be undertaken to better assess these factors for each patient.

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