Pediatric Patient-Reported Outcomes Assessment: A Case Study in Epidermolysis Bullosa

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BACKGROUND

Pediatric Patient-Reported Outcomes Assessment

- Identifying the age or developmental stage at which children can reliably and reproducibly report their health status is challenging.
  - Children as young as 3 years of age have reported reliable assessment of concrete concepts such as pain.[1,2] However, research supports a more conservative estimate of 9 or 10 years of age for children reporting on subjective concepts like behavior.[3]
- No established guidelines exist for age cutoffs for self-reporting. The Critical Path Institute (C-Path) recommends that specific age boundaries should be determined, in part, by how abstract or concrete the reported concept is and further suggests the following cutoffs[4]:
  - Age 7 years is often cited as the lower bound of the age range for self-reporting.
  - In patients aged 7 to 11 years, mixed validity and reliability results have been observed, such that a combination of self- and observer-reporting may be best.
  - In patients aged 11 years and older, psychometric testing has demonstrated that self-reporting is generally acceptable.
- Consideration of age alone is generally inadequate. Interindividual variability in comprehension and willingness/motivation to respond also should be assessed.

Epidermolysis Bullosa—A Rare Disease

- Epidermolysis bullosa (EB) is a family of genetic skin fragility disorders, clinically characterized by blistering of the skin in response to friction or minor trauma.[5]
- Widespread, recurrent wounds in patients with generalized EB caused by skin blistering can lead to disfigurement, disability, and premature death in early adulthood, mainly from a particularly aggressive form of cutaneous squamous cell carcinoma.[6]
- EB is extremely rare, with an estimated prevalence (all subtypes) of 0.10 to 0.60 cases per 10,000 population in the European Union. In the United States, 1 out of every 50,000 live births is affected by EB.[7]
- There is no cure for EB. The current standard of care for EB is supportive; palliative wound care consists of changing dressings and monitoring the wound site for excessive exudate and/or infection.

Health-Related Quality-of-Life Issues in Epidermolysis Bullosa

- Published literature highlights the following important health-related quality-of-life (HRQOL) issues specific to patients with EB[5,8-15]:
  - Limitations in physical functioning (e.g., impact of pain or itch on sleeping, eating, writing, bathing/showering, moving around inside and outside the house, shopping, playing sports)
  - Emotional, social, and psychological effects (e.g., frustration, embarrassment, anxiety, depression, teasing/staring, relationships with friends and family)
  - Aspects specific to wound treatment (e.g., pain during wound dressing changes).

OBJECTIVE

- To identify and evaluate HRQOL measures for use with a pediatric population (aged 3 to < 18 years) with EB.

METHODS

- A structured PubMed search was conducted using Medical Subject Heading search terms.
- Of the 143 abstracts identified, 40 were appropriate for further evaluation; 33 articles underwent full-text review.
- The following measurement properties were evaluated for each HRQOL measure based on standard criteria[16,17]:
  - Practicality
    - Availability of age-appropriate version(s)
    - Number of items (i.e., respondent burden)
    - Recall period
  - Content validity
    - Relevant content for patients with EB
    - Age relevance of concepts addressed
  - Psychometric properties
    - Validity (known groups, construct)
    - Reliability (test-retest, internal consistency) established in EB population
  - Use in previous EB studies
  - Responsiveness to change in EB clinical trials

RESULTS

The review identified 8 HRQOL measures implemented in studies with patients with EB (Table 1).

Table 1. HRQOL Measures Implemented in EB Studies

Generic Measures	Dermatology-Specific Measures	EB Disease-Specific Measure
• Short Form-36 (SF-36) • EuroQol 5 Dimensions (EQ-5D) • EQ-5D Youth Version (EQ-5DY, also known as the EQ-5D [Child])	• Dermatology Life Quality Index (DLQI) • Children's Dermatology Life Quality Index (CDLQI)ᵃ • Dermatology Quality of Life Scales (DQOLS) • Skindex-29	• Quality of Life in Epidermolysis Bullosa (QOLEB)

ᵃ The CDLQI is available in text and cartoon versions.

Summary of Key Measurement Properties

Table 2 presents the key characteristics for the HRQOL measures used in published EB studies. Table 3 presents the key psychometric properties for the HRQOL measures.

Table 2. Key Characteristics of HRQOL Measures Used in Published EB Studies

Measure	Age-Relevant Concepts Addressed	Recall Period	No. of Items
SF-36	18+ years	4 weeks	36
EQ-5D	12+ years	Today	6
EQ-5DY	8+ years	Today	6
DLQI	17+ years	1 week	10
CDLQI	4–16 years	1 week	10
DQOLS	13+ years	Current	41
Skindex-29	18+ years	4 weeks	29
QOLEB	10+ years	Not specified	17

Table 3. Key Psychometric Properties for HRQOL Measures Evaluated for EB

Measure	Content Validity Established for EB	Validity Established for EBᵃ	Reliability Established for EBᵇ	Evidence of Responsiveness to Change in EB Studies
SF-36	Not evaluated	Not evaluated	Not evaluated	Tabolli et al., 2009[13] • Health status was worse in patients with large skin involvement • Patients with EB reported statistically lower physical scale scores compared with the general population • Patients with EB reported only slightly lower mental health scores compared with the general population
EQ-5D	Not evaluated	Not evaluated	Not evaluated	Tabolli et al., 2009[13]
EQ-5DY	Not evaluated	Not evaluated	Not evaluated	Tabolli et al., 2009[13]
DLQI	Not evaluated	Not evaluated	Not evaluated	Horn and Tidman, 2002[10] • Potential floor effects for patients with more severe EB on items that they may never have been able to do • DLQI distinguished between different subtypes of EB Margari et al., 2010[12] • No clear correlation between DLQI score and EB severity, possibly due to limited sample size Venugopal et al. 2010[14] • No significant change between week 0 and week 4 (1 patient)
CDLQI (text and cartoon versions)	Not evaluated	Not evaluated	Not evaluated	Horn and Tidman, 2002[10] • CDLQI (text version) distinguished between different subtypes of EB Lara-Corrales et al., 2012[5] • No significant difference in CDLQI scores between treatment and placebo groups (version not specified)
DQOLS	Not evaluated	Not evaluated	Not evaluated	• Evidence of responsiveness not reported
Skindex-29	Not evaluated	Not evaluated	Not evaluated	Tabolli et al., 2009[13] • Patients with higher perceived disease severity had significantly higher scores on all scales • No significant difference among the various types and subtypes of EB, but patients with JEB consistently had the highest scores
QOLEB	Frew et al., 2009[8] Qualitative interviews for item generation: • 26 patients (15 adults aged > 18 years, 11 children) • 33 unaffected family members • 11 health professionals • 70 total	Frew et al., 2009[8] Construct validity for 17-item version: • $\alpha = 0.92$ Discriminant validity: • Ability to discriminate between different subtypes of EB • $R < 0.5$ ($P < 0.01$) for all subtypes Convergent validity for 17-item version; correlations with: • DLQI: $R = 0.774$ • Stanford Health Assessment Questionnaire for Mobility: $R = 0.78$ • HADS: $R = 0.57$ for anxiety, $R = 0.58$ for depression	Frew et al., 2009[8] Test-retest reliability for 25-item version: • Spearman's $R = 0.843$ ($P < 0.01$) Internal consistency for 17-item version: • $\alpha = 0.92$ ($P < 0.01$)	Venugopal et al. 2010[14] • No significant change in QOLEB scores between week 0 and week 4

HADS = Hospital Anxiety and Depression Scale; JEB = junctional epidermolysis bullosa.
ᵃ Including known-groups and construct (convergent, divergent) validity.
ᵇ Including test-retest and internal consistency reliability.

DISCUSSION

- 8 HRQOL measures were identified and reviewed. As expected, no single HRQOL measure covers the full experience of EB across the age spectrum of pediatric patients.
- The EQ-5DY, a generic measure of HRQOL, may potentially be used to compare the burden of EB in pediatric patients aged 8 to 15 years with the burden of other pediatric illnesses.
- The CDLQI covers the greatest portion of the age range of interest (4-16 years); this measure also is available in two different child-friendly formats for administration (cartoon and text); however, it lacks content validity in patients with EB.
- The QOLEB was the only instrument for which content was derived from and psychometric properties were established in patients with EB.
- The QOLEB items focus on emotional and functional HRQOL domains. Despite pediatric input during development:
  - Not all QOLEB content is relevant to children/adolescents:
    - Item #12: Have you needed to, or do you need to, modify your home (installing ramps, etc.) due to your EB?
    - Item #15: How are you or your family affected financially by your EB?
  - Age-appropriate versions are not available. During the development and validation of this questionnaire:
    - Children younger than 10 years included their parents' advice when completing the questionnaire.
    - Children who were unable to read or who were younger than 8 years had their parents complete the questionnaire.

LIMITATIONS

- Parental concerns were not evaluated in this study.

CONCLUSIONS

- EB is an extremely rare disease that has a profound impact on patients' HRQOL.
- The rarity of EB makes assessment of HRQOL challenging and creates practical difficulties for the following activities:
  - Developing new disease-specific questionnaires (e.g., limited number of patients available for concept elicitation and psychometric testing)
  - Testing of existing HRQOL questionnaires (e.g., limited number of patients available for assessing content validity)
  - Developing new language versions of measures (i.e., limited number of patients available for linguistic validation).
- An HRQOL instrument that evaluates age-appropriate concepts for EB was not identified. Content validity was lacking in the majority of measures evaluated.
- The broad age range of patients with EB, from young children to adolescents and young adults, means that a single measure is unlikely to be suitable for all patients.
  - The impact of EB will vary by age, consistent with normal childhood growth and development. Thus, instrument content also may need to vary by age group.
  - Appropriate format, question structure, and mode of completion for HRQOL measures also will vary by age.
- Further research is needed to document and assess HRQOL concepts in pediatric patients with EB.

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