A systematic review of the natural history of recessive dystrophic epidermolysis bullosa

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Introduction: In recent years, a number of new translational therapies for different forms of epidermolysis bullosa (EB) have started to reach early phase clinical trials and yet more potential treatments are in the pipeline. In order to evaluate the effectiveness of any new intervention, there is a need for meaningful and robust outcome measures which, in the context of numerous and clinically heterogeneous subtypes of EB, can be difficult to define. In addition, most severe forms of EB show disease progression over time, such as scarring, oesophageal strictures, anaemia and the development of squamous cell carcinomas (SCCs). To identify endpoints relevant for clinical trials, therefore, an understanding of the natural history of EB is essential so that any benefits of an intervention, or lack thereof, can be determined. This systematic review was initiated to delineate what is already known about the natural history of one of the main target types of EB for new therapies, recessive dystrophic EB (RDEB).

Methods: A systematic literature review was conducted as shown below in Figure 1.

Inclusion criteria	Exclusion criteria
1980-present	Pre-1980
Written or translated into English	
Human studies	Animal studies
Intervention or case studies	
Papers that partially or completely discuss RDEB	General EB papers

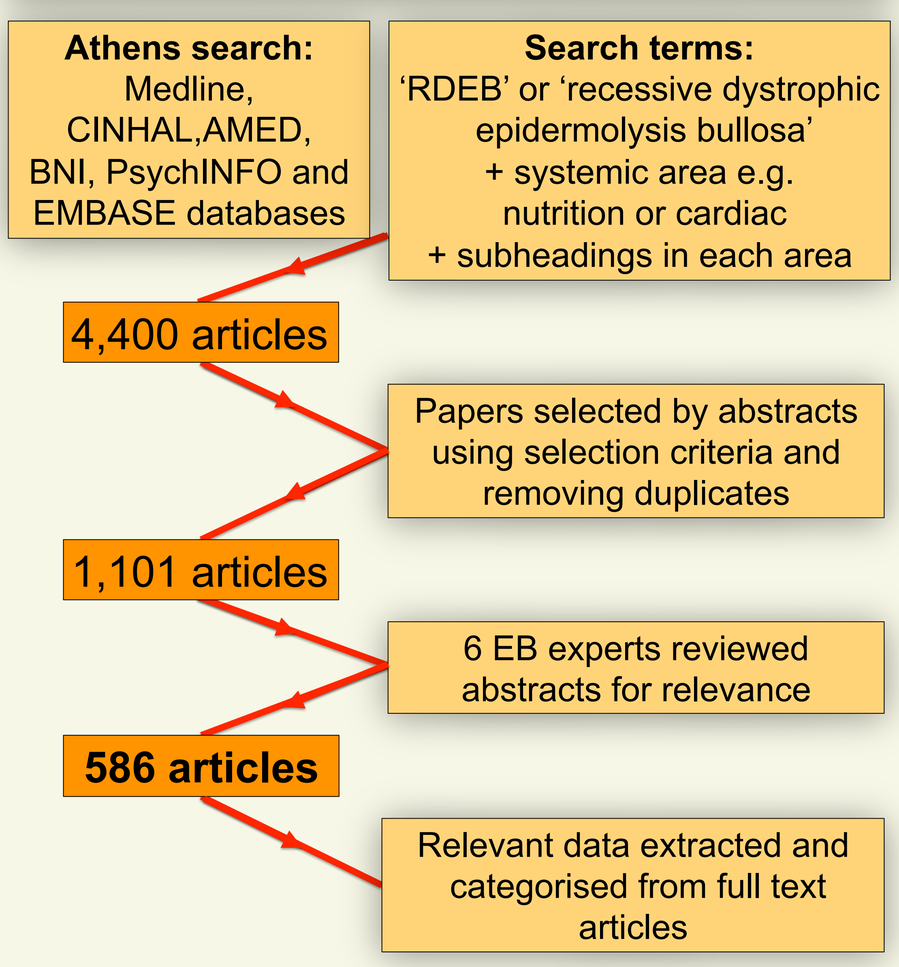

Figure 1: Systematic literature review.

Results: Data was amalgamated according to RDEB subtype and the system or complications described. Where possible, information about the age of onset of a complication or procedure was extracted (Table 1). Papers from the National Epidermolysis Bullosa Registry (NEBR) data provided most information and included a denominator meaning that incidence and cumulative risk could be calculated; other sources, however, lacked this information.

	Number of patients					
	GS-RDEB	GI-RDEB	RDEB-I	RDEB NOS	Total	Comments
Aplasia cutis	8	8	5	5	26	All present feet/legs. Healed few weeks – 3 y
Cardiomyopathy	9	-	-	11	20	Mean age onset 11.6 y (2-28 y) Death in 9/20, mean 0.5 y after diagnosis
Dysphagia	5	-	4	43	52	Mean age onset in GS-RDEB 18.2 y (7-41 y)
EB naevi	6	2	-	4	12	Mean age onset 4.6 y (0.3-10 y)
ENT complications	-	-	-	12	12	Includes stridor, dyspnoea, otitis externa, sensorineural hearing loss
Eye complications	2	-	-	11	13	Includes corneal abrasions, symblepharon, reduced vision
Gastrostomy tube insertion	56	-	-	7	63	Mean age 8.2 y (0.4-18.5 y)
Growth delay	41	4	-	-	45	No information about onset of delay
Bone mineral density	6	-	-	-	6	L2-L4 Z scores mean -2.7 (-1.26 to -4.53)
Hand/foot surgery	13	1	1	130	145	No information about onset of deformity
Genitourinary	22	6	-	6	34	Includes IgA nephropathy, amyloid, renal failure glomerulonephritis, urethral stricture, phimosis
SCC	42	5	1	28	76	Mean age first SCC in GS-RDEB 28.6 y (6-48 y)

Table 1: Main complications or features identified by the systematic review by RDEB subtype and system. GI-RDEB, generalised intermediate RDEB; GS-RDEB, generalised severe RDEB; RDEB-I, RDEB inversa; RDEB NOS, RDEB not otherwise specified.

Discussion: This systematic review identified a large number of papers which include information about clinical and laboratory features in RDEB, however there are significant limitations to the information gathered:

- Most papers are single case reports or series of small numbers of patients
- Many reports do not provide details of the specific RDEB subtype
- Amalgamation of RDEB or other EB subtypes makes analysis about specific RDEB patients difficult
- Many reports describe complications or interventions but without age of onset
- Data on psychosocial, quality of life and health economics is particularly scarce
- The NEBR, which includes data on over 3000 US EB patients collected over a 16 year period, provides incidence and cumulative risk data by RDEB subtype in a number of clinical areas

Conclusions: Collectively, the current literature on RDEB does not provide a clear picture of the natural history of the various systems which can be affected; specifically, information on the age of onset and progression of different complications, psychosocial aspects, laboratory parameters, quality of life and disease severity measures is scant. This highlights the need for research into these aspects of RDEB with sufficient granularity to be sensitive to disease progression and to inform putative outcome measures for future clinical trials for this group of diseases. Longitudinal data collected from a well-characterised cohort of patients would provide invaluable intra-individual information about disease progression over time. Inclusion of economic data e.g. dressing, medication and carer costs, would in addition provide justification for investment into novel and potentially costly new therapies for EB.