Original Article

Prevalence and Outcomes of Primary Immunodeficiency in Hospitalized Children in the United States

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What is already known about this topic? Primary immunodeficiency diseases (PIDDs) are a set of chronic disorders that increase susceptibility to infections. Individuals with these diseases are more likely to use health care resources.

What does this article add to our knowledge? Using a large, nationally representative pediatric database, we determined the prevalence and clinical outcomes of children hospitalized in the United States with PIDDs.

How does this study impact current management guidelines? These findings highlight the need for physicians to screen, diagnose, and treat PIDDs. We have identified a baseline set of inpatient clinical outcomes for patients with PIDD that future studies can use to improve hospitalization rates and outcomes in children with PIDD.

BACKGROUND: Primary immunodeficiency diseases (PIDDs) are rare yet life-threatening chronic conditions in children. The prevalence and outcomes of PIDDs in the pediatric population in the United States are not well understood.
OBJECTIVE: The objectives of this study were to (1) determine the epidemiology of children hospitalized with PIDD in the United States and (2) characterize the clinical outcomes of hospitalized children with PIDDs.
METHODS: Retrospective cohort analysis of the 2003-2012 Kids' Inpatient Database of children aged 2-18 years admitted with a primary or secondary diagnosis code of PIDD was performed. Secondary immunodeficiency diseases were excluded.
RESULTS: There were 26,794 pediatric patients hospitalized with a diagnosis of a PIDD from 2003 to 2012. The national prevalence of all PIDDs per 100,000 was 66.6, 82.2, 97.4, and 126.8 in 2003, 2006, 2009, and 2012, respectively. The highest prevalence was in children 0-5 years of age (15,105 hospitalizations; 56%). There was no difference in prevalence between B-cell defects and T-cell defects. PIDDs affected all ethnic populations equally. Respiratory-related diagnoses were the most common comorbidity by an organ system. Overall mortality was 1.99%. Age was inversely correlated with clinical outcome. Children 0-5 years had higher mortality (424 deaths, 79.85%), mean hospital charges ($35,480), and length of stay (LOS) (5.6 days) compared with older age cohorts.
CONCLUSIONS: The prevalence of PIDDs in the hospitalized pediatric population in the United States may have increased over time. Younger age is associated with higher mortality, hospital costs, and LOS. Further study is needed to determine cost-effective management strategies to improve outcomes in infants and young children with PIDD. © 2017 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2017;■:■-■)

Key words: *Primary immunodeficiency diseases; Morbidity; Mortality; Ethnicity; Prevalence*

Primary immunodeficiency diseases (PIDDs) are a set of life-threatening chronic disorders that are often diagnosed in childhood and increase susceptibility to infections. Approximately 40% of PIDD diagnoses are made before the age of 18.[1] The International Union of Immunological Societies have reported at least 300 different PIDDs, and new intrinsic defects of the immune system are continually being discovered.[2] These disorders result in significant morbidity and mortality, including increased hospitalization rates.[1] The Immune Deficiency Foundation (IDF) conducted national surveys on PIDDs from 1995 through 2007 and found that roughly half of people with PIDDs reported suffering permanent functional impairments before diagnosis.[1,3,4] Diagnosing PIDDs in a timely manner is

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Abbreviations used
HCUP- Health Care Cost and Utilization Project
ICD-9- International Classification of Diseases, Ninth Revision
IDF- Immune Deficiency Foundation
KID- Kids' Inpatient Database
LOS- Length of stay
PIDDs- Primary immunodeficiency diseases
PSU- Primary sampling unit

challenging, and patients can have symptoms for several years before a proper diagnosis is made.[5,6]

Individual PIDDs are believed to be rare diseases; however, the overall prevalence of PIDDs in the United States is not characterized. Most epidemiologic studies of PIDDs were performed outside of the United States or in homogeneous populations.[6-26] The IDF created the United States Immune Deficiency Network in 2003 to serve as a registry for PIDDs with 42 sites across 22 states entering data.[27] Although disease registries can help gather data on rare diseases, they are limited often by the number of enrolled patients and findings are not generalizable to broader populations.

Given improvements in genetic testing and early identification, PIDDs are diagnosed more quickly and accurately than ever before. With improved diagnosis and medical advances over the past several decades, the prevalence of PIDDs has likely increased. Data from 2 large claims databases from 2001 to 2007 reported the prevalence in adults and children with PIDDs increased from 38.9 to 50.5 per 100,000 among privately insured and from 29.1 to 41.1 per 100,000 among publicly insured persons.[28] To date, there have been no large studies specifically investigating the hospitalization rates, costs, and outcomes of PIDDs in the US pediatric population. We used a large, nationally weighted pediatric database to characterize the overall burden of PIDDs in the United States. The objectives of this study were to (1) determine the epidemiology of children hospitalized with PIDD in the United States and (2) characterize the clinical outcomes of hospitalized children with PIDDs.

METHODS

Study design and data collection

The Kids' Inpatient Database (KID) is an administrative database developed for the Healthcare Cost and Utilization Project (HCUP), sponsored by the Agency for Healthcare Research and Quality. This pediatric all-payer inpatient database is the largest in the United States and includes children's hospitals, academic centers, and community hospitals. The KID is designed to analyze national trends in health care utilization, access, charges, quality, and outcomes for patients under 21 years of age.[29] Data are produced every 3 years from 1997 through 2012 with the number of states in the KID growing from 22 to 44 during that time. Each data set has roughly 2 to 3 million discharges (unweighted), which corresponds to a national estimate of 6 to 7 million (weighted) discharges per data set.

The primary outcome of this study was hospitalized disease prevalence. Secondary outcomes included demographics, associated comorbidities by an organ system, adjusted charges of hospitalization, length of stay (LOS), and mortality. The inclusion criteria were patients aged <18 discharged with a primary International Classification of Diseases, Ninth Revision (ICD-9) diagnosis code (279.0-3, 279.8, 279.9) of a PIDD from 2003 to 2012 (Table E1, available in this article's Online Repository at www.jaci-inpractice.org). Patients with a concurrent diagnosis of a secondary immunodeficiency were excluded, including human immunodeficiency virus, malignancy, nutritional deficiency, or metabolic disorder because these conditions can cause a secondary immunodeficiency. However, known genetic abnormalities—for which a specific ICD-9 code exists—that have a predominant immunologic defect were included such as DiGeorge syndrome. These were not considered to be secondary immunodeficiencies for the purpose of this study. These inclusion and exclusion criteria have been used in previous studies.[27,28,30-32]

Data analysis

Analyses were conducted using the KID survey discharge weights to account for the strata and primary sampling unit (PSU), including clustering within hospital, following the practices recommended by HCUP.[33] When only a single PSU was sampled from a stratum in the data, the stratum was conservatively centered at the population mean rather than the stratum mean. The overall distributions of select clinical and demographic characteristics were determined using Pearson's χ^2 statistic when comparing categorical distributions. Logistic regressions with survey weights were employed to examine associations between etiology and mortality at each age category (0-5, 6-10, 11-15, or older than 15 years of age). LOS and hospital charge data were skewed, and were log-transformed before linear regression testing for differences among diagnoses within each age category; where LOS was recorded as 0 days, it was treated as 0.5 days before log transformation; geometric means are presented for these variables. Wald tests were used to determine the significance of coefficients in the model. Analyses were conducted using R 3.3 and the survey 3.31 package.[34,35]

Per the Institutional Review Board of the University of Illinois at Chicago, this study was deemed not to involve human subjects as analysis of de-identified data constitutes non-human subject research and was exempt.

RESULTS

Study subjects (Table I)

The prevalence of hospitalization was inversely proportional to age ($P < .001$). The highest prevalence was found in the 0- to 5-year age cohort with a prevalence of 15,105 ($P < .001$). There was a male predominance (56.5%, $P < .001$). Public versus private insurance was used equally. There was no variation by patient income quartile. Ethnicity was correlated with the ethnic population of the US-based on US census data.[36]

Prevalence of PIDD (Tables II and III)

The KID included a weighted national estimate of 7.4 million discharges in 2003 to 6.7 million in 2012 with a total of over 29 million discharges during this 9-year period. The overall prevalence of hospitalized PIDDs increased from 66.6 per 100,000 in 2003 to 126.8 per 100,000 in 2012 (Table II). During this 9-year period, the total population prevalence of hospitalized PIDDs was 92.4 per 100,000. B-cell and T-cell PIDD increased during this period from 30.4 to 70.4 per 100,000 and 35.5 to 55.4 per 100,000, respectively, but combined immune deficiencies did not significantly increase during that time. The highest total number of hospitalizations (11,376) by a specific