

Epidemiology of Epidermolysis Bullosa in the Antipodes

The Australasian Epidermolysis Bullosa Registry With a Focus on Herlitz Junctional Epidermolysis Bullosa

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Objective: To present epidemiologic and clinical data from the Australasian Epidermolysis Bullosa (EB) Registry, the first orphan disease registry in Australia.

Design: Observational study (cross-sectional and longitudinal).

Setting: Australian private dermatology practice, inpatient ward, and outpatient clinic.

Patients: Systematic case finding of patients with EB simplex, junctional EB (JEB), and dystrophic EB and data collection were performed throughout Australia and New Zealand from January 1, 2006, through December 31, 2008. Patients were consecutively enrolled in the study after clinical assessment and laboratory diagnosis. Medical records were retrospectively examined, and physicians involved in EB care were contacted to obtain patient history. A Herlitz JEB case series was prepared from registry data.

Main Outcome Measures: Demographics and prognosis of patients with Herlitz JEB.

Results: A total of 259 patients were enrolled in the study: 139 with EBS, 91 with dystrophic EB, 28 with JEB, and 1 with Kindler syndrome. Most enrollees were Australian citizens (n=243), with an Australian prevalence rate of 10.3 cases per million. The age range in the registry was birth to 99 years, with a mean and median age of 24.1 and 18.0 years, respectively. Ages were similar in patients with EBS and dominant dystrophic EB but were markedly lower in patients with JEB. Patients with Herlitz JEB (n=10) had the highest morbidity and mortality rates, with a mean age at death of 6.8 months. Sepsis, failure to thrive, and tracheolaryngeal complications were the leading causes of death.

Conclusions: The Australasian EB registry is the first registry in Australia and New Zealand to provide original data on age, sex, ethnicity, and geographical and disease subtype distribution. The Australasian Herlitz JEB cohort witnessed a high infant mortality rate and poor prognosis overall.

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EPIDERMOLYSIS BULLOSA (EB) refers to a group of genodermatoses characterized by the excessive susceptibility of the skin to separate from underlying tissues after minimal mechanical trauma. Three major types of EB exist, distinguished by the ultrastructural level of blister formation: EB simplex (EBS), junctional EB (JEB), and dystrophic EB (DEB), which, respectively, describe epidermolytic, lucidolytic, and dermolytic patterns of blistering.¹ In addition, there is a fourth type, Kindler syndrome, which features blistering at various levels. Further distinction can be made between dominant DEB and recessive DEB (RDEB) based on the greater clinical severity of recessive subtypes.

Although several registries for EB exist overseas, no epidemiologic or clinical

data have been published for the Australasian cohort of patients living with EB. Such data have become recently available with the emergence of the Australasian Epidermolysis Bullosa Registry (AEBR), permitting the contribution of Australia's experience of EB to the medical literature. This is the first orphan disease registry to be established in Australia.

METHODS

The AEBR was developed during 2005 and established on November 8, 2006, at St George Hospital in Sydney, subsequent to gaining ethics approval from the South Eastern Sydney and Illawarra Human Research Ethics Committee. Patients were consecutively enrolled in the registry with written informed consent from the Sydney Children's Hospital, St George Hospital, Dr Murrell's private dermatology practice,

The Children's Hospital at Westmead, The Royal Children's Hospital, Mater Children's Hospital, and the Dystrophic Epidermolysis Bullosa Research Associations of Australia and New Zealand.

Patient diagnoses were confirmed by a combination of clinical assessment by EB dermatologists, immunofluorescence mapping, and transmission electron microscopy. Recruitment occurred predominantly within Australia; however, a few patients were recruited from New Zealand (n=16).

Comprehensive data collection was performed at the time of patient enrollment using a data instrument, with additional data collection performed on subsequent presentations. The data collection fields used were influenced by research previously performed by the National Epidermolysis Bullosa Registry in the United States, located at The University of North Carolina at Chapel Hill and Stanford University.² Data collection fields included patient demographics; past and current medical history; family history; diagnostic laboratory studies; areas of blistering or erosion; tracheolaryngeal complications; gastrointestinal complications; weight and growth development; hair, teeth, and nail findings; ocular complications; and genitourinary complications.

Wherever available, preexisting hospital outpatient and inpatient clinical records along with private dermatologic practice notes were examined for each patient. Physicians responsible for the care of patients with Herlitz JEB (JEB-H) were additionally contacted by telephone or electronic mail for further clinical information.

Data were then entered into a password-protected database using Microsoft Access, version 11.8166.8221 (Microsoft Corporation, Redmond, Washington) from January 1, 2006, through December 31, 2008. In January 2009, data sets were extracted and analyzed using Microsoft Excel and SPSS statistical software, version 16.0.1 (SPSS Inc, Chicago, Illinois). Results were stratified by major EB type wherever relevant, and a JEB-H case series was prepared from registry data.

RESULTS

DEMOGRAPHICS

The AEBR contained 259 patients with a confirmed diagnosis of EB: 131 male and 128 female patients. Of these, 139 (53.7%) had EBS, 91 (35.1%) had DEB, 28 (10.8%) had JEB, and 1 (.4%) had Kindler syndrome. Further EB subclassifications were available for 176 patients, whereas 83 patients had no further subclassification because of insufficient data (**Table 1**).

Most patients in the AEBR were Australian (n=243), with a small number from New Zealand (n=16). Of the Australian patients, 146 were from the state of New South Wales, 34 from Victoria, 29 from Queensland, 23 from South Australia, 5 from Western Australia, 4 from Tasmania, and 2 from the Australian Capital Territory (**Figure 1**).

Among the 113 patients who reported their ethnicity (**Table 2**), most were white (n=70), followed by indigenous Australian (n=11), Chinese (n=4), Arabic (n=4), Italian (n=3), and Lebanese (n=3). There were a small number from other ethnicities, including Afghani, Maltese, Indonesian, Turkish, African, Bulgarian, Czech, Danish, Greek, Iraqi, Portuguese, Serbian, Tongan, and Ukrainian.

The patients' ages in the registry (n=247) ranged from birth through 99 years, with a mean age of 24.1 years and a median age of 18.0 years. The patients' ages, stratified by major EB type, are presented in **Table 3**. The EBS (n=133),

Table 1. Patient Diagnoses in the Australasian Epidermolysis Bullosa Registry

| Epidermolysis Bullosa Subtype | No. (%) of Patients (N=259) ^a |
|------------------------------------|--|
| Epidermolysis bullosa simplex | 139 (53.7) |
| Undetermined subtype | 73 (28.2) |
| Dowling-Meara | 27 (10.4) |
| Weber-Cockayne | 17 (6.6) |
| Koebner | 13 (5.0) |
| Mottled pigmentation | 5 (1.9) |
| Superficialis | 4 (1.5) |
| Dystrophic epidermolysis bullosa | 91 (35.2) |
| Dominant | 46 (17.8) |
| Recessive severe generalized | 17 (6.6) |
| Recessive severe generalized other | 17 (6.6) |
| Undetermined subtype | 11 (4.3) |
| Junctional epidermolysis bullosa | 28 (10.8) |
| Non-Herlitz | 13 (5.0) |
| Herlitz | 11 (4.2) |
| With pyloric atresia | 3 (1.2) |
| Laryngo-onycho-cutaneous syndrome | 1 (0.4) |
| Kindler syndrome | 1 (0.4) |

^aPercentages may not total 100 because of rounding.

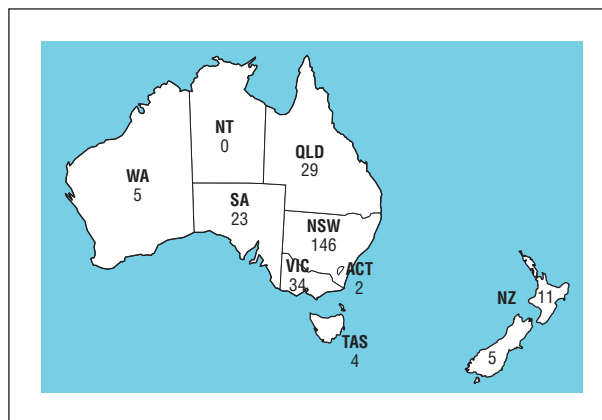


Figure 1. Distribution of Australian and New Zealand patients in the Australasian Epidermolysis Bullosa Registry. ACT indicates Australian Capital Territory; NSW, New South Wales; NT, Northern Territory; NZ, New Zealand; QLD, Queensland; SA, South Australia; TAS, Tasmania; VIC, Victoria; and WA, Western Australia.

dominant DEB (n=55), RDEB (n=34), and JEB (n=25) patient cohorts had median ages of 20.0, 18.0, 22.5, and 2.0 years, respectively, and age ranges of birth through 99, 0 through 73, 0 through 78, and 0 through 35 years. Patients with no date of birth entered were excluded from the analysis (n=11).

THE JEB-H COHORT

Seventeen patients in the registry had died as a result of EB: patients with the JEB-H subtype experienced the highest mortality rates (n=10), followed by patients with severe generalized RDEB (n=4), JEB with pyloric atresia (n=2), and non-Herlitz JEB (n=1). Most patients with JEB died during infancy, whereas most patients with severe generalized RDEB died in early adulthood of metastatic skin cancer. The mean age at death for the patients

Table 2. Ethnicity of Patients in the Australasian Epidermolysis Bullosa Registry

| Ethnicity | No. (%) of Patients (N=259) ^a |
|--|--|
| Unreported | 146 (56.4) |
| White | 70 (27.0) |
| Indigenous Australian | 11 (4.2) |
| Arabic | 4 (1.5) |
| Chinese | 4 (1.5) |
| Italian | 3 (1.2) |
| Lebanese | 3 (1.2) |
| Afghani | 2 (0.8) |
| Indonesian | 2 (0.8) |
| Maltese | 2 (0.8) |
| Turkish | 2 (0.8) |
| Others (African, Bulgarian, Czech, Danish, Greek, Iraqi, Portuguese, Serbian, Tongan, Ukrainian) | 1 per group (0.4 each) |

^aPercentages do not total 100 because of rounding.

Table 3. Patient Age Distribution by Epidermolysis Bullosa Type

| Epidermolysis Bullosa Type | Mean Age, y | Median Age, y | Age Range (SD), y |
|-----------------------------------|-------------|---------------|-------------------|
| EBS (n=133) | 26.2 | 20.0 | 0-99 (1.8) |
| DDEB (n=55) | 21.8 | 18.0 | 0-73 (2.4) |
| RDEB adjusted ^a (n=32) | 24.5 | 22.0 | 0-60 (2.6) |
| RDEB unadjusted (n=34) | 27.6 | 22.5 | 0-78 (3.2) |
| JEB (n=25) | 7.9 | 2.0 | 0-35 (2.2) |

Abbreviations: DDEB, dominant dystrophic epidermolysis bullosa; EBS, epidermolysis bullosa simplex; JEB, junctional epidermolysis bullosa; RDEB, recessive dystrophic epidermolysis bullosa.

^aTwo patients with RDEB are extreme outliers at ages 76 and 78 years.

with severe generalized RDEB was 29.4 years, with an age range of 23 through 35 years. **Table 4** lists the age at death and recorded causes of death for deceased patients in the registry.

Of the 11 patients with JEB-H in the registry, 10 had sufficient recorded data to investigate disease course and prognosis. All 10 patients died within the first 12.7 months of life, with a mean age at death of 6.8 months, an age range of 2.0 through 12.7 months, and an SD of 0.9 month.

A major cause of death in the JEB-H cohort was sepsis; deepithelized skin resulted in frequent infection for all infants, with 4 of 10 patients progressing to sepsis and 3 of 10 patients dying from sepsis-related complications. *Staphylococcus aureus*, group A *Streptococcus*, and *Staphylococcus capitis* were isolated from blood cultures before death. Blister and erosion formation most frequently occurred over the buttocks and perineum in a diaper pattern of distribution, followed by blistering on the legs and arms. The frequency of blistering over various body parts, recorded on initial and subsequent hospital presentations, is summarized in **Table 5**.

Malabsorption with secondary failure to thrive was the second major cause of death in the JEB-H cohort, affecting most infants. All JEB-H patients demonstrated a progressive nutritional decline as they advanced through life, falling well below the first percentile typically by 3 months of

Table 4. Causes of Death for Patients in the Australasian Epidermolysis Bullosa Registry

| Epidermolysis Bullosa Subtype | Age at Death | Cause of Death |
|-------------------------------|--------------|--|
| JEB with PA | 0 mo | Renal failure |
| JEB-H (patient 1) | 2 mo | Toxic shock |
| JEB with PA | 4 mo | Gastrointestinal hemorrhage |
| JEB-H (patient 2) | 5 mo | Tracheal strictures |
| JEB-H (patient 3) | 5 mo | Sepsis and multisystem organ failure |
| JEB-H (patient 4) | 5 mo | Unavailable |
| JEB-H (patient 5) | 5 mo | Gastrointestinal hemorrhage |
| JEB-H (patient 6) | 6 mo | Malabsorption and prolonged apneic episodes |
| JEB-H (patient 7) | 7 mo | Malabsorption, anemia, and aberrant electrolytes |
| JEB-H (patient 8) | 8 mo | Sepsis and chronic malabsorption |
| JEB-H (patient 9) | 8 mo | Unavailable |
| JEB-H (patient 10) | 12 mo | Pneumonia within a background of chronic malabsorption |
| JEB-nH | 15 y | Cardiomyopathy |
| RDEB-SG | 23 y | Metastatic squamous cell carcinoma |
| RDEB-SG | 35 y | Metastatic squamous cell carcinoma |
| RDEB-SG | 30 y | Renal failure |
| RDEB-SG | 34 y | Metastatic squamous cell carcinoma |

Abbreviations: JEB, junctional epidermolysis bullosa; H, Herlitz; nH, non-Herlitz; PA, pyloric atresia; RDEB, recessive dystrophic epidermolysis bullosa; SG, severe generalized.

Table 5. Recorded Areas of Blistering in the Herlitz Junctional Epidermolysis Bullosa Cohort

| Area of Blistering | Recorded Frequency, % |
|---|-----------------------|
| Buttocks and perineum (diaper distribution) | 20 |
| Legs and thighs | 18 |
| Arms and forearms | 15 |
| Inside mouth | 14 |
| Abdomen | 10 |
| Fingers | 8 |
| Axillae | 6 |
| Back | 6 |
| Face | 6 |
| Neck | 6 |
| Feet | 6 |
| Trunk | 5 |
| Hands | 5 |
| Elbows | 5 |
| Cornea | 2 |
| Scalp | 2 |

age. Six of 10 patients were recorded to have received nutritional intervention, with 4 receiving nasogastric tube feeding on at least 1 occasion and 3 receiving gastrostomy feeding. Oral erosions were noted in 9 patients, whereas 6 demonstrated an iron deficiency pattern of anemia.

Tracheolaryngeal complications were a third major cause of death, with bullae forming in the tracheolaryngeal tract of 7 of 10 infants overall. Of the 10 infants, 5 demonstrated a hoarse cry, 2 developed tracheal structuring, 2 exhibited inspiratory stridor, 2 experienced mild respiratory distress, 2 had intermittent apneic episodes, and 1 received a tracheostomy at 3 months of age.

Table 6. Recorded Prevalence of Epidermolysis Bullosa (per Million)

| Country | EBS | JEB | DEB |
|-------------------------------|------|-----|-------------------|
| United States ² | 4.6 | 0.4 | 2.4 |
| Croatia ⁴ | NA | NA | 19.2 ^a |
| Finland ⁵ | 15.1 | 0.2 | 8.8 |
| Japan ⁶ | 4.0 | 0.2 | 3.5 |
| Northern Ireland ⁷ | 28.0 | 0.7 | 3.0 |
| Scotland ⁸ | 28.6 | NA | 20.4 |
| Sweden ⁹ | NA | 8.0 | NA |
| South Africa ¹⁰ | 0.8 | 0.7 | 1.2 |
| Norway ¹¹ | 24.3 | NA | 9.3 |
| Australia, AEBR | 5.6 | 0.7 | 3.9 |
| New South Wales | 10.5 | 2.1 | 8.0 |
| New Zealand, AEBR | 2.9 | 0.0 | 1.0 |

Abbreviations: AEBR, Australasian Epidermolysis Bullosa Registry; DEB, dystrophic epidermolysis bullosa; EBS, epidermolysis bullosa simplex; JEB, junctional epidermolysis bullosa; NA, not applicable.

^aSevere generalized recessive dystrophic epidermolysis bullosa only.

Nail abnormalities along with multiple cutaneous bullae and erosions were a prominent early physical finding in this cohort, with 6 of 10 patients overall developing nail dystrophy ($n=3$), anonychia ($n=1$), or subungual erosions ($n=3$) within several days of birth. A hoarse cry ($n=1$) and hyperkeratosis of the palms and soles ($n=1$) were other manifestations observed during this period. Other complications occurring throughout life include gastroenteritis or frequent diarrhea ($n=3$), gastroesophageal reflux ($n=3$), pneumonia ($n=2$), corneal ulceration ($n=2$), and facial granulation tissue formation observed ($n=2$).

COMMENT

The AEBR is the first orphan disease registry in Australia, and since its inception in 2006, it has continued to increase in size and profile locally. However, the registry has likely only recruited a small proportion of the true population with EB in Australia. This is thought to be because of the relatively limited recruitment time, geographical limitations faced by the registry, and the expectation that less severe EB subtypes are less likely to present clinically.

Based in New South Wales, the registry's geographical limitations are readily apparent when examining the considerably higher recruitment rate observed in New South Wales compared with other states. After adjustments for population size,³ New South Wales recruited 20.6 patients with EB per million compared with 14.4, 6.8, and 6.4 per million, respectively, for the next 3 highest states: South Australia, Queensland, and Victoria. As awareness of the registry continues to grow in other states and with the possibility of establishing additional registry operating sites, this discrepancy will perhaps be addressed in the foreseeable future.

Another recognized issue is the underrecruitment of patients with less severe forms of EB, particularly individuals with EBS. With the living Australian cohort comprising 125 patients with EBS, 15 with JEB, and 81 with DEB, the prevalence rate based solely on registry cases is 5.8 EBS, 0.7 JEB, and 3.8 DEB cases per million (10.3 per million

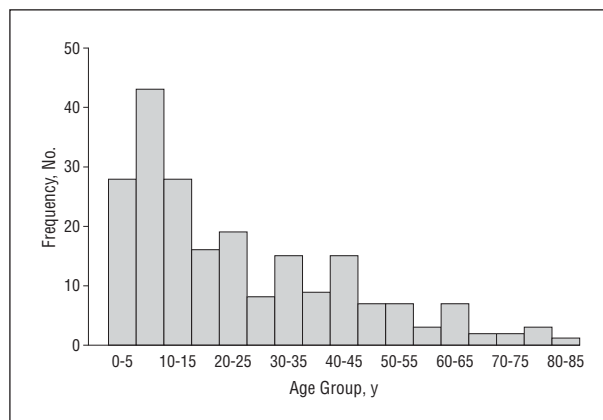


Figure 2. Frequency histogram of patient ages in the Australasian Epidermolysis Bullosa Registry.

overall). The rates of EBS, JEB, and DEB in the New South Wales population, which provide the most reliable indicator of prevalence based on high recruitment in this state, are 10.5, 2.1, and 8.0 cases per million, respectively.

Although the nationwide prevalence of JEB and DEB according to AEBR data are fairly consistent with epidemiologic studies performed overseas,^{2,4-11} the EBS prevalence in Australia is lower than the rates reported in most countries (**Table 6**). The extent of missed EBS recruitment in Australia is evident by a Tasmanian study¹² published in 1963 describing 83 cases of EBS in 1 extended family, whereas the AEBR by contrast has only 3 recorded cases from Tasmania.

As has been suggested by other studies, underreporting of EBS may result from its milder phenotype providing insufficient impetus for clinical presentation.^{2,8} In addition, because EB is rare there may be a lack of knowledge about the disorder, resulting in missed diagnoses or a reduced likelihood of some physicians to refer patients for further investigation. One study in Scotland⁸ found that 30% of interviewed patients with EBS or dominant DEB had never seen a dermatologist, whereas in the experience of the AEBR investigators, many patients with EBS had had their conditions misdiagnosed as eczema or had otherwise regarded their skin disease as normal.

By contrast, it is reasonable to suggest that the AEBR has enrolled a greater proportion of individuals living with DEB and JEB. These subtypes require a greater use of the health care system because of their relative severity and, accordingly, patients with these subtypes are more likely to have their conditions diagnosed. One of the great successes of the AEBR to date relating to this factor has been the successful lobbying of the Australian federal government to provide a dedicated budget to subsidize the costs of wound dressings for patients with EB and their families, demonstrating the practical value of an orphan disease registry.

The data obtained from the registry suggest that the AEBR represents a reasonable cross-section of the true population with EB, with essentially equal numbers of males and females and a diverse age range. However, a significant rightward skew exists in the patients' ages overall (**Figure 2**), indicating that the more severe JEB and DEB subtypes have prevented individuals from progressing to

old age or that many older individuals have not been identified by the registry. Although the former may be true, it is more likely that many older individuals with milder forms of EB have not yet been recruited into the registry because their inclusion would dilute the effect of premature mortality in the less common subtypes.

The comparison of the patients' ages by EB type (Table 3) also broadly reflects the clinical severity of the EB types; it indicates that most subtypes of EBS and dominant DEB are compatible with a normal lifespan, whereas RDEB and JEB subtypes by contrast are associated with higher morbidity rates and premature mortality. This relationship is well reflected in the literature^{2,13-16} and is furthermore apparent with the number of deceased patients in the registry who had had JEB and RDEB (Table 4). Underreporting of EBS deaths may have occurred because the registry relies on notification by relatives when patients with milder phenotypes die in nonhospital environments.

Herlitz JEB was associated with the greatest mortality rates in the AEBR, with an infant mortality rate higher than that reported in the United States. The US registry found that 44.7% of infants with JEB-H had died within their first year of life¹³ compared with 9 of 10 infant deaths in the AEBR. However, the leading causes of death experienced in the US JEB-H cohort were consistent with those experienced in the AEBR.

A few explanations may be offered as to why the Australasian cohort of JEB-H infants experienced such high mortality rates. First, these rates may occur simply because of the lower number of infants with JEB-H in the AEBR, making a precise interpretation of infant mortality difficult. Second, these rates may occur because, as we observed, some Australasian families had decided against pursuing surgical interventions: parents' wishes for nonaggressive management were documented in 2 cases after discussions on prognosis. Although most Australasian infants with JEB-H displayed tracheolaryngeal involvement, ultimately only 1 received a tracheostomy, compared with 24.4% in the United States.¹⁴

Our study did not suggest either tracheostomy or gastrostomy contributes to long-term survival. One infant (patient 5) underwent tracheostomy and gastrostomy feeding at 3 and 5 months, respectively, but nevertheless declined nutritionally and died of gastrointestinal hemorrhage at 5.8 months. Two other infants (patients 9 and 10) received gastrostomy feeding at 5 and 8 months, respectively, but died 3 to 4 months later. Although it is probable that these infants benefited from surgical interventions in the short term, they eventually succumbed to other complications of their disease.

In relation to the early detection of JEB-H disease, an indicator in the AEBR cohort was the presence of nail involvement in combination with generalized blistering within days of birth. Its specificity for JEB-H is difficult to ascertain, given that other subtypes of EB have been recorded with nail abnormalities later in life²; however, the presence of this finding within the first day of life may provide an early sign to physicians that a neonate may be affected with JEB-H.

With regard to supportive care of infants with JEB-H, attention should be given to avoiding unnecessary physical trauma during daily care and handling. The disease

course in JEB-H is based largely on the recurrent deepithelialization of the skin, resulting in recurrent infections, chronic blood loss, increased nutritional demands, and suppressed appetite, all of which contribute to potential sepsis, anemia, malabsorption, and failure to thrive. The mechanical fragility of these infants is emphasized by the high number of erosions found over the diaper area, which likely arose from regular diaper changes and friction against the diaper fabric. Excessive handling of these infants should be minimized, with nonstick, silicone-based bandages applied to existing erosions. Dressings with absorbent backings, held in place with outer dressings, provide some protection against physical trauma by cushioning the forces sustained and reducing maceration of the skin. A high rate of intraoral blistering has also been observed, which can further contribute to poor feeding; however, this factor is more difficult to address.

Last, there are several things to note when interpreting the results from our JEB-H cohort. The small cohort size limits an accurate reporting of true complication rates; however, the study's retrospective nature suggests that reported rates are likely to be conservative in nature. Underreporting of complications has likely occurred for several reasons. First, medical records outside New South Wales are less accessible, resulting often in incomplete documentation. Second, records accessed had some variability in their quality, depending on the degree of documentation and the physician's familiarity with EB. Third, this study was reliant on all manifestations being recognized and recorded during all clinical presentations, which was not likely to have occurred. Despite the limited number of infants with JEB-H, the Australasian cohort remains one of the largest JEB-H case series ever reported to date and provides a wealth of clinical data regarding the complications, disease course, and life expectancy of this rare skin disorder.

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Author Contributions: Mr Kho had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Murrell. *Acquisition of data:* Murrell, Kho, Rhodes, S. J. Robertson, Su, Varigos, I. Robertson, Hogan, and Orchard. *Analysis and interpretation of data:* Kho. *Drafting of the manuscript:* Kho. *Critical revision of the manuscript for important intellectual content:* Kho and Murrell. *Statistical analysis:* Kho. *Obtained funding:* Murrell. *Administrative, technical, and material support:* Rhodes and Murrell. *Study supervision:* Murrell and Rhodes.

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Archives Web Quiz Winner

Congratulations to the winner of our March quiz, Vijay Zawar, MD, DNB, DVD, consultant dermatologist, Nashik, India. The correct answer to our March challenge was *lichen planus pemphigoides* (LPP). For a complete discussion of this case, see the Off-Center Fold section in the April *Archives* (Ramaswamy PV, Clark T, Wilkel C, Zhou L. Bullae, scaly papules, and plaques. *Arch Dermatol*. 2010;146[4]:439-444).

Be sure to visit the *Archives of Dermatology* Web site (<http://www.archdermatol.com>) to try your hand at the interactive quiz. We invite visitors to make a diagnosis based on selected information from a case report or other feature scheduled to be published in the following month's print edition of the *Archives*. The first visitor to e-mail our Web editors with the correct answer will be recognized in the print journal and on our Web site and will also receive a free copy of *The Art of JAMA II*.