Consensus-based Guidelines for the Provision of Palliative and End-of-Life Care for People Living with Epidermolysis Bullosa

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Introduction

- Inherited epidermolysis bullosa (EB) is a cluster of rare (~11.1 per one million live births), heterogeneous, genetic skin and mucosal fragility disorders with multi-system and secondary effects, in which painful blistering and erosions occur in the skin and mucosae in response to friction/mechanical trauma.
- EB is incurable and potentially life-limiting, thereby requiring a palliative (not just end-of-life) approach to care.
- Knowledge and experience related to the provision of palliative and end-of-life care for people living with EB is minimal.
- This is the first internationally actionable clinical practice recommendations for the provision of palliative and end-of-life care that applies to all people living with EB, their caregivers, and their medical practitioners.

Methodology

Phase 1: In 2018, Debra International (DI) consulted with the international EB community and identified palliative care in EB as a high priority area for development. In the same year, an international, interdisciplinary panel was established to undertake the guideline development process.

Phase 2: Survey for EB patients and carers and for international clinical experts. Utilizing the Delphi technique, the panel developed a questionnaire that sought the opinions of people living with EB, their carers, and medical providers who treat EB on the topic of EB and palliative care that was subsequently circulated electronically throughout the EB community world-wide.

Phase 3: Primary Panel Meeting. The first face to face panel meeting was held at the first World Congress for EB conference (London, UK, January 2020). The panel used the PICO and priority ranking methods to formulate three broad clinical questions and six outcomes (Symptom Control, Quality of Life, Survivorship, Satisfaction, Grief, and Mental Health/Well-being) that served as the basis of the systematic search terms.

Phase 4: Systematic Literature Searches. The panel conducted an exhaustive and systematic literature search to identify articles that served as the basis of the manuscript. Articles and conference abstracts were not limited based on language, year published, journal published in, author's or study's country of origin, or EB type. Articles published in lay media (e.g., newspapers, magazines, blog posts, etc.) were not included.

Phase 5: Article Appraisals and GRADEpro summary tables. Full-text articles were obtained and appraised first using modified CASP and GRADE terms and a second time by two research specialists to ensure consistency. MP reviewed the identified CPGs using the AGREE II instrument. Due to a limited number of available multilingual reviewers, articles not published in English were reviewed once. Articles were declined if they did not directly address one or more of the clinical outcomes; if they were associated with, or better addressed by, another completed CPG. A total of 85 articles were used in this CG. Each included article was grouped into one or more of the clinical outcome categories, graded using GRADE methodology, and summarized in a GRADEpro "Summary of Findings Table". The articles used in this CG cover a multitude of research types (e.g., single case studies, clinical practice guidelines, literature reviews, control matched, expert opinion, grey literature, etc.) and participant types (people living with EB, carers, providers).

Phase 6: Recommendation Panel Meeting. In October 2021, the panel met a second time virtually (due to the COVID-19 pandemic) and used findings in the appraised articles, expert opinion, and panel consensus to formulate the recommendations used in this CG.

Phase 7: Editorial. The draft manuscript was reviewed by all the panel, and their input was included. The authors addressed all the reviewer panel's comments in the final editing stage before submission. The DI coordinator conducted the Appraisal of Guidelines for Research & Evaluation (AGREE II) tool cross check, to increase the quality of practice guidelines in rare diseases. MP submitted the article for journal peer review process and addressed all reviewer and editor comments in the final edition. Manuscript published in *Orphanet Journal of Rare Diseases* on 04 September, 2023.

Results—Key Recommendations

Question 1: What are the best practices to manage the symptoms of, and improve survivorship for, EB over the lifespan?

- EB is a disease that is best treated within an interdisciplinary team (IDT) that optimally consists of the person living with EB and their carers at the core in addition to a dermatologist, paediatrician/primary care physician, specialist nurse, wound care specialist, surgeon, oncologist, psychologist, pain specialist, palliative care specialist, gastroenterologist, physiotherapist, occupational therapist, and a social worker. Each team member's role is clearly established shortly after the birth of a baby with EB and are adjusted to meet the child's evolving needs.
- Focus on achievable goals over the *entire* lifetime, with the goal of managing physical/emotional suffering while respecting the autonomy and individuality of each person, and providing psychoeducation to the person living with EB, their family, and carers in a way they can fully understand.
- Provide adequate pain and itch control.
- Fully inform the patient of all treatment options (including no treatment) in an age-appropriate manner.
- NG/NJ feeding tubes are not recommended due to risk of internal and external trauma and difficulties securing them to the face.
- Focus exclusively on comfort care for severe JEB.
- Palliative sedation may be considered to relieve refractory symptoms at end-of-life.
- Providers should use self-care practices.

Question 2: Are there recommendations and interventions to improve mental health; quality of life; and overall life satisfaction with respect to cultural, religious, and other belief-systems of people living with EB?

- Consider the whole person living with EB rather than just their visible lesions.
- As clinical severity increases, so does the need for a holistic treatment approach.
- People living with EB must have the same opportunities to feel useful and to be a contributing member of society just like those who do not have EB.
- Provide multi-faceted healthcare education to benefit patients/carers to encourage active engagement in one's own decision making over lifespan.
- Address the mental health of parents, carers, and providers.
- Family members need long-term support.

Question 3: What are the best practices to identify individuals who are grieving as a result of EB and to assist them in improving their ability to cope with that grief?

- Provide psychosocial support for parents to address trauma unique to parents of a child with EB.
- Healthcare providers should provide a strong support system throughout the dying process and ongoing bereavement support following death.
- Healthcare providers should be allowed to attend funerals of their patients if allowed by the family.

Conclusions and Relevance for Patient Care

Palliative care for people living with inherited EB begins at diagnosis and spans their lifetime. Despite the lack of a cure, there are many interventions that can be potentially used to improve quality of life and reduce suffering. Because of EB's rarity and multiple comorbidities as well as the impact on the life of the person living with EB, it is critical that all treatment is interdisciplinary with the person living with EB, and his/her/their family and carers at the treatment team's center.

This internationally developed guideline provides the most up-to-date evidence and consensus-based guidance and recommendations for the provision of the highest level of effective, culturally appropriate, and evidence-based palliative and end-of-life care treatments across the lifespan to improve outcomes and quality-of-life for those people living with EB, their carers, and all healthcare providers involved in their care. The guideline also identifies knowledge gaps and encourages future research in palliative care and end-of-life treatments for all people living with EB.

Conflicts of Interest

These guidelines were funded by DEBRA UK and endorsed by DEBRA International, the views or interests of the funding body have not influenced the final recommendations for clinical practice. With two exceptions (KMC and GS), this panel of researchers has no financial conflicts of interest. KMC declared a potential conflict from her professional work coordinating guidelines for DEBRA International. GS declared a potential conflict from his NICHD-funded postdoctoral fellowship (T32GM008562). Therefore, neither of these authors were involved in the final recommendation editions of the manuscript or post review panel feedback. All reviewers declared that they have no potential conflicts of interest with respect to the publication of this guideline.

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