

The incidence of immune thrombocytopenic purpura in children and adults: A critical review of published reports

Deirdra R. Terrell,^{1*} Laura A. Beebe,¹ Sara K. Vesely,¹ Barbara R. Neas,¹
Jodi B. Segal,² and James N. George^{1,3}

Reports of the incidence of ITP are few and their methodology is variable. Accurate estimates of the incidence of immune thrombocytopenic purpura (ITP) are important to understand the medical and public health impact of the disease. To critically review all published reports on the incidence of ITP in children and adults, all articles identified on the Medline database (searched January 1, 1966–August 7, 2009) that reported data on the incidence of ITP were retrieved. Articles which directly estimated the incidence of ITP were selected for review. Eight articles reported the incidence of acute ITP in children. After review, four were determined to have the strongest estimates, based on the method of patient identification and study design. The lowest incidence estimate in these four studies was 2.2 per 10⁵ children/year (95% confidence interval 1.9, 2.4) and the highest incidence estimate was 5.3 per 10⁵ children/year (95% confidence interval 4.3, 6.4). Three studies reported the incidence of ITP in adults. The estimate from the article with the strongest methodology reported an incidence estimate of 3.3 per 10⁵ adults/year. The current strongest estimate of the incidence of acute ITP in children is between 1.9 and 6.4 per 10⁵ children/year; for adults the current strongest estimate of the incidence of ITP is 3.3 per 10⁵ adults/year. An important limitation of these studies is that they are primarily from Europe and may not be generalizable to all regions. Am. J. Hematol. 85:174–180, 2010. © 2009 Wiley-Liss, Inc.

Introduction

Knowledge of the incidence of ITP is essential to understand its medical and public health impact, but studies of the incidence of ITP are few [1]. Incidence data reported in reviews are often derived from previous reviews and secondary sources [2–4]. A difficulty for studies on ITP is that it is a syndrome which may have multiple pathogenetic mechanisms [5] and there are no clinical or laboratory parameters to establish its diagnosis with accuracy [6]. Therefore the diagnosis of ITP requires the exclusion of other etiologies of isolated thrombocytopenia, which is often difficult [6,7]. However, in spite of these difficulties, it is important to have a clear understanding of the incidence of ITP because the development of new therapeutic agents has led to an increased focus on clinical research on ITP [6,7]. Therefore to provide the strongest current estimate of the incidence of ITP, we aimed to identify all articles reporting primary data and we critically evaluated the methodology of each study. For this study, we analyzed each identified study in depth to understand how choices of study design and methodology and the included population influenced the reported incidence. Our goal was to identify a best estimate of ITP incidence for use in research and health services planning.

Methods

Article identification. To identify all relevant articles, Ovid software was used to search the Medline database from January 1, 1966 to August 7, 2009. Articles were identified by combining the MeSH subheading restricted to major topic heading idiopathic thrombocytopenic purpura and keywords describing ITP [idiopathic thrombocytopenic purpura, immune thrombocytopenic purpura, autoimmune thrombocytopenic purpura, ITP] with the MeSH subheading restricted to major topic heading and keyword incidence. Additionally the restricted MeSH subheading thrombocytopenia was combined with restricted MeSH subheadings and keywords [prospective studies, longitudinal studies, cohort studies, and follow-up studies]. The bibliographies of all retrieved articles as well as bibliographies of current reviews and texts were searched for additional relevant articles including those published before 1966. The search was limited to English-language articles. Limitations of the search strategy may be that we only identified articles that were indexed on Medline and that only one of the authors (DRT) reviewed all titles and abstracts to identify articles.

Article selection. Articles were included if they contained primary data on the incidence of ITP. The numerator of the incidence estimate had to be clearly stated and the denominator had to be population-based. Articles describing the incidence of all-cause thrombocytopenia were only included if patients with ITP could be identified within the overall estimate.

Article assessment. Information was abstracted independently by a hematologist (JNG) and an epidemiologist with experience in hematology (DRT). Articles were evaluated separately for children, adults, and combined estimates of children and adults. Articles describing the incidence of acute and chronic ITP in children were evaluated separately. If the authors described the population as “newly diagnosed” or “acute,” they were classified as acute ITP; if the authors described the population as “chronic,” the study was classified as chronic ITP. The one study of chronic ITP defined it as thrombocytopenia that had persisted for longer than 6 months [8]. No articles combined incidence estimates of children with acute and chronic ITP. The designations of acute ITP in the reviewed articles is the same as the designation of “newly diagnosed ITP” recommended by the International Working Group (IWG) [6]; however the designation of chronic ITP in the reviewed article [8] is not as precise as the terms “persistent ITP” and “chronic ITP” recommended by the IWG [6].

Studies were compared to determine the stronger incidence estimates based on a hierarchy of criteria: (1) the diagnosis of ITP, (2) collection of patients, and (3) other aspects of the methodology. Studies with stronger incidence estimates were those that established the diagnosis of ITP according to current clinical practice [2,3,9]. Prospective

¹Department of Biostatistics and Epidemiology, College of Public Health, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma; ²Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland; ³Department of Medicine, College of Medicine, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma

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*Correspondence to: Deirdra R. Terrell, Department of Biostatistics and Epidemiology, College of Public Health, University of Oklahoma Health Sciences Center, P.O. Box 26901 Room CHB 358, Oklahoma City 73126-0901, OK. E-mail: deirdra-terrell@ouhsc.edu

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TABLE I. Incidence of ITP in Children

Study	Country	Methodology	Accrual years	Sample size	Reported results/10 ⁵ children/year	Age of subjects	Inclusion criteria
Acute ITP in children							
1 ¹¹	Denmark	Retrospective chart review	1959–1969	154	1.1	Birth-15 years	Isolated idiopathic thrombocytopenia, validated by chart review
2 ¹²	United States	Retrospective chart review	1993–2003	409	4.0	Birth-18 years	ICD-9-CM code 287.3, ITP diagnosis validated by chart review
3 ¹³	England	Prospective cohort	1980–1994	70	4.8	Birth-14 years	Not described
4 ¹⁴	Norway	Population registry	1996–1997	92	5.3	Birth-14 years	Diagnosed by pediatrician, follow-up questionnaires asking if ITP diagnosis was revised
5 ¹⁵	Scandinavia	Population registry	1998–1999	506	4.8	Birth-14 years	Diagnosed by pediatrician, at least 1 platelet count <30,000/ μ L
6 ¹⁶	United Kingdom	Active surveillance	1995–1996	427	~3.0	Birth-15 years	Diagnosed by pediatric hematologist or pediatrician, follow-up survey collected data on presentation and course
7 ¹⁷	Germany	Active surveillance	1996–1997	323	2.2	\geq 4 weeks-16 years	At least 1 platelet count <30,000/ μ L and bleeding symptoms
8 ¹⁸	Kuwait	Not described	1981–1986	60	12.5	1–14 years	Mucocutaneous bleeding, confirmatory bone marrow aspirate
Chronic ITP in children							
1 ⁸	Sweden	Prospective registration	1984–1994	26	0.46	Birth-14 years	Isolated thrombocytopenia, which persisted for more than six months after initial diagnosis of ITP

collection of patients was considered to be stronger than retrospective collection of patients. When patients were collected prospectively, the investigators had *a priori* control over who was included in the study and how the information was collected, stored, and analyzed specifically for their study. With retrospective collection of patients, the investigators had to rely on data collected for purposes other than their study, and information on ITP diagnosis, clinical features and presentation was limited to interpretation of what had been previously recorded. When retrospective studies had complete information, then other aspects of the methodology were compared such as validation of the diagnosis by chart review. If multiple estimates were considered to have epidemiologically strong methodology, 95% confidence intervals (CI) were used to assess overlap of the estimates. Primary data from the articles was used to recalculate point estimates and provide 95% asymptotic CI based on the Poisson distribution [10].

Results and Interpretation

Acute ITP in children

Eight articles reported primary data on the incidence of acute ITP in children (Table I). Accrual of patients for these studies spanned 44 years, from 1959 [11] to 2003 [12]. Three different study designs were utilized: (1) retrospective chart review [11,12], (2) prospective registration or prospective cohort [13–15], and (3) active surveillance [16,17]. One article did not describe the study design [18]. Across the studies, the lower age limit ranged from birth to one year; the upper age limit ranged from 14 to 18 years. Direct comparison of reported study results was limited due to differences in criteria for patient identification. One study required at least one platelet count less than 30,000/ μ L [15]; one study required both one platelet count less than 30,000/ μ L and bleeding symptoms [17]; one study required the children to have a bone marrow aspirate and mucocutaneous bleeding [18]; two studies accepted the diagnosis of ITP by local pediatricians or pediatric hematologists without defining explicit criteria [14,16]; in two studies the diagnosis was validated by chart review using as criteria for diagnosis the presence of isolated thrombocytopenia without an apparent alternative etiology [11,12]; one study did not describe inclusion criteria [13].

The methodologies, accrual years, reported results, and inclusion criteria of the eight individual studies of acute ITP in children are described according to study designs in Table I.

Retrospective chart review. Medical records from all pediatric and medical departments in Denmark were reviewed to identify all children less than 16 years of age who were diagnosed with isolated thrombocytopenia from 1959 to 1969 [11]. Although the population denominator was not reported, it could be derived from the reported number of children with isolated thrombocytopenia (433) and the calculated incidence (3.2 per 10⁵ children/year) that the population of children less than 16 years in Denmark during this period was 1,233,969. Of the 433 children with isolated thrombocytopenia, 154 (36%) children met the authors' definition of idiopathic thrombocytopenia; these children may be assumed to have ITP. Although the authors did not report an incidence estimate for children with idiopathic thrombocytopenia, we calculated the incidence as 1.1 per 10⁵ children/year. Strengths of this study include data were reported for the entire country of Denmark and medical record confirmation of the diagnosis. However, the population denominator was not reported and children with infection-related thrombocytopenia were considered in a distinct category and were not included in the authors' designation of idiopathic thrombocytopenia. Therefore this incidence estimate may be conservative because ITP in children is often associated with an infectious illness [4].

The other retrospective medical chart review study documented the presenting features and response to therapy of children with ITP at the University of Alabama (UAB) at Birmingham Children's Hospital of Alabama, Division of Pediatric Hematology-Oncology [12]. The hospital was described as the "primary referral site for pediatric subspecialty care for more than 75% of the state" [12]. Clinic records (inpatient and outpatient) were reviewed to identify all children with the International Classification of Disease, 9th version, Clinical Modification (ICD-9-CM) code of 287.3 treated between July 1993 and June 30, 2003. Retrieved medical records were examined to exclude duplicates and alternative diagnoses. Inclusion criteria were not stated, however the presenting platelet counts ranged from 0 to 120,000/ μ L (median, 10,000/ μ L) and the children ranged in age from 1 month to 17 years. The total number of children with ITP was 409. Using an average of 41 cases of ITP per year and the population of children in Alabama (0–18

years) in 2000 (1.1 million) [12], they estimated the incidence at 4 per 10^5 children/year. A strength of the study was the medical review confirmation of diagnosis; however mild ITP may have been treated by local physicians without referral to a hospital and some patients would have been referred to other hospitals. Also some adolescents may have been treated by adult hematologists.

Prospective registration/prospective cohort. The first prospective cohort study [13] aimed to describe the frequency, clinical circumstances, and outcome of intracranial hemorrhage in childhood ITP. The incidence of ITP was an incidental observation and few details on determination of the incidence were described. The study identified 70 children over a 15 year duration (1980–1994) in a catchment area with a population of 480,000. Whether this population represented only children or all persons is not stated. The reported incidence of acute ITP was 4.8 per 10^5 children/year. Although this study did not describe how the cohort of children was identified or diagnosed as having ITP, a strength of this study was the prospective design.

The second prospective study [14] was a population-based registration of acute ITP cases using questionnaires sent to all hospitals with pediatric departments in Norway from January 1, 1996 to December 31, 1997. The authors stated the standard of care in Norway for persons less than 15 years of age is that they are hospitalized and treated in pediatric departments. The diagnosis of ITP by the local pediatrician was accepted for any child age birth through 14 years; a follow-up questionnaire asked if the diagnosis of ITP had been revised for any registered child. All 25 pediatric departments that managed patients with ITP participated in the registration. Ninety-two children with ITP were identified. Follow-up information was received for 87 of 92 (95%) patients; no diagnoses were subsequently revised. The population of children less than 15 years old in Norway was 860,000. The reported incidence was 5.3 per 10^5 children/year. A strength of this study was the prospective registration of patients in which several reminder questionnaires were sent out prompting physicians to register incident ITP patients; the follow-up questionnaire validated the initial diagnosis. However, the questionnaires were not sent to five hospitals with limited pediatric departments because it was assumed that children with suspected ITP would be referred to the hospitals with larger pediatric departments, and this assumption was not validated. Also it was not stated if the standard of care in Norway was to hospitalize children with acute ITP; children with ITP who were not hospitalized would not have been identified.

The third prospective study [15] was a prospective registration of hospitalized children in all Scandinavian countries to document the incidence, treatment practice and factors predicting chronic disease in children with a new diagnosis of ITP from January 1, 1998 through December 31, 1999. Some centers continued to enroll patients in 2000. Ninety-eight pediatric departments registered ITP patients and enrollment occurred in all five countries. The authors stated that registration was more than 90% complete in all countries. Inclusion criteria required that the child, age birth through 14 years, had at least one platelet count less than $30,000/\mu\text{L}$. The authors assumed that a child with a platelet count less than $30,000/\mu\text{L}$ would need treatment and therefore would almost always be referred to a pediatric department. Five hundred-six children were enrolled; the population of children less than 15 years of age in the five countries was 4.6 million, yielding an incidence estimate of 4.8 per 10^5 children/year. Strengths of the study were the prospective registration and the large number of patients identified. Although the study required children to have a platelet count less than $30,000/\mu\text{L}$, the authors cite previously

published data that less than 10% of children with ITP present with a platelet count above $30,000/\mu\text{L}$ ¹⁷ and that their goal was to identify children who required treatment.

Active surveillance. The goal of the first study using an active surveillance design [16] was to assess the practices of UK physicians treating childhood acute ITP. Questionnaires were sent to pediatric hematologists and pediatricians in the entire UK approximately every 3 months over a 14-month period (April 1, 1995–May 31, 1996). The initial survey asked physicians if they had seen a new patient with ITP age birth to 15 years in the previous three months. If a case was reported, then a follow-up questionnaire was sent to collect information on date of birth, date of presentation, gender, information on disease presentation, and treatment. The overall response to the initial surveys, asking if a new ITP patient had been seen within the last 3 months, was 94%; the overall response of receiving follow-up information on cases was 76%. Four hundred twenty-seven children with ITP were identified; the population of children less than 16 years old in the UK was reported as “approaching 13 million” [16]. The reported incidence was ~ 3 per 10^5 children/year. The strengths of this study include an active surveillance method for identifying patients and the high survey response rate for the initial survey. Although the follow-up questionnaire response was only 76% this probably did not affect the incidence estimate because the primary goal of the follow-up information was to assess treatment practices of UK physicians. Weaknesses were the imprecise population estimate reported and the three-month time interval between questionnaires could have resulted in underreporting of mild or rapidly resolving cases of ITP.

In another study, [17] surveys were sent to the medical directors of pediatric departments and pediatric hematology units of all hospitals in Germany, once each month between October 1, 1996 and September 30, 1997, asking if they had seen a new patient with acute ITP within the previous month. If a patient was reported, then a follow-up questionnaire was sent to gather information on date of birth, gender, presentation, and treatment. The overall response to the initial surveys, asking if a new acute case of ITP had been seen within the previous month, was 94%; the overall response for receiving follow-up information was 89%. The authors stated “practically all children with acute ITP” will be initially evaluated at a hospital. Inclusion criteria required the child to be at least 4 weeks old and less than 17 years old with the presence of at least one platelet count less than $30,000/\mu\text{L}$ and bleeding symptoms. A total of 323 children were reported; the population of children less than 17 years in Germany was ~ 15 million. The incidence estimate was 2.2 per 10^5 children/year. The strengths of this study were active surveillance for identifying patients and the high survey response rates for both the initial and follow-up questionnaires. The study only included children with severe acute ITP, those with a platelet count less than $30,000/\mu\text{L}$ and bleeding symptoms, but other studies have documented that over 90% of children initially present with bruising or petechiae [16] and a platelet count less than $30,000/\mu\text{L}$ [16,17,19].

Study design not explicitly stated. The study from Kuwait [18] enrolled children who were diagnosed with ITP in the Pediatric Department of Farwania Hospital. Although there was no explicit description of the study design, it was probably a retrospective chart review. Required criteria for the diagnosis of ITP were thrombocytopenia in the absence of other causes, mucocutaneous bleeding, and a confirmatory bone marrow aspirate. Sixty children were identified during six years (1981–1986). The population of children aged 1–14 years in their hospital catchment area was

TABLE II. Incidence of ITP in Adults and Combined Estimates for Children and Adults

Study	Country	Methodology	Accrual years	Sample size	Reported results/ 10 ⁵ adults/year	Age of subjects	Inclusion criteria
1 ²⁰	Denmark	Retrospective chart review	1973–1995	221	2.6	16 years and older	ICD-8-CM code or ICD-10 CM code representing thrombocytopenia, validated by chart review and platelet count less than 100,000/ μ L
				NR	2.3		ICD-8-CM code or ICD-10 CM code representing thrombocytopenia, validated by chart review and platelet count less than 50,000/ μ L
			NR	3.3	2.7	ICD-8-CM code or ICD-10 CM code representing thrombocytopenia, validated by chart review and platelet count less than 100,000/ μ L	
							1985–1995
2 ²¹	United Kingdom	Prospective registration	1993–1999	245	1.6	16 years and older	At least one platelet count less than 50,000/ μ L and confirmatory bone marrow aspirate and biopsy
3 ²²	United Kingdom	Retrospective secondary analysis	1992–2005	840	3.9	18 years and older	Read or Oxford Medical Information System diagnosis code representing thrombocytopenia in the General Practice Research Database
Combined incidence estimate (children and adults)							
1 ²³	Sweden	Retrospective chart review	1964–1968	152	2.5	All ages	Hospital discharge ICD code 296.03 and platelet count less than 100,000/ μ L validated by chart review
2 ²⁴	United Kingdom	Retrospective secondary analysis	1990–2005	1145	3.9	All ages	Read or Oxford Medical Information System diagnosis code representing thrombocytopenia in the General Practice Research Database

^a NR, not reported.

reported as 125,010 and the reported incidence was 12.5 per 10⁵ children/year. Weaknesses were the study design was not explicitly stated and the reported incidence estimate of 12.5 per 10⁵ children/year is much higher than all previous studies which is inconsistent with this study's strict inclusion criteria (requirement of bone marrow aspiration).

Chronic ITP in children

One study reported prospective registration of children from all pediatricians in the Northern Health Region (excluding Barrow) of the UK to determine the incidence and natural history of chronic ITP [8]. The authors conducted an additional search using the network of the Northern Region Consultant Haematologists Group. Chronic ITP was defined as isolated thrombocytopenia (platelet count less than 150,000/ μ L) which had persisted for more than six months. Patients were identified between June 1984 and May 1994. Twenty-six children met the inclusion criteria. The population of children younger than 15 years of age in this region was 564,000 and 586,000 for the years 1985 and 1992; the incidence of chronic ITP was 0.46 per 10⁵ children/year. There were no identified weaknesses of this study.

ITP in adults

Three articles reported primary data on the incidence of ITP in adults. The following study designs were used: (1) retrospective chart review [20], (2) prospective registration [21], and (3) retrospective secondary analysis [22]. Two studies defined adults as persons age over 15 years [20,21] whereas one study used over 17 years [22]. The methodologies, accrual years, reported results, and inclusion criteria of the three individual studies of ITP in adults are described according to study designs in Table II.

Retrospective chart review. The study from Denmark [20] was a retrospective medical chart review to identify patients seen in the hospitals and clinics in the county of Funen from April 1, 1973 through December 31, 1995. Inclusion criteria required patients to be residents of the county of Funen at the time of diagnosis of ITP, greater than 15 years of age, and the ITP had to be documented by one or more International Classification of Disease 8th version, Clinical Modification diagnosis codes (ICD-8-CM) or International Classification of Disease 10th version, Clinical Modification diagnosis codes (ICD-10-CM). Patients' records were then reviewed to validate the diagnosis of ITP by requiring a platelet count less than 100,000/ μ L in the absence of an alternative cause. The population over age 15 for the county of Funen in 1984, the mid-point of the study, was 368,491; 221 patients were identified; the incidence was 2.6 per 10⁵ adults/year. An additional incidence estimate was reported for patients who presented with a platelet count less than 50,000/ μ L; 2.3 per 10⁵ adults/year. This study covered 22.75 years and the number of adults diagnosed with ITP increased during the course of the study, beginning in the late 1980s. This was assumed to result from an increase of asymptomatic patients diagnosed by routine platelet counts with newer automated cell counting technology. Additional calculations were performed for 1985–1995, the incidence during this period for patients with platelet counts less than 100,000/ μ L was 3.3 per 10⁵ adults/year; for patients with platelet counts less than 50,000/ μ L, the incidence was 2.7 per 10⁵ adults/year. To identify ITP patients diagnosed outside of the hospital and clinic medical care system from 1985–1995, questionnaires were sent to general practitioners, internists, and dermatol-

ogists who worked in the county of Funen asking how many ITP patients they remembered treating in the past two years without referring them to the hospital system. When the referral questionnaires were sent was not stated. Based on the responses, approximately two patients per year with presenting platelet counts less than 50,000/ μL were diagnosed outside the hospital and clinic system. These additional patients would result in an increase of the incidence estimate from 2.7 to 3.2 per 10^5 adults/year. The strengths of the study were (1) the long duration of data collection, (2) the inclusion of patients with mild as well as moderate to severe thrombocytopenia, (3) separate incidence estimates for patients diagnosed before and after 1985, to account for a change of laboratory practice with frequent routine platelet counts, (4) separate incidence estimates for moderate and severe thrombocytopenia, and (5) questionnaires sent to general practitioners, internists, and dermatologists outside the Funen hospital and clinic system to estimate how many patients with platelet counts less than 50,000/ μL were potentially missed by the primary analysis. The only weakness of the study may be limitations of recall of the surveyed physicians who were outside the hospital and clinic system.

Prospective registration. The second study was a prospective registration of adults, age over 15 years, who were diagnosed with ITP by hematologists in the Northern Health Region of England from January 1, 1993 through December 31, 1999. Enrolled patients were required to have at least one platelet count less than 50,000/ μL and also a confirmatory bone marrow aspirate and biopsy [21]. Follow-up information was collected until June 30, 2000 and included signs and symptoms at presentation and response and requirement of therapy. A total of 245 adults met the inclusion criteria. The population in the Northern Health Region was 3.08 million; the reported incidence was 1.6 per 10^5 adults/year. The study's strengths include the large number of patients collected for analysis and the prospective method of identifying patients. A weakness of the study was the requirement for bone marrow confirmation of the diagnosis, which is not recommended by UK guidelines for patients less than 60 years old unless there are atypical clinical features [3]. Also patients with mild thrombocytopenia would not have been included.

Retrospective secondary analysis. The third study was a retrospective secondary analysis of adults (age greater than 17 years) in the UK's General Practice Research Database (GPRD) [22]. The authors stated the GPRD contains descriptive information from greater than 370 general practices covering ~5.3 million patients. It was further stated that participating GP offices were representative of the UK and patients in the GPRD are demographically similar to the age, sex, and geographic regions of the UK [22]. For this analysis, a person had to be registered in the GPRD during the years 1992–2005 and have at least one of the following Read or Oxford Medical Information system diagnosis codes: D313000 (idiopathic thrombocytopenic purpura), D313.12 (idiopathic thrombocytopenic purpura), D313012 (ITP-idiopathic thrombocytopenic purpura), 42P2.11 (auto-immune thrombocytopenia), or 2871C (thrombocytopenia idiopathic). In an effort to include only incident cases, the researchers required one continuous year of observation time in the GPRD before the first recorded ITP diagnosis code. Eight hundred-forty adults met the inclusion criteria and there were 21,749,623 person-years of follow-up during the 14 year study period for an incidence estimate of 3.9 per 10^5 adult/person-years [22]. Strengths of the study were the large number of persons with ITP identified and the long follow-up. However, the diagnosis of ITP was based on administrative codes without a chart review to validate the diagno-

sis and without requirement for any clinical characteristics. Furthermore, the incidence estimate may include prevalent cases that did not seek care for their disease the previous 12 months or sought care at a provider that did not participate in the GPRD.

Combined estimate of ITP in children and adults

Two articles reported primary data on the combined incidence of ITP in adults and children. The first study was a retrospective chart review [23], and the second study was a retrospective secondary analysis [24]. The methodologies, accrual years, reported results, and inclusion criteria of the combined incidence estimates are described by study designs in Table II.

The first study reviewed medical records to identify all cases of thrombocytopenia diagnosed in any hospital in the Uppsala Health Service region of Sweden from 1964-1968 [23]. Thrombocytopenia was defined as a discharge ICD (1955) code of 296.03 and a platelet count less than 100,000/ μL . Five hundred-eleven discharge codes represented thrombocytopenia, of those 152 patients were identified as idiopathic or essential thrombocytopenia; the mean platelet count was 30,000/ μL . The region population was 1.2 million persons. Although the study only reported the incidence of all-cause thrombocytopenia, the incidence of idiopathic thrombocytopenia could be calculated from the reported data (2.5 per 10^5 persons/year). A strength of the study was that the data were collected for an entire health region in Sweden. A weakness was that all patients were diagnosed in a hospital and patients with milder thrombocytopenia or minimal bleeding symptoms may not have been identified.

The final study was another retrospective secondary analysis of the UK's GPRD. The authors stated that patients of all ages were included if registered with one of ~350 practices that contributed data from 1990-2005 [24]. The goal of the study was to report current sex and age specific incidence estimates of ITP and compare the survival of ITP patients with matched controls. The diagnosis of ITP was based on at least one of the following Read or Oxford Medical Information system diagnosis codes: D313000 (idiopathic thrombocytopenic purpura), D313.12 (idiopathic thrombocytopenic purpura), D313012 [idiopathic thrombocytopenic purpura (ITP)], D313.11 (Evan's syndrome), 42P2.11 (auto-immune thrombocytopenia), or 2871C (thrombocytopenia idiopathic). If a person's first ITP diagnosis code occurred during 1990-2005 they were considered an incident case and if the person had an ITP diagnosis code before 1990 they were considered a prevalent case and not included in the analysis. Additional items obtained from the GPRD were platelet counts, history of a splenectomy, comorbid conditions, and prescriptions for drugs commonly associated with drug-induced thrombocytopenia within 60 days of diagnosis date. A chart review of each case was not completed; however, a random sample of 150 charts was reviewed to establish positive value predictive (PVP). One thousand one hundred forty-five persons met inclusion criteria during 29.2 million person-years of follow-up resulting in an overall incidence estimate of 3.9 per 10^5 /person-years. Person-years of follow-up were not reported separately for children and adults; however, incidence estimates were reported: children (age <18 years) 4.2 per 10^5 /person-years and adults (age \geq 18 years) 3.8 per 10^5 /person-years [24]. A PVP of 91% was reported based on review of 102 charts. Strengths of the study were the large number ($N = 1,145$) of persons identified and the long period (reported as 15 years) of follow-up. However, the diagnosis of ITP was based on administrative codes with a chart review of only a small sample of charts. A PVP

of 91% is high; however, this indicated there were 9% of charts in the sample that were billed for ITP and did not have ITP. When examining the entire 1,145 persons described as incident ITP, 100 (8.7%) had a comorbid condition associated with thrombocytopenia diagnosed before or within six months after the first ITP diagnosis, 12 (1.0%) had a prescription for quinidine within 60 days before the ITP diagnosis, and 44 (3.8%) had a history of splenectomy before the first recorded diagnosis of ITP. The authors recalculated the incidence estimate removing the 100 persons with comorbid conditions which resulted in a decreased estimate (3.6 per 10⁵/person-years). Regarding the 44 persons who had a splenectomy before diagnosis of their ITP, it seems more likely that these patients were actually prevalent rather than incident ITP cases. Finally, only 747 (65.2%) had at least one recorded platelet count and only 65.9% of them had a platelet count <100,000/ μ L.

Discussion

Our review has documented that the number of studies estimating the incidence of ITP is few, studies have been performed across many years, during different eras of clinical practice, the geographic diversity of the studies is limited, different diagnostic criteria have been used to identify patients with ITP, and different study designs with different goals have been utilized. Fogarty and Segal have recently published a concise summary of selected publications describing data on the epidemiology of ITP but their review did not include formal or critical assessments of the strengths of study designs and methodologies [1]. They concluded that it was not possible to provide a summary estimate of the incidence because of the many differences among published studies [1]. Different from their review [1], we critically analyzed each individual study based on measures of study design and methodology, allowing an objective assessment of the strengths and weaknesses of each study. Also different from the review of Fogarty and Segal, who reviewed only recent published reports [1], we performed a comprehensive review of all published literature, identifying four additional articles not included in their review [11,13,16,18] in addition to the two more recent articles [22,24]. Similar to Fogarty and Segal, [1] we concluded that data from the individual studies cannot be combined to provide a summary estimate of the incidence of ITP. However we believe that detailed analysis of each study can provide the basis for an objective assessment of the best current estimate of the incidence of ITP. A critical review of these data at this time is important because of the increasing focus on the pathogenesis and management of ITP [5–7].

We determined the stronger estimates of the incidence of acute ITP in children based on study methodology and diagnosis of ITP according to current clinical practice [2,3,9]. One study [13] did not describe how ITP was diagnosed and two [11,18] did not diagnose ITP according to current clinical practice [2,3,9]. The remaining five studies included one with retrospective collection of patients [12] and four with prospective collection of patients [14–17]. The retrospective study apparently had complete data collection, however the numerator only included children seen at one referral hospital [12] and therefore not all children were identified. Among the remaining four studies, two [15,17] required children to have a platelet count less than 30,000/ μ L at least once since the goal of the studies was to identify children who may need treatment. The restriction to children with platelet counts less than 30,000/ μ L is not an important limitation because 95% of children with ITP present with platelet counts less than 30,000/ μ L [17]. Our interpretation is that all four studies [14–17] which identified

acute ITP in children by prospective methods provide strong incidence estimates. All [14–17] accrued patients after 1985, when the frequency of ITP appeared to increase with the widespread use of automated blood cell counters and routine blood counts. The slight differences in the age definitions in these studies may limit their comparability. The incidence estimates in these four studies were 2.2 [17], 3.0 [16], 4.8 [15], and 5.3¹⁴ per 10⁵ children/year. To determine if these estimates overlapped, we used the primary data to recalculate the point estimates and 95% CI results were: 2.2 (1.9, 2.4) [17], 2.8 (2.5, 3.1) [16], 4.8 (4.4, 5.2) [15], and 5.3 (4.3, 6.4) [14]. Only two studies [14,15] had overlapping CIs. Based on the lowest and highest estimates, we conclude that the current strongest estimate of the incidence of acute ITP in children is between 1.9 and 6.4 per 10⁵ children/year.

The single reported incidence estimate for chronic ITP in children [8], defined as a platelet count less than 150,000/ μ L six months or longer after the initial diagnosis, was 0.5 per 10⁵ children/year.

The incidence estimates of ITP in adults ranged from 1.6 to 3.9 per 10⁵ adults/year. One study [21] did not diagnose ITP according to current clinical practice [2,3,9]. The remaining two studies both identified patients retrospectively [20,22], but one did not validate the diagnosis of ITP by chart review [22] and may have included other conditions in the estimate. Our interpretation is that the strongest incidence estimate for ITP in adults is provided by the study of Frederiksen and Schmidt [20] because of the comprehensive identification of patients validated by chart review and the inclusion of all patients presenting with platelet counts less than 100,000/ μ L and also less than 50,000/ μ L. For adults with platelet counts less than 100,000/ μ L presenting after 1985, the incidence estimate was 3.3 per 10⁵ adults/year.

Our interpretation is that the strongest estimate of the combined incidence in children and adults is the estimate by Marieke, et al. [24] because it is the most current overall population estimate. Patients were diagnosed by a physician during the period 1990–2005 using current guidelines. The incidence estimate was 3.9 per 10⁵/person-years, which may be an overestimate due to the lack of medical chart review to confirm the diagnosis of ITP.

An important limitation of our review is the inability to provide a summary estimate of the incidence of ITP because of the diverse features among published studies [1]. However this review provides a critical assessment of each individual study. A limitation of the studies that we interpreted to have the strongest methodologies [8,14–17,20,24] is that they are all from western Europe. Although geographic and racial disparities among patients with ITP have not been reported, they may exist [25] and therefore these data may not be generalizable to all regions. This observation emphasizes the need for further epidemiological investigations of ITP in non-European populations.

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