JAMA Dermatology | Original Investigation

Epidemiology of Inherited Epidermolysis Bullosa Based on Incidence and Prevalence Estimates From the National Epidermolysis Bullosa Registry

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IMPORTANCE Accurate estimation of the incidence and prevalence of each subtype of epidermolysis bullosa (EB) is essential before clinical trials can be designed and sufficient funding allocated by government agencies and third-party insurers for the care of these individuals.

OBJECTIVE To determine the incidence and prevalence of inherited EB stratified by subtype in the United States during a 16-year period.

DESIGN, SETTING, AND PARTICIPANTS Prospective cross-sectional and longitudinal study. Data were obtained from 3271 patients consecutively enrolled in the National Epidermolysis Bullosa Registry from January 1, 1986, through December 31, 2002, using a detailed instrument created with the assistance of the National Institutes of Health. Analyses were performed in January 1999 and April 2015. Participants were patients of all ages with EB.

MAIN OUTCOMES AND MEASURES Extensive clinical and laboratory data were collected on patients who were subclassified and serially revalidated based on published diagnostic recommendations by an international panel of experts. Pertinent to this report, estimates were made of the incidence and prevalence during 2 time frames.

RESULTS During the first 5 years of funding of the registry, the overall incidence and prevalence of inherited EB were 19.60 and 8.22 per 1 million live births, respectively. When reassessed over the entire 16 years of the study, the prevalence rose to 11.07, whereas the overall incidence remained unchanged at 19.57 cases. Changes were also observed within some disease subsets as increased numbers of patients were identified, recruited, followed up longitudinally, and resubclassified as needed over time. For example, in 2002, the prevalence of EBS overall and localized EBS had increased considerably by 30.4% and 25.5%, respectively, whereas the prevalence of generalized intermediate EBS declined by 76.7% as a result of later subclassification of some of those patients into other subtypes. In contrast, no significant change was noted in the overall prevalence of JEB or generalized severe JEB, although there was a 73.0% decline in the prevalence of generalized intermediate JEB.

CONCLUSIONS AND RELEVANCE Precise estimates of the incidence and prevalence of each major subtype of inherited EB in the United States are now available that should assist investigators in choosing which subtypes are amenable to properly designed, large-scale, clinical trials.

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JAMA Dermatol. 2016;152(11):1231-1238. doi:10.1001/jamadermatol.2016.2473
Published online July 27, 2016.

Accurate determination of the incidence and prevalence of a rare disease is critical before clinical trials on promising therapies can be properly designed and orchestrated. Statistically significant results cannot be achieved if there are insufficient numbers of individuals available for participation, with the latter often limited by inherent problems in the recruitment and retention of severely affected patients residing in geographically distant areas. This difficulty is particularly the case with inherited epidermolysis bullosa (EB), given the number of different subtypes within even its 3 most common ones (simplex, junctional, and dystrophic), the frequency of early mortality in some patients, and the likelihood that the types and locations of their specific genetic mutations may influence treatment success.[1]

In 1986, the National Institutes of Health established the multicenter National Epidermolysis Bullosa Registry (NEBR) to best characterize this disease at the epidemiological, clinical, ultrastructural, and molecular levels. In 1999, the initial estimates of the incidence and prevalence were reported based on data derived from the first 1700 enrollees.[2] The final estimates from this project are now reported, the result of 16 years of cross-sectional and longitudinal data collection on 3271 patients and revalidation of data based on the most recently accepted classification scheme for this disease.

Key Points

Question What are the incidence and prevalence of each major type and subtype of inherited epidermolysis bullosa (EB)?

Findings The overall incidence and prevalence of inherited EB based on 16 years of data collection across the United States were 19.57 and 11.07 per 1 million live births and per 1 million population, respectively. Similar data are reported for each major EB subtype.

Meaning These data, based on recruitment and lengthy observation of the largest EB cohort yet assembled, should assist in the design of statistically valid clinical trials and be of use by those involved in the allocation of health care for rare diseases.

Methods

Data were obtained from 3271 patients consecutively enrolled in the NEBR from September 1, 1986, through April 30, 2002, using a detailed instrument created with the assistance of the National Institutes of Health and reviewed and approved by the US Office of Management and Budget and the institutional review boards at each of the following participating institutions: The Rockefeller University (New York, New York), The University of Alabama at Birmingham, The University of North Carolina at Chapel Hill, Washington University in St Louis (St Louis, Missouri), Stanford University (Stanford, California), and University of Washington (Seattle). Details of the instrument have been published previously.[3] Written informed consent was obtained from every adult participant and from each participating child and his or her parents. When too young or immature to provide written informed consent, verbal assent was obtained and documented. As will be discussed elsewhere, rigorous epidemiological case finding methods were used to identify and recruit participants throughout the United States. Diagnosis was confirmed by state-of-the-art techniques available throughout the study window, including immunofluorescence antigen mapping, EB-specific monoclonal antibody studies, or transmission electron microscopy. With only rare exceptions, diagnostic testing was performed on the proband of each affected kindred. These tests were performed at no cost to any participant by the core diagnostic laboratory of the NEBR Clinical Coordinating Center. Subclassification by EB subtype was based on the latest consensus report[1] of an international panel of EB experts, with changes in classification made on the basis of longitudinal follow-up if or when changing clinical or laboratory findings suggested that reclassification was warranted.

Patients were separated into mutually exclusive EB subtypes known to exist at the time of the study. These subtypes include the following: localized EB simplex (EBS) (previously called Weber-Cockayne EBS), generalized severe EBS (previously called Dowling-Meara EBS), generalized intermediate EBS (previously called Koebner EBS), EBS with mottled pigmentation, EBS with muscular dystrophy, all other EBS, generalized severe junctional EB (JEB) (previously called Herlitz JEB), generalized intermediate JEB (previously called non-Herlitz JEB), dominant dystrophic EB (DDEB) (previously separated into Pasini and Cockayne-Touraine subtypes), bullous dermolysis of the newborn, severe generalized recessive dystrophic EB (RDEB) (previously called Hallopeau-Siemens RDEB), RDEB inversa, generalized intermediate RDEB (previously called non–Hallopeau-Siemens RDEB), other RDEB, and EB type unknown.

Original statistical analyses were conducted in January 1999 with a software program (SAS; SAS Institute Inc) under the supervision of the project's biostatistician and the staff of the NEBR Data Coordinating Center. Final analyses were performed in April 2016 with another software program (Stata, SE 12.1; StataCorp LP).

Results

Estimates of the incidence and prevalence of inherited EB were performed on data obtained from 3271 patients after each patient was confirmed to be included only once in our database (ie, not being listed under different surnames owing to changing marital status). The diagnosis and subclassification were revalidated using the most recently published criteria by an international consensus panel.[1]

Table 1 compares the estimated prevalence of each major EBS and JEB subtype during the first (1990) and final (2002) data analysis periods. In 2002, the prevalence of EBS overall and localized EBS had increased considerably by 30.4% and 25.5%, respectively, whereas the prevalence of generalized intermediate EBS declined by 76.7% as a result of later subclassification of some of those patients into other subtypes. In contrast, no significant change was noted in the overall prevalence of JEB or generalized severe JEB, although there was a 73.0% decline in the prevalence of generalized intermediate JEB.

Table 1. Prevalence of Inherited Epidermolysis Bullosa (EB) Types and Subtypes in the United States, January 2002 vs 1990, Based on the National Epidermolysis Bullosa Registry (NEBR)

EB Subtype	January 2002 NEBR		Prevalence of NEBR, 1990[a]
	No.	Prevalence[a]	
EBS			
All subtypes	1711	6.00	4.60
Localized	1122	3.94	3.14
Generalized intermediate	98	0.34	1.46
Generalized severe	117	0.41	[b]
EBS-MP	7	0.02	[b]
EBS-MD	3	0.01	[b]
All other	364	1.28	[b]
JEB			
All subtypes	139	0.49	0.44
Generalized severe	22	0.08	0.07
Generalized intermediate	29	0.10	0.37
All other	88	0.31	[b]
DEB			
Unknown mode	119	0.42	0.47
DDEB			
All subtypes	426	1.49	0.99
Pasini and Cockayne-Touraine	71	0.25	[b]
Pretibial	11	0.04	[b]
BDN	27	0.09	[b]
All other	317	1.11	[b]
RDEB			
All subtypes	386	1.35	0.92
Generalized severe	102	0.36	0.42
Inversa	18	0.06	[b]
Generalized intermediate	40	0.14	[b]
Unknown subtype	196	0.69	[b]
All other	30	0.11	[b]
EB			
Type unknown	376	1.32	0.80

Abbreviations: BDN, bullous dermolysis of the newborn; DDEB, dominant dystrophic EB; DEB, dystrophic EB; EBS, EB simplex; EBS-MD, EBS muscular dystrophy; EBS-MP, EBS mottled pigmentation; JEB, junctional EB; RDEB, recessive dystrophic EB.

[a] Per 1 million population.

[b] Not further subclassified at the time of original analysis and publication in 1999.

Table 1 also compares the prevalence of each major subtype of dystrophic EB (DEB) and EB type unknown at the 2 time points. Only a modest 10.6% reduction was seen in those with DEB in whom the genetic mode of transmission was unknown due to reclassification and addition of newer subtypes, whereas increases of 50.5% and 46.7% in the overall prevalence of DDEB and RDEB, respectively, were noted at the time of final assessment. In contrast, the prevalence of generalized severe RDEB decreased by 14.2% as a result of reclassification into other subtypes.

Table 2 compares incidence estimates for EBS and JEB at the first and final evaluations. The overall incidence of EBS was reduced to 7.87 cases per 1 million live births (26.8% decrease), as was the incidence of localized EBS and all other EBS subtypes combined (decrease of 46.1% and increase of 6.6%, respectively). Incidence estimates for JEB (overall), generalized severe JEB, and all other JEB subtypes combined also changed (increases of 9.4%, 21.9%, and 6.4%, respectively).

Table 2 lists the estimated incidence in DEB and EB type unknown during the 2 periods. The incidence of DEB of unknown mode of transmission increased by 80.5% owing to increased numbers of patients enrolled and their inability to be further accurately subclassified without definitive molecular testing. The overall incidence of RDEB and DDEB increased by 49.5% and decreased by 25.9%, respectively, consistent with molecular analysis findings on smaller numbers of patients in other cohorts who were initially classified as having spontaneous mutations for DDEB, based on clinical and immunohistochemical findings and no family history of other affected relatives, who were later proven to have RDEB (primarily the milder generalized variant) when mutations could be defined. Finally, the incidence of EB type unknown in the NEBR cohort increased by 117.4% by the time of final analysis.

Comparing data from 1990 and 2002, the overall prevalence of inherited EB increased from 8.22 to 11.07 per 1 million live births, whereas no significant change was noted in the incidence (19.60 vs 19.57 cases per 1 million live births). This finding is consistent with the identification and enrollment of greater numbers of patients with milder forms of EBS having no risk of premature death. **Table 3** and **Table 4** compare our final estimates with those reported in other cohorts worldwide.

Table 2. Incidence of Inherited Epidermolysis Bullosa (EB) Types and Subtypes in the United States, 1986 to 2002 vs 1986 to 1990, Based on the National Epidermolysis Bullosa Registry (NEBR)

EB Subtype	1986-2002 NEBR		Incidence of NEBR, 1986-1990[a]
	No.	Incidence[a]	
EBS			
All subtypes	468	7.87	10.75
Localized	218	3.67	6.81
Generalized intermediate	26	0.44	[b]
Generalized severe	69	1.16	[b]
EBS-MP	4	0.07	[b]
EBS-MD	2	0.03	[b]
All other	149	2.51	[b]
JEB			
All subtypes	159	2.68	2.45
Generalized severe	30	0.50	0.41
Generalized intermediate	9	0.15	[b]
All other	120	2.02	[b]
DEB			
Unknown mode	88	1.48	0.82
DDEB			
All subtypes	126	2.12	2.86
Generalized	12	0.20	[b]
Pretibial	3	0.05	[b]
BDN	19	0.32	[b]
All other	92	1.55	[b]
RDEB			
All subtypes	181	3.05	2.04
Generalized severe	34	0.57	0.41
Inversa	6	0.10	1.63
Generalized intermediate	18	0.30	[b]
Unknown subtype	115	1.93	[b]
All other	8	0.13	[b]
EB			
Type unknown	141	2.37	1.09

Abbreviations: BDN, bullous dermolysis of the newborn; DDEB, dominant dystrophic EB; DEB, dystrophic EB; EBS, EB simplex; EBS-MD, EBS muscular dystrophy; EBS-MP, EBS mottled pigmentation; JEB, junctional EB; RDEB, recessive dystrophic EB.

[a] Per 1 million live births.

[b] Not further subclassified at the time of original analysis and publication in 1999.

Discussion

Estimates of the incidence and prevalence of inherited EB may be critically affected by a variety of factors. Differences in the types of referral sources used or the methods by which patients are recruited may greatly influence how optimally and completely patients are captured within a target population. For example, incomplete capture would be expected from heavy reliance from only one source, such as patient self-referrals, referrals from health care professionals, hospital records (the accuracy of which will depend on correct coding by physicians), or lay organization membership rolls. In each of these approaches, more mildly affected individuals would not be expected to be captured because they might not routinely reach the attention of physicians. In addition, some of these individuals might also have been inadvertently misclassified. The gold standard for case finding uses aggressive epidemiological techniques, coupled with state-of-the-art diagnostic testing, and will be far more likely to more completely and correctly identify affected individuals than retrospective review of hospital or clinic records, other less rigorous sampling techniques (capture-recapture[9] or other), recruitment via advertisements in medical and lay media, or passive reliance on referral by physicians, patients, or their families.

Epidemiological estimates will also be influenced by the study population chosen for sampling (ie, inclusive sampling of a well-defined geographic area vs patients seen in a more restricted population, such as those within the catchment area of one or more hospitals, clinics, or practices). Sample size is an important factor: the larger the number of patients studied, the more robust and statistically valid such estimates will be. Duration and means of sampling (ie, once vs repeated at well-defined intervals) are also critical factors because both will not only increase the sample size but also increase the quality of the data being generated. In addition, errors in patient classification or subclassification, as well as those in recording or entry of patient information, can make estimates obtained from an otherwise well-recruited and well-sampled patient population meaningless. For example, in the case of the NEBR, reevaluation and revalidation of diagnosis, either at the time of initial referral to our team or during the 16 years of

Table 3. Comparison of US Prevalence Estimates With Other Epidermolysis Bullosa (EB) Cohorts Worldwide

EB Subtype	United States (2002 NEBR)	Australia[4] (2006-2010) (n = 259)	British Columbia[2] (1991)	Italy[5] (2005)	Italy[6] (1991-2007) (n = 880)	Croatia[7] (1960-1987)	Japan[8] (1983)	Spain[9] (2011) (n = 152 DEB)	Romania[10] (2006-2012) (n = 89)	Northern Ireland[11] (1996) (n = 44 EBS)	Lothian, Scotland[12] (1992) (n = 259)	Northern Ireland[11] (1962-1984) (n = 80)	Norway[13] (1995)	South Africa[2] (1990)
EBS														
All subtypes	6.0	5.8	NR	NR	NR	1.5	2.9-4.0	NR	NR	12.5	28.6	28	23[a]	NR
Localized	3.9	3.1	NR	NR	NR	0.4	NR	NR	NR	NR	NR	25.5	14.5	NR
Generalized intermediate	0.3	NR	NR	NR	NR	1.1	NR	NR	NR	NR	NR	1.3	1.4	NR
Generalized severe	0.4	NR	NR	NR	NR	NR	NR	NR	NR	NR	0.6	NR	NR	NR
All other	1.3	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
JEB														
All subtypes	0.5	0.7	NR	NR	NR	NR	0.1-0.2	NR	NR	NR	NR	NR	2.0	NR
Generalized severe	0.1	NR	NR	NR	NR	0.4	NR	NR	NR	NR	NR	NR	NR	NR
All other	0.4	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
DEB														
All subtypes	3.3	3.8	NR	NR	NR	NR	NR	6.0	NR	NR	20.4	NR	NR	NR
DDEB														
All subtypes	1.5	NR	NR	NR	NR	NR	1.1-1.5	NR	NR	NR	NR	NR	7.1	NR
RDEB														
All subtypes	1.4	NR	NR	NR	NR	NR	1.5-2.1	NR	NR	NR	NR	NR	2.3	NR
Generalized severe	0.4	NR	NR	NR	NR	6.1	NR	NR	NR	NR	NR	NR	0.7	NR
Inversa	0.06	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
All other	60.9	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
EB														
Type unknown	1.3	NR	NR	NR	NR	1.1	NR	NR	NR	NR	NR	NR	NR	NR
Total														
Overall prevalence	11.1	10.3	9.9	10.1	15.4	9.6	5.6-7.8	NR	4.4	NR	49.0	NR	54	2.82

Abbreviations: DDEB, dominant dystrophic EB; DEB, dystrophic EB; EBS, EB simplex; JEB, junctional EB; NEBR, National Epidermolysis Bullosa Registry; NR, not reported; RDEB, recessive dystrophic EB.

[a] The prevalence is 42.0 if including the only kindred with EBS in Ogna, Norway, reported by Gedde-Dahl and Anton-Lamprecht.[13]

Table 4. Comparison of US Incidence Estimates With Other Epidermolysis Bullosa (EB) Cohorts Worldwide

EB Subtype	United States (1986-2002 NEBR)	British Columbia[2] (1952-1989)	Norway[13] (1947-1994)	Croatia[7] (1960-1987)	Sweden[2,13] (1965-1994)	the Netherlands[14] (1988-2011)[a]	Italy[5] (2005)	Italy[6] (1991-2007)	Northern Ireland[11] (1962-1984)	Romania[10] (2006-2012)	Japan[15] (1983)
EBS											
All subtypes	7.87	NR	>9.7	NR	NR	NR	NR	NR	0.9	NR	NR
Localized	3.67	NR	>6.0	NR	NR	NR	NR	NR	NR	NR	NR
Generalized intermediate	0.44	NR	2.0	NR	NR	NR	NR	NR	NR	NR	NR
Generalized severe	1.16	NR	1.7	NR	NR	NR	NR	NR	NR	NR	NR
All other	2.61	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
JEB											
All subtypes	2.68	NR	7.0	NR	>8.0	NR	NR	NR	0.03	NR	NR
Generalized severe	0.50	NR	4.6	NR	7.1	4.0	NR	3.8	NR	NR	0.68
All other	2.17	NR	NR	NR	NR	NR	NR	0.68	NR	NR	NR
DEB											
Unknown mode	1.48	NR	NR	NR	NR	NR	NR	NR	0.3	NR	NR
DDEB											
All subtypes	2.12	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
RDEB											
All subtypes	3.05	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Generalized severe	0.57	NR	5.6	19.2	NR	NR	NR	NR	NR	NR	NR
Inversa	0.10	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
All other	2.36	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
EB											
Type unknown	2.37	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Total											
Overall incidence	19.57	17.9	NR	NR	NR	NR	20.1	NR	NR	25	3.8

Abbreviations: DDEB, dominant dystrophic EB; DEB, dystrophic EB; EBS, EB simplex; JEB, junctional EB; NEBR, National Epidermolysis Bullosa Registry; NR, not reported; RDEB, recessive dystrophic EB.

[a] Per 1 million live births.

follow-up, resulted in substantial changes in the final diagnosis assigned (36.4% for EBS, 92.7% for JEB, −32.6% for DEB of unknown genetic transmission mode, 80.1% for DDEB, 198.0% for RDEB, and −46.8% for DEB subtype unknown).

Every effort was made by the NEBR to methodically identify, recruit, and diagnosis patients with EB throughout the United States during 16 years of continuous federal funding. Based on its rigorous study design and implementation, I am confident that the NEBR was able to generate accurate estimates on the incidence and prevalence of the major EB subtypes for several reasons. First, we repeatedly contacted every practicing dermatologist and pediatrician in the United States, serially advertised the resources of the project in many major specialty journals and at clinical and research meetings, worked with the primary EB lay organization in the United States to encourage enrollment through its newsletter and word of mouth, and then pursued aggressive epidemiological case finding of other family members and affected acquaintances after the identification of affected probands on a state-by-state basis. This search was facilitated by having 4 regionally distributed NEBR Clinical Centers, so as to best provide access to the project by patients with EB and their physicians. Based on statistical calculations on the numbers of patients needed for valid calculations, we also pursued longitudinal follow-up on a regular basis on all severe EB subtypes and on a randomly chosen subpopulation of patients with milder subtypes. Finally, we provided free state-of-the-art diagnostic testing (transmission electron microscopy, immunofluorescence antigenic mapping, and EB-specific monoclonal antibody studies) on every patient, testing that was otherwise unavailable in most areas of the United States at that time. On the basis of the ready access to free state-of-the-art diagnostic testing through this project, it is likely that the NEBR captured almost every patient with a severe generalized form of simplex, junctional, or dystrophic EB during those 16 years, as well as sampled a representative percentage of milder cases because it assembled the largest well-characterized population of patients with EB in the world, thereby providing a means by which the incidence and prevalence could be accurately estimated.

Despite our best efforts, there are limitations to the estimates reported herein. For example, 11.6% (381 of 3271) of our enrollees could not be further subclassified into any of the 3 major EB subtypes recognized at that time owing to the unavailability or inadequacy of tissue harvested for diagnostic purposes (ie, no visible cleavage plane or alteration in expression of skin antigens). Although their records were retained for possible further study, these individuals were not included in our final estimates of the incidence and prevalence by EB subtype. Unfortunately, molecularly defined mutations had not been discovered during the early part of the project, and for reasons of cost molecular testing was unavailable for routine performance later, preventing further attempts at characterizing this undefined subset of the total NEBR population. It should also be noted that some of the rarer EB subtypes were either not captured or were as yet unknown during the study, preventing generation of accurate estimates of their prevalence or incidence.

We are encouraged as to the validity of our originally reported estimate of the overall incidence of inherited EB in the United States, based on how closely the final estimate matches the earlier data, with the inclusion of data on more than an additional 1550 patients and with further refinement in their subclassification, based on additional information serially obtained and validated over time. The overall incidence of inherited EB in the United States is unchanged (19.60 cases per 1 million live births from 1986 to 1990 vs 19.57 cases from 1986 to 2002). However, our large sample size has demonstrated a higher prevalence of inherited EB (11.07 per 1 million live births in January 2002 vs 8.22 in 1990), presumably a reflection of the inclusion of greater numbers of patients having less lethal forms of EB. As further support of the accuracy of our estimates, our findings closely match those seen by several other smaller EB study populations investigated elsewhere.

Of particular importance is the near-doubling of our sample size. Coupled with further reassessment of our entire study population, this sample allowed us to more accurately subclassify approximately one-third and one-half of patients initially listed as having DEB and EB type unknown, respectively, who were initially so classified.

Although our prevalence estimates are similar to those observed in the Australian registry,[4] as well as in those reported from several other countries[7,8,13] (Table 3), it is likely that they cannot be generalized everywhere. For example, there have been marked differences reported in the prevalence of EBS and severe generalized JEB in Scotland[12] and the Netherlands,[14] respectively. While conjectural, it is possible that smaller populations residing within confined geographic areas may harbor increased pools of specific types or subtypes of affected patients and silent carriers. Other reasons as yet unknown may also contribute to such discordances. Variations in the incidence and prevalence have also been reported among certain ethnic or religious groups owing to differences in the frequencies of mutations residing within a given population (eg, within some Middle Eastern subpopulations[16,17]) or the frequency of consanguinity present.[18] Whereas our estimate of the overall incidence of inherited EB is closely in line with data from British Columbia[2] and Italy[5,6] (Table 4) using different methods than ours, some subtype incidences diverged considerably among some other countries or populations for reasons possibly similar to those for prevalence.[10,11,13,15,19,20]

Recently, the lay organization Dystrophic Epidermolysis Bullosa Research Association of America reported a different incidence for JEB (3.59 cases per 1 million live births) than was previously observed by the NEBR (2.04 cases per 1 million live births).[21] This finding was based on information retrospectively obtained via telephone calls that were received by its EB nurse educator, comprising 71 reported patients between 2007 and 2011 and the use of US Census data collected through only 2010. When corrected for the actual 5-year study window, this incidence would actually be 3.44 cases. Although intriguing, the study had considerable limitations in its design, including the method of sampling and the lack of any means of validating the diagnosis in most patients (ie, only rare patients had their diagnosis confirmed by molecular means). In contrast, inclusion in the NEBR database demanded rigorous

confirmation of diagnosis by immunofluorescence antigen mapping, EB-specific monoclonal antibody studies, or electron microscopy. Infants dying of EB but lacking diagnostic confirmation were not included in the NEBR calculations, suggesting that the NEBR estimates for the incidence and prevalence, particularly in the case of generalized JEB, may indeed underestimate the true values. As a result, all that can be said with some degree of confidence is that the incidence of JEB in the United States falls between the rigorously determined estimate of the NEBR and the incidence recently described by the American EB lay organization.

Conclusions

Estimates of the incidence and prevalence of most known EB subtypes in the United States are now available based on final analysis of the data collected by the NEBR on a cohort of 3271 well-characterized patients from 1986 to 2002. Such estimates should assist investigators in designing clinical trials that have the potential of achieving adequate biostatistical power, as well as for use by governmental agencies responsible for the allocation of funding for health care.

ARTICLE INFORMATION

Accepted for Publication: June 3, 2016.

Published Online: July 27, 2016. doi:10.1001/jamadermatol.2016.2473.

Conflict of Interest Disclosures: None reported.

Funding/Support: This study was supported in part by the National Institutes of Health.

Role of the Funder/Sponsor: The funding source had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Additional Contributions: The National Epidermolysis Bullosa Registry (NEBR) project is indebted to the National Institutes of Health for 16 years of funding for both the Clinical Centers and Data Coordinating Center of the NEBR, as well as the many physicians and nurses who assisted by referral or recruitment and initial assessment of the project's study participants.

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