Cause-Specific Risks of Childhood Death in Inherited Epidermolysis Bullosa

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Objective To determine the cause-specific risks of death in children with epidermolysis bullosa (EB).

Study design Data were collected throughout the continental United States between 1986 and 2002 by the National EB Registry. The study design is cross-sectional (n = 3280), containing within it a nested randomly sampled longitudinal subcohort (n = 450).

Results The risk of death during infancy and childhood was greatest in junctional EB (JEB), with cumulative and conditional risks of 40% to 44.7% by age 1 in both JEB subtypes, rising to 61.8% in children with JEB, Herlitz subtype and 48.2% in those with JEB, non-Herlitz subtype (JEB-nH) by age 15. In decreasing order, sepsis, failure to thrive, and respiratory failure were the major causes of death in children with JEB, plateauing by age 2 to 6. A small minority of children with epidermolysis bullosa simplex, Dowling-Meara subtype was at risk for death by age 1 (cumulative risk, 2.8%), with sepsis and respiratory failure accounting for cumulative risks of 1.9% and 0.9%. Only a minority of children with recessive dystrophic epidermolysis bullosa, Hallopeau-Siemens subtype was at risk of death (cumulative risk = 8% by age 15). Renal failure also rarely accounted for death in children with JEB-nH.

Conclusions Infants and children with inherited EB, particularly those with JEB, are at significant risk of death as a result of disease complications. (J Pediatr 2008;152:276-80)
gitudinal components,\textsuperscript{11,12} One of its major goals was to determine the risk of selected extracutaneous outcomes in inherited EB, including premature death. During its 16 years of continuous federal funding, 3280 patients throughout the continental United States were enrolled and evaluated. The demographics of this study population have been shown to closely mirror those of the US population as a whole, allowing generalization across the nation.\textsuperscript{13} The distribution of patients by major EB type and subtype also has been shown to closely mimic that seen within much smaller cohorts of EB patients elsewhere in the world, further suggesting that these data are applicable to EB patients everywhere.\textsuperscript{13} On the basis of rigorous analysis of this registry’s database, we present data on both cumulative and conditional risks for cause-specific risks of death during the first 15 years of life for each major subtype of this disease.

**METHODS**

Data were obtained from 3280 consecutively enrolled EB patients who were seen on behalf of the National Epidermolysis Bullosa Registry between September 1986 and April 2002, when federal funding for this NIH-supported project formally ended. During these 16 years, work was carried out by a number of co-investigators at several institutions (see the Institutional Affiliations section). The authorship of the present publication represents the research team at the project’s Data Coordinating Center, which took ultimate responsibility for data validation and the performance and interpretation of all biostatistical analyses, in addition to playing a pivotal role in data collection from most of the project’s patients, their families, and referring physicians.

A comprehensive data instrument, containing nearly 1000 possible data entries, was used. This instrument comprised a detailed questionnaire, which included patient demographics, past and present medical history, family history, and socioeconomic variables, as well as physical examination findings and diagnostic laboratory test results. During the last 5 years of funding, all the work was confined to the University of North Carolina at Chapel Hill and Stanford University and was conducted under the auspices and approval of the NIH-supported General Clinical Research Centers and the Institutional Review Boards at these 2 universities.

Whenever possible, each enrollee was seen and examined at least once by 1 of the project’s principal investigators. The diagnosis of EB was confirmed in each case by immunofluorescence antigenic mapping, EB-specific monoclonal antibody studies, and transmission electron microscopy.\textsuperscript{6} Each patient was further subclassified as to EB subtype using a widely used classification scheme that was reported in 1991\textsuperscript{14} and updated in 2000 by an international panel of EB experts.\textsuperscript{6}

We separated our patient population into various mutually exclusive EB subtypes, following the detailed criteria of the most recent classification scheme\textsuperscript{6}: EBS, Weber-Cockayne (EBS-WC); EBS herpetiformis, Dowling–Meara (EBS-DM); EBS, Koebner (EBS-K); EBS, all others (EBS-O); JEB, Herlitz (JEB-H); JEB, non-Herlitz (JEB-nH); DDEB; generalized RDEB, Hallopeau-Siemens (RDEB-HS); and generalized RDEB, non-Hallopeau-Siemens (RDEB-nHS). Only 17 patients with RDEB inversa were enrolled in the project, and because none of these experienced premature mortality, none was included in the present analyses. Sufficient data existed on 2750 patients (83.8%) (Table I; available at www.jpeds.com) enrolled within the National Epidermolysis Bullosa Registry project to permit subclassification into these major EB subtypes. This served as the final subpopulation from which data on premature death were extracted.

Approximately 450 well-classified subjects were further randomly selected for longitudinal follow-up on an every-2-year basis during the last 10 years of this project.\textsuperscript{12} This nested subpopulation was chosen so as to maximally sample those EB subtypes most at risk for significant extracutaneous complications, to include premature death. Causes of death were determined through a review of death certificates, interviews with surviving family members, and examination of medical records.

Data collection was entered into specially designed templates originally based on Clinfo and later on EpInfo software (Centers for Disease Control, Atlanta, GA). SAS datasets (SAS Institute, Cary, NC) were subsequently generated to facilitate the performance of life table analyses.

All biostatistical analyses were conducted under the supervision of the project’s designated biostatistician (C.S.), who was masked as to the identity of each subject. Computer-generated graphs were created using Excel (Microsoft, Seattle, WA).

**RESULTS**

**Premature Death and EB: All Causes**

Table II (available at www.jpeds.com) summarizes the mean and median ages at time of death among participants in the National EB Registry. Deaths during childhood were most common in patients with JEB-H and JEB-nH, with a low frequency seen in those with each EBS subtype other than EBS-WC.

Figure 1 summarizes the cumulative risk of death, cause unspecified, for each major EB subtype. No deaths occurred during the first 15 years of life in patients with EBS-WC and DDEB, consistent with the relative mildness of skin and extracutaneous disease activity in these subtypes. In marked contrast, 40.0% to 44.7% of all children with JEB died within the first year of life, with cumulative risks rising to 61.8% in JEB-H and 48.2% in JEB-nH by age 15. The highest conditional risk of death for patients with JEB-H and JEB-nH was during the first year of life (44.7% and 40.0%, respectively), with the second-highest conditional risk at age 1 to 2 years (JEB-H, 9.1%; JEB-nH, 9.0%). The risk of premature death during the first year of life in all other EB subtypes was only 1.1% to 2.8%, the highest in EBS-DM (with both cumulative and conditional risks of 2.8%). Among the remaining EB subtypes at risk for death during childhood, the one with the highest cumulative risk was RDEB-HS, rising to 8.0% by age 15.
Death From Failure to Thrive

Death from failure to thrive was a risk only in JEB, with cumulative (and identical conditional) risks of 16.7% in JEB-H and 4.0% in JEB-nH by age 1 (Figure 2). The cumulative risk reached a plateau of 20.5% in JEB-H by age 2.

Death From Sepsis

Sepsis was reported as a cause of death in all but 2 EB subtypes by age 1 (range, 0.4% [RDEB-nHS] to 19.5% [JEB-nH]) (Figure 3). By age 15, the cumulative risk of death from sepsis in JEB-nH had risen to 24.2%. The subtype with the second-highest cumulative risk of death from sepsis within early childhood was JEB-H, with a risk of 11.4% by age 1 and 17.5% by age 8 and older. Of note, most deaths in EBS-DM could be attributed to sepsis, with a mortality rate of 1.9% by age 1.

Death From Pneumonia

Pneumonia was attributed as the cause of death during early childhood primarily in JEB, with cumulative risks of 3.0% and 0.7% by age 1 and 3.0% and 1.7% on or after age 2 in JEB-H and JEB-nH, respectively (Figure 4; available at www.jpeds.com). Cumulative risk of death from pneumonia in RDEB-nHS was only 0.4% by age 1 and 1.1% by age 15. Death from pneumonia was not seen in RDEB-HS until late childhood (first occurring after age 10), with a cumulative risk of 1.8% noted by age 15.

Death From Respiratory Failure

During the first 15 years of life, death attributed to respiratory failure, cause otherwise unspecified, occurred almost exclusively in JEB (Figure 5). By age 1, the conditional risks were 8.7% in JEB-H and 9% in JEB-nH. By age 4, the cumulative risk had reached a plateau value of 13.8% in children with JEB-nH, whereas a plateau (14.1%) was not reached until age 6 in JEB-H. Among EBS infants, only those with EBS-DM were at risk for premature death from respiratory failure (cumulative risk of 0.9% by age 1). During later childhood, children with EBS-O, RDEB-HS, and RDEB-nHS also were at risk, with cumulative risk of 0.4% to 1.1% by age 15.

Death From Renal Failure

As reported previously, during the first 15 years of life, renal failure was attributed as the cause of death only in
patients with JEB-nH, with a cumulative risk of only 0.7% at age 1 and older.\textsuperscript{15}

**Death From Squamous Cell Carcinoma**

During the first 15 years of life, no deaths from squamous cell carcinoma in any EB type or subtype were noted in our database.

**DISCUSSION**

There are no published data that can assist physicians in accurately assessing the risk of premature death in any subtype of EB. This explains why some parents of children with EB who have now survived into late childhood or early adulthood have told us that they were incorrectly advised to expect their child’s death within the first few months of life. There is a widespread lack of understanding by nondermatologists of the often-subtle clinical differences among EB subtypes. In addition, sophisticated diagnostic testing techniques capable of accurately subclassifying EB patients are available in only a few reference laboratories worldwide. There are as yet no evidence-based data describing the natural history of each major EB subtype. Each of these limitations prevents accurate prognostication. The resultant misclassification, although unintentional, may directly affect the level of care provided to some children. The National EB Registry receives frequent calls from primary care physicians asking for advice on how aggressively therapeutic interventions should be pursued, in the absence of knowing the specific subtype of EB present. This undoubtedly reflects a lack of appreciation of the likely causes of death during infancy and childhood, the expected timing of such events, and the EB subtypes for which these are clinically of most concern. It is for this reason that the present study has been conducted.

Decades ago, infant mortality from infection was a major concern in all subtypes of inherited EB, due primarily to the unavailability of sophisticated wound care products, the lack of application of burn unit techniques to the care of EB children, and the absence or incorrect use of broad-spectrum topical and systemic antibiotics.\textsuperscript{16} In most older dermatology and pediatric textbooks and reviews, sepsis was the factor most commonly cited as the major cause of death in infants with EB. Anecdotally, this still appears to be a major risk factor for children with EB in some third-world countries. Over the past 20 years, however, various outstanding synthetic dressings have been developed and used extensively in the day-to-day care of children with EB. The availability of such dressings, coupled with selective but more aggressive use of systemic and topical antibiotics, may explain why (as demonstrated by the present data) infant mortality from sepsis remains a clinically significant concern in the US EB population only in those children with severe junctional subtypes.

Why are children with JEB still at risk for death from sepsis? Although this question cannot be definitively answered by our data, severely affected JEB infants commonly require prolonged hospitalization during the first year of life, due in part to concurrent severe failure to thrive. They also are often hospitalized during early childhood for worsening upper-airway disease. As such, it is possible that potentially life-threatening, hospital-acquired infections may contribute to the risk of premature death in these particular children. In support of the latter, in 1 case series of children with EB treated for severe tracheolaryngeal involvement, 2 patients ultimately died of Candidal septicemia secondary to contamination of long-standing indwelling catheters in the setting of chronic systemic antibiotic therapy.\textsuperscript{17} It also is known, based on in vitro assays, that children with JEB have altered cellular immunity.\textsuperscript{18} This suggests the possibility that secondary immunosuppression as a result of chronic malabsorption of nutrients across eroded small intestinal mucosa and the repeated loss of blood constituents through open wounds on the skin might further contribute to impaired surveillance of blood-borne pathogens. Of note, a small subset of infants with the most severe form of EB simplex, EBS-DM, also is at risk for death from sepsis (comprising about 2/3 of all EBS-DM deaths within the EB Registry study population). This finding is consistent with previous case reports of increased mortality in infants with EBS-DM.\textsuperscript{19}

Death from failure to thrive also is a major concern, primarily in JEB-H, the most severe subtype of inherited EB. With a cumulative risk of about 20% by age 2, this accounts for nearly 40% of all deaths in children with JEB-H during early childhood. A much lower cumulative risk in all other JEB subtypes is consistent with the usual presence of smaller amounts of actively involved skin, as well as the infrequency of significant growth retardation or other signs of secondary malnutrition, in these patients.

It is well known that children with both major JEB subtypes, and also rarely those with 2 EBS subtypes (DM and a rare EBS subtype associated with muscular dystrophy), are at significant risk for the development of severe tracheolaryngeal strictures or stenoses during infancy and early childhood,\textsuperscript{20} and that tracheostomy may be life-saving in this setting. Death from other causes of acute airway obstruction, the result of sudden blister formation or soft tissue edema within or above the level of the true vocal cords, also has been noted in case reports and small case series, again almost exclusively in the setting of JEB. Airway obstruction was not specifically reported as a primary or secondary cause of death on any death certificate in our study population, making it impossible to accurately assess the true magnitude of this risk. Death from respiratory failure was reported in many patients, however. Whether or not this latter diagnosis represents a surrogate marker for upper airway obstruction cannot be proven, although it is likely that most of these deaths were indeed caused by such a mechanism. Of importance, by age 5 to 6 the cumulative risk of death from respiratory failure was approximately 14% in both JEB subtypes. Of note, the shapes and timing of these curves are very similar to those calculated from the EB Registry database for the cumulative risks of tracheolaryngeal strictures and stenosis,\textsuperscript{20} indicating that both very likely represent the same phenomenon. As such, these data support the notion that suffocation from upper airway...
occlusion represents another clinically significant concern in infants and small children with JEB.

The only specific pulmonary cause of death reported on the death certificates in our study population was pneumonia. This was noted in infancy and early childhood only in JEB, and only at a very low frequency. Whether or not this complication was mutually exclusive of septicemia cannot be determined from the data available for analysis. It is also possible that some of these deaths may have been the result of chronic aspiration pneumonitis secondary to disease-associated narrowing of the lumen within the upper airway, rather than purely of a primary infectious etiology.

Renal failure is an uncommon cause of death in inherited EB. Whereas the cumulative risk of death from renal failure is approximately 12.3% in RDEB-HS patients by age 35, due to secondary renal amyloidosis or poststreptococcal glomerulonephritis, it is exceedingly rare during the first 15 years of life and has been seen only in JEB-nH, with a cumulative risk of <1% at age 1 and older.

Squamous cell carcinoma is the most common cause of mortality in patients with RDEB, especially in those with the severe Hallopeau-Siemens subtype. In RDEB, these tumors first arise in chronic nonhealing skin wounds during mid- to late adolescence, with death from distant metastases occurring in the vast majority of patients within 5 years of diagnosis of the primary tumor. Data collected through 2002 by the EB Registry (unpublished data, Fine JD, 2007) have failed to demonstrate any significant risk of death from squamous cell carcinoma during infancy or childhood. But meticulous skin surveillance by mid-adolescence is strongly recommended, because it is still possible that such a tumor might arise during the latter half of the second decade of life.

Taken together, our data demonstrate that the risk of death among EB infants and children differs markedly by EB subtype in terms of specific cause, magnitude of risk, and timing of onset. It is also clear that most children with EB who survive the first 12 to 24 months of life will live into at least adulthood, provided that meticulous, aggressive medical care is provided.

These data hopefully will be of practical value to neonatologists, pediatricians, and medical geneticists as they attempt to counsel parents and accurately prognosticate the natural history of this disease. These data also should assist the pediatrician in selecting the most appropriate time for surveillance for specific complications of this disease, and thereby in providing optimal multidisciplinary care.

We gratefully acknowledge the contributions of several other physicians to patient recruitment and data collection on behalf of the Registry throughout at least portions of its existence, most notably Drs Joseph McGuire and Eugene Bauer (Stanford University), D. Martin Carter (Rochester University), Virginia P. Sybert (University of Washington), and Amy Stein, Joy DeLeoz, Sarah Cash, and David T. DeVries (University of North Carolina at Chapel Hill). A list of National Epidermolysis Bullosa Registry Collaborating Institutions is available at www.jpeds.com.

REFERENCES

APPENDIX

National Epidermolysis Bullosa Registry
Collaborating Institutions


Table I. Distribution of patients by EB subtype

<table>
<thead>
<tr>
<th>EB subtype</th>
<th>Number of patients</th>
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<tbody>
<tr>
<td>EBS-WC</td>
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<tr>
<td>EBS-K</td>
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<tr>
<td>EBS-DM</td>
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<td>EBS-O</td>
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<tr>
<td>JEB-H</td>
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<tr>
<td>JEB-nH</td>
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<tr>
<td>DDEB</td>
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<tr>
<td>RDEB-HS</td>
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</tr>
<tr>
<td>RDEB-nHS</td>
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</tr>
<tr>
<td>RDEB inversa</td>
<td>17</td>
</tr>
<tr>
<td>Total</td>
<td>2750</td>
</tr>
</tbody>
</table>

Table II. Mean and median ages at time of death among National EB Registry subjects*

<table>
<thead>
<tr>
<th>EB subtype</th>
<th>% of patients who had died</th>
<th>Age at time of death (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean</td>
</tr>
<tr>
<td>EBS-WC</td>
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</tr>
<tr>
<td>EBS-K</td>
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</tr>
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<td>EBS-O</td>
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<td>JEB-H</td>
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<td>RDEB inversa</td>
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<td>52.26</td>
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</table>

*As of January 31, 2002.

Figure 4. Cumulative risk of death from pneumonia in inherited EB.