Poster

CO26

Targeted Literature Review Exploring Burden of Disease in Junctional and Dystrophic Epidermolysis Bullosa

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Background and Objective

- Epidermolysis Bullosa (EB) is a debilitating group of rare genetic dermatological conditions, characterized by skin fragility and persistent wounds[1] (**Figure 1**).
- The wound burden of EB causes significant challenges in daily living, impacts health-related quality of life (HRQOL) of both patients and carers, and results in substantial costs for healthcare systems and families.[1]
- Junctional (JEB) and Dystrophic Epidermolysis Bullosa (DEB) comprise the most severe subtypes of EB.
- Despite this, comprehensive studies assessing the burden of illness for these severe subtypes are limited.

Figure 1. Understanding epidermolysis bullosa*

*Scan or follow the link below to view a video to aid understanding of EB.

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https://my.scimobi.com/links/BiKu9XsrBC

- **Objective: A targeted literature review (TLR) to update understanding of the clinical, economic, and humanistic burden of JEB and DEB to inform decision makers of treatments for severe EB.**

Methods

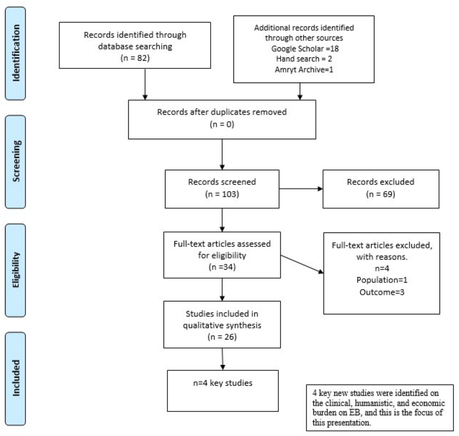
- A TLR was conducted using PRISMA Guidelines on Sept 18th, 2023 to identify new full-text articles reporting on clinical, economic, and humanistic burden of EB using a complementary approach of database searching (PubMed and Google Scholar) and handsearching of reference lists and other grey literature sources. Studies were selected based on inclusion and exclusion criteria detailed below. Following screening of eligible articles, a limited number of new studies were selected to conduct a qualitative synthesis of real-world burden data from the past 5 years, based on relevance, timeliness, and quality of the studies.
- Inclusion Criteria:
  - Observational Study
  - Includes patients with DEB or JEB
  - Comparison: patients without EB or with other subtypes; patients with differing severity of EB (mild, moderate, severe)
  - Outcomes measuring Clinical, Economic, and/or Humanistic Burden
- Exclusion Criteria:
  - Not written in English
  - Animal studies
  - Involves patients of other types of EB, Simplex EB, Kindler syndrome and EB Acquisita
  - Non-peered review research
- Database search strategies included the following key terms, but were not limited to:

Clinical Burden;
Wound Burden, Pain and Itch, Strictures and stenoses, Malnutrition/failure to thrive, Anemia, Pseudosyndactyly, Microstomia, Congestive heart failure and cardiomyopathy, Ocular manifestations, Reduced mobility /Osteoporosis, Premature mortality, Squamous cell carcinoma, Procedures i.e. Esophageal dilation, Scalp blistering and hair loss (scarring alopecia), nail dystrophy and loss, Milia, Infections, Constipation, Musculoskeletal contractures

Humanistic Burden;
iscorEB, ABILIHAND, Birmingham EB Severity score, FDLQI, InToDermQOL, QOLEB, EQ-5D-VAS, ADLs, Achenbachs, Child Behaviour Checklist, GHQ-12, Graphic Tests, Strengths and Difficulties Questionnaire, Pain and Purities Scales, PQAS, VAS, Wechsler Intelligence Scale

Economic Burden;
Medical Costs, wound care costs, Hospitalization costs, Cost effectiveness, Healthcare Resource Utilization

Figure 2. PRISMA Diagram



Search Results

- Database searches and screening yielded a limited set of literature with 4 relevant new studies identified.
- Results of the database search are shown in **Figure 2** and identified the following 4 studies:[3-6]
  - Evaluation of Clinical and Oral Findings in Patients with EB (**Yavuz et al., 2023**.)
  - Itch in recessive dystrophic EB: findings of PEBLES, a prospective register study (**Mellerio et al., 2023**)
  - Gender and burden differences in family caregivers of patients affected by 10 rare diseases (**Chiarotti et al., 2023**)
  - Understanding the socioeconomic costs of dystrophic EB in Europe: a costing and HRQOL study (**Angelis et al., 2022**)
- Further hand searching identified 2 additional relevant new studies:[7,8]
  - The challenges of living with and managing EB: insights from patients and caregivers (**Bruckner et al., 2020**)
  - Clinical characteristics, healthcare use, and annual costs among patients with DEB (**Feinstein et al., 2022**)

Results – Clinical Burden (n=4 studies)

Clinical burden was described in 4 new studies reporting the burden of wounds, complications, pain and itch in EB (Yavuz et al., 2023; Mellerio et al., 2023; Bruckner et al., 2023; Feinstein et al., 2022)

- **Yavuz et al., 2023: Evaluation of Clinical and Oral Findings in Patients with EB**
  - Prospective Turkish study of patients with EB (N=26) reporting clinical and oral findings, family history and associations between dental caries, parental consanguinity, gender, age, EB type, clinical and oral symptoms, anomalies, lesion distribution, and gender.
  - The study reported that EB was associated with malnutrition, anemia, growth retardation and tooth decay, among other clinical characteristics:
    - Intraoral bullae and lesions was reported in 92% of cases, ankyloglossia and vestibular sulcus insufficiency in 73% of cases, and microstomia and maxillary atrophy in 69% of cases, found in all EB types.
    - Patients reported malnutrition (80.7%), anemia (46%), growth retardation (61.5%), eye issues (42%), gastrointestinal issues (76.9%), hair loss (38%), hand/nail abnormalities (88%), and renal issues (n=1).
- **Mellerio et al., 2023: Itch in recessive DEB (RDEB): findings of PEBLES, a prospective register study**
  - A United Kingdom (UK) cohort study of itch in patients with RDEB in the PEBLES registry (N=50)
  - Reported a strong correlation (r>0.8) of EB with all Leuven Itch Scale (LIS) items. Itch was frequent, present in the preceding month in 93% of reviews. Itch severity and distress were significantly greater in severe (RDEB-S) and pruriginosa (RDEB-Pru) subtypes compared to intermediate RDEB (RDEB-I).
- **Bruckner et al., 2020: The challenges of living with and managing EB: insights from patients and caregivers**
  - A United States (US) survey investigating the challenges of adult patients (n=63) and caregivers (n=93) for simplex, JEB, and DEB (dominant and recessive, DDEB and RDEB)[7].
  - Patients with RDEB reported the greatest wound burden, with approximately 60% of patients and caregivers reporting wounds covering > 30% of total body area.
  - RDEB patients also reported the greatest disease burden, spending the longest amount of time on wound care (37% spent >4 h/day) and reporting the highest levels of acute pain (5.6 out of 10) and itch (6.7 out of 10).
- **Feinstein et al., 2022: Clinical characteristics, healthcare use, and annual costs among patients with DEB**
  - A retrospective US claims database study of 412 patients (36% DEB)
  - The study reported the most common comorbidities were mental health disorders, malnutrition, and constipation. Rates of cutaneous squamous cell carcinoma ranged from 0% (DDEB) to 4.4% (RDEB).
  - Among patients with pain scores (n = 218, 52.9%), on average, patients reported moderate pain (mean [SD] recorded values ranged from 1.3 [2.3] to 5.0 [3.7] out of 10).

Results – Humanistic Burden (n=4 studies)

Humanistic patient and carer burden was reported in 4 new studies and described wound care-time and itch increasing the HRQoL burden for patients and caregivers in DEB.

- **Chiarotti et al., 2023: Gender and burden differences in family caregivers of patients affected by 10 rare diseases**
  - Family caregivers of patients with rare diseases in Italy were surveyed for caregiver burden levels and QoL.
  - Caregivers of EB patients (n=16) reported high Zarit burden scores (mean= 32.4), reduced EQ-5D VAS scores (mean= 78.1), and high care-time (mean= 64.2 hours/week). The worst HRQoL scores were reported by caregivers of patients with EB, mucopolysaccharidosis and scleroderma.
- **Mellerio et al., 2023: Itch in recessive dystrophic EB: findings of PEBLES, a prospective register study**
  - This UK cohort study showed that EB-related itch was associated with reduced HRQOL, with correlations between total QoLEB scores and LIS.
- **Angelis et al., 2022: Understanding the socioeconomic costs of DEB in Europe: a costing and HRQOL study**
  - Cross sectional study of adults with DEB (N=91) in 5 European countries (UK, Germany, France, Italy, Spain)
  - The mean EQ-5D index score for adult DEB patients ranged between 0.304 (UK) and 0.541 (Germany), with an EU5 average of 0.456, whereas the mean EQ-5D VAS score ranged between 47.5 (Germany) and 70.0 (France), with an EU5 average of 61.9.
  - Caregiver mean EQ-5D index was 0.749 (SD, 0.277), and ranged from 0.713 (UK) to 0.855 (Germany)
  - The average Barthel Index score of patients represented moderate dependence at 78.1 (n = 65, SD = 22.9).
  - The Zarit burden for caregivers was moderate across all countries with average score of 31.0 (n=49, SD,13.7)
- **Bruckner et al., 2020: The challenges of living with and managing EB: insights from patients and caregivers**
  - Patients and caregivers reported that EB negatively impacts activities of daily living, socialization, and emotional well-being. On a scale of 1 to 10 where 1 was defined as “do not feel” and 10 was defined as “feel very strongly.” A rating of ≥ 5 was reported by 88.9% of patients and 82.8% of caregivers for frustrated, 74.6% of patients and 52.7% of caregivers for embarrassed, 69.8% of patients and 57.0% of caregivers for worried or anxious, and 66.6% of patients and 34.4% of caregivers for depressed

Results – Economic Burden (n=3 studies)

Three new studies reported economic burden, highlighting high healthcare resource use (HCRU), and substantial direct medical (treatment and healthcare costs) and non-medical costs (formal social care and caregiver time) and indirect costs (productivity loss), which were highest in the most severe subtypes of EB, such as DEB.

- **Angelis et al., 2022: Understanding the socioeconomic costs of DEB in Europe: a costing and HRQOL study**
  - Overall, average EU5 annual cost per patient was estimated at €53,359, ranging from €18,783 (France) to €79,405 (Germany).
  - Average EU5 annual direct medical costs were estimated at €8,357: ranging from €5,658 (France) to €12,576 (Germany). Average direct non-medical costs were estimated at €41,353, ranging from €11,961 (France) to €57,000 (Germany).
  - EB results in lower productivity and employment for both patients and caregivers: average indirect costs were estimated at €3,649, ranging from €1,025 (Italy) to €9,930 (UK).
  - Costs varied across patients with different disability but also between children and adults.
- **Feinstein et al., 2022: Clinical characteristics, healthcare use, and annual costs among patients with DEB**
  - A US claims database study reported HCRU and direct medical costs over a 12-month follow-up.
  - Over 1 year, patients had 19.7 ambulatory visits, 22.8% had an emergency department visit, and 23.8% had an inpatient stay. Prescriptions included antibiotics (56.6%), pain medications (48.3%), and itch medications (50.7%).
  - Direct medical costs among patients with claims data (n = 92) ranged from $22,179 for EB unspecified to $48,419 for DEB (type unknown).
  - Mean annual cost of bandages paid for by insurance (not including out-of-pocket costs) among patients with bandage use to range from $131 for DDEB to $22,679 for those with DEB (type unknown). The estimated annual cost was $5341 for patients with RDEB.
- **Bruckner et al., 2020: The challenges of living with and managing EB: insights from patients and caregivers**
  - Even with healthcare insurance coverage, a significant proportion of US patients had unmet out of pocket expenses, including dressings: on average, monthly unreimbursed costs ranged from $262 to $682.

Conclusions

- **This TLR identified a limited number of new real-world studies describing the substantial clinical, humanistic and economic burden of EB, which is exacerbated in patients living with severe JEB and DEB subtypes.**
- **Six key new studies were identified, which included 642 patients with EB (>60% DEB) and 210 caregivers across 7 countries.**
- **Additional real-world studies are needed to further characterize the true clinical, humanistic and economic burden of severe EB (especially in JEB) carried by patients, caregivers, healthcare systems and society.**
- **Such health economic and outcome research can help to support clinical development and patient access to novel treatments that are urgently needed for this devastating condition.**

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