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# The Natural History of Severe Recessive Dystrophic Epidermolysis Bullosa – 4 Phases Which May Help Determine Different Therapeutic Approaches

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## INTRODUCTION

Inherited epidermolysis bullosa (EB) is a rare group of disorders characterized by skin fragility and mechanically induced blistering. There are four main types: EB simplex (EBS), junctional EB (JEB), dystrophic EB (DEB), and Kindler EB (KEB).

In DEB skin cleavage is beneath the lamina densa and caused by mutations in the collagen VII gene. The recessive form is the most severe [1]. Patient with severe recessive dystrophic EB (RDEB) shows four distinct phases of disease progression over time, each bringing its own challenges. Understanding the natural disease progression throughout life will help guide towards practical and potentially helpful interventions tailored best to those stages. The four phases in the natural history of RDEB we describe are schematically represented in Figure 1.

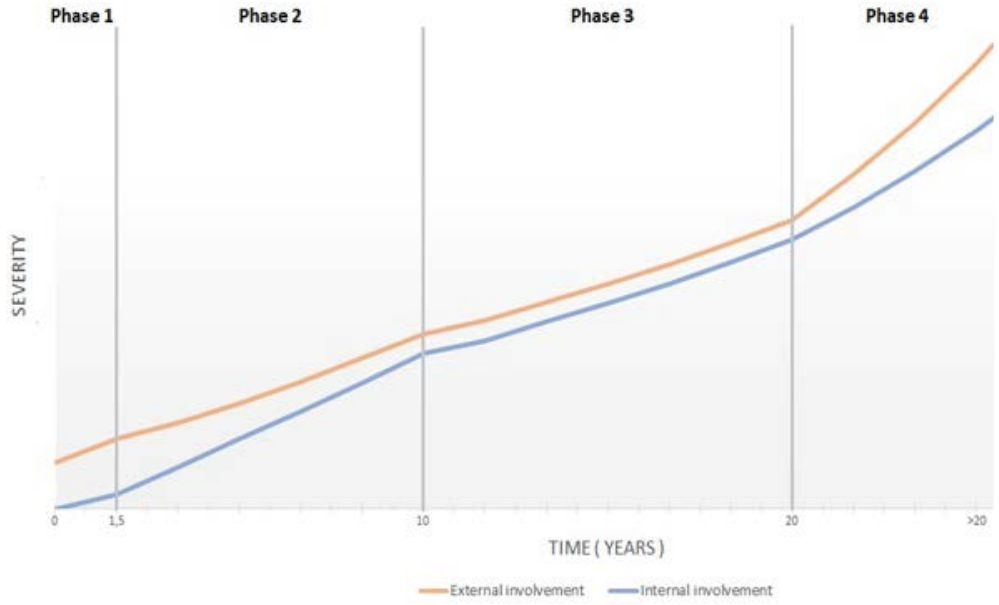


**Figure 1:** The schematic timeline represents the internal and external compromise in RDEB patients.

The first phase of severe RDEB is from 0 to 18 months. Newborns with RDEB can have large areas of absent skin with a predilection for the extremities. These wounds can take weeks to re-epithelialise, despite meticulous nursing care. During the first months, adequate weight gain is seen with intense dietetic input and inflammatory markers are often normal.

The second phase lasts from 18 months to 10 years of age. Here there is a tendency for weight to falter and the first signs of anaemia to develop resulting from increasing levels of systemic inflammation, an indicator of increasing wound burden and bacterial colonization. In a study of 157 children with RDEB, low levels of hemoglobin, iron, vitamin D and albumin with high levels of C-reactive protein, and absence of collagen VII immunostaining in the skin correlated significantly with delayed growth [2].

The growth delay observed in the second year of life suggests a correlation with weaning. Due to increasing oral and oesophageal mucosal damage causing pain and dysphagia, oral intake is often reduced. Patients start experiencing constipation, often exacerbated by iron supplementation, reducing oral intake. Nutritional requirements are high due to the increasing wound burden and children being more mobile leading to further skin damage.

In both phases, wounds often heal within 21 days but are generally dynamic and reoccurring. Very few wounds fail to heal and are chronic [3].

Systemic inflammation levels increase steadily during these first two phases. This reflects worsening internal involvement and creates an important window of opportunity for anti-inflammatory therapies, such as allogeneic mesenchymal stem cell infusions. Wounds heal with scarring, leading to contractures and the first manifestation of oesophageal strictures. Potential antifibrotic agents, such as losartan, could decrease the elevated TGF-β signaling seen in the skin of RDEB patients and might prove a useful therapeutic option as reported in ongoing clinical trials.

In the third phase, from age 10 to 20 years, cutaneous and systemic involvement are both significant. Increasing levels of chronic inflammation affect major pathways: the growth hormone insulin-like growth factor 1 axis results in growth failure, bone regulatory pathways lead to osteopenia, osteoporosis and fractures, iron metabolism leads to anemia and the hypothalamic-pituitary-gonadal axis results in pubertal delay. At this stage, many wounds are chronic and do not heal within 21 days and anti-inflammatory therapies are likely to be much less effective.

In the fourth phase, from 20 years onwards, there is a steady progression of disease severity externally and internally. Patients are at high risk for developing squamous cell carcinoma, a life-threatening complication of severe RDEB. Tumors are usually well differentiated but rapidly growing, often on the extremities with a median survival of 2.4 years for this EB subtype (Mellerio JE, personal communication). Anti-inflammatory and antifibrotic therapies during this phase are unlikely to lead to meaningful improvement.

Understanding the natural history and mechanism of disease progression in RDEB will help early instigation of the most effective interventions and target the most effective treatments during each phase of this complex and debilitating disease.

## CONFLICTS OF INTEREST

None.

## FUNDING SOURCES

None.

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