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Patterns of Inpatient Care for Newly Diagnosed Immune Thrombocytopenia in US Children's Hospitals

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WHAT'S KNOWN ON THIS SUBJECT: Clinically significant bleeding in pediatric immune thrombocytopenia (ITP) is rare. Evidence-based guidelines for the management of pediatric ITP recommend that patients with mild or no bleeding be followed with observation alone.

WHAT THIS STUDY ADDS: Many pediatric patients with newly diagnosed ITP continue to be managed in the inpatient setting. Bleeding events are rare in this setting. Although geographic variability exists, intravenous immunoglobulin is the most commonly used inpatient ITP treatment in the United States.

abstract

OBJECTIVE: Although recent evidence-based guidelines for the management of immune thrombocytopenia (ITP) recommend a conservative, observation-based approach for the majority of patients with newly diagnosed pediatric ITP, current practice patterns are unknown. This study used the Pediatric Health Information System database to examine patterns of inpatient care in newly diagnosed ITP in freestanding US children's hospitals and to examine geographic differences in care.

METHODS: Data were extracted from Pediatric Health Information System for all newly diagnosed ITP admissions aged 1 to 18 years discharged between January 2008 and December 2010. Clinical data obtained included age, gender, length of stay, diagnoses, medications, and discharge status.

RESULTS: We identified 2314 unique patients meeting the study diagnosis of newly diagnosed ITP. Noncutaneous bleeding occurred in 12% of patients (intracranial hemorrhage 0.6%), with epistaxis the most commonly reported symptom. Ninety percent of hospitalized patients received ITP-directed therapy, with intravenous immunoglobulin G the most commonly used therapy (78% of patients). We identified significant variation by geographic region in treatment strategies, length of stay, hospital charges, and likelihood of readmission.

CONCLUSIONS: A substantial number of children with newly diagnosed ITP continue to be hospitalized and receive intravenous medications, although the majority of these patients do not have clinical bleeding events during the admission. By using these results as a backdrop, future studies will be able to identify if the number of ITP admissions, costs of care, and geographic variability in care decrease with the dissemination and implementation of recently published guidelines. *Pediatrics* 2013;131:880–885

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KEY WORDS

ITP, pediatric, epidemiology

ABBREVIATIONS

anti-D—anti-D immunoglobulin
ED—emergency department
ICD-9-CM—*International Classification of Disease, Ninth Revision, Clinical Modification*
ITP—immune thrombocytopenia
IVIG—intravenous immunoglobulin G
PHIS—Pediatric Health Information System

Ms Kime and Dr O'Brien contributed equally to this work.

Ms Kime carried out the initial analyses, drafted the initial manuscript, and approved the final manuscript as submitted; Dr Klima carried out the initial analyses, reviewed and revised the manuscript, and approved the final manuscript as submitted; Dr Rose carried out the validation study, reviewed and revised the manuscript, and approved the final manuscript as submitted; and Dr O'Brien conceptualized and designed the study, supervised data analysis, assisted in drafting the initial manuscript, revised the manuscript, and approved the final manuscript as submitted.

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Immune thrombocytopenia (ITP) is an autoimmune disorder associated with both increased platelet destruction by autoantibodies, as well as suboptimal platelet production. Newly diagnosed ITP is typically observed in previously healthy children and often self-resolves within 6 months.[1] Despite having severe thrombocytopenia, with platelet counts $<20\,000/cm^3$, most patients present with only mild cutaneous manifestations such as bruising and petechiae. A reported 3% of children suffer serious bleeding, including severe epistaxis, extensive skin and mucosal hemorrhage, and gastrointestinal bleeding.[2] The rare but most feared complication is intracranial hemorrhage, occurring in <1% of children affected by ITP.[2–5]

Treatment of ITP is directed toward rapidly increasing the platelet count. A 2010 international consensus report on the investigation and management of primary ITP, however, states that most children with newly diagnosed ITP lack significant bleeding symptoms and may be managed without therapy at the discretion of doctor and patient.[5] The report also recommends that only those patients with clinically significant bleeding be admitted to the hospital. Similarly, the American Society of Hematology's recently published evidence-based guidelines for ITP recommend that those patients with mild or no bleeding be followed with observation alone, regardless of platelet count.[6] These recommendations are based on the rarity of significant bleeding in ITP and lack of data showing that treatment decreases the risk of serious bleeding. The impact of these recent guidelines on hospitalization patterns, treatment patterns, and health care utilization in pediatric ITP cannot be measured unless we understand baseline clinical practice.

However, the majority of published data regarding ITP management patterns comes from voluntary patient registries and does not include tracking of hospitalization patterns or health care costs. Our objective was to use the Pediatric Health Information System (PHIS) database to examine current patterns of inpatient care in pediatric patients with newly diagnosed ITP in freestanding US children's hospitals with the aim of comparing choice of therapy, average length of stay, outcomes, and charges among geographic regions. Because of continued controversies over the optimal management of newly diagnosed ITP, we hypothesized that substantial variation exists in current pediatric ITP practice patterns.

METHODS

Database

We examined data from the PHIS, a proprietary database of Child Health Corporation of America (Shawnee Mission, KS). PHIS contains comprehensive clinical and financial data submitted by Child Health Corporation of America members, 43 freestanding non-for-profit tertiary care and noncompeting children's hospitals across the United States. These hospitals represent >75% of all freestanding US children's hospitals. Patients within PHIS are deidentified with unique medical identification numbers, which allow individual patients to be followed over time. The data undergo numerous reliability and validity checks before inclusion in the database. Our use of deidentified data from PHIS was deemed exempt by the Nationwide Children's Hospital Institutional Review Board. One of the 43 hospitals was excluded because of incomplete clinical data during the study period. We also excluded 2 additional hospitals from financial analyses because of incomplete financial data.

Study Population

Data for this study were extracted from PHIS for all inpatients with newly diagnosed ITP aged 1 to 18 years discharged between January 2008 and December 2010. Patients were identified as having ITP if assigned an *International Classification of Disease, Ninth Revision, Clinical Modification* (ICD-9-CM) diagnostic code of 287.31. We excluded patients <12 months of age as ITP is rare in this age group. In an attempt to obtain a study population of newly diagnosed rather than persistent or chronic ITP patients, we limited our analysis to the first ITP hospitalization in the study period for patients with multiple ITP hospitalizations. We also required a 6-month period with no inpatient diagnoses of ITP before the hospitalization of interest. Finally, in an attempt to eliminate coding errors, we excluded patients who also had an alternate diagnosis associated with thrombocytopenia, including aplastic anemia (284) and leukemia (204-208).

Clinical data obtained for all study patients included age at discharge, gender, length of stay, medications/blood product transfusions, diagnoses, procedures, and discharge status. Diagnoses of interest included those suggestive of significant bleeding, including intracranial hemorrhage (ICD-9-CM codes 430.00–432.9), menorrhagia (626.2), gastrointestinal hemorrhage (569.30, 578.00–578.90), and epistaxis (784.70). We searched pharmacy files for the following medications: intravenous immunoglobulin G (IVIG), anti-D immunoglobulin (anti-D), and corticosteroids. Total charges were obtained when available, as well as itemized charges including clinical, imaging, laboratory, supply, pharmacy, and miscellaneous charges. The PHIS data set contains charges that are adjusted by the Health Care Financing Administration wage/price index for a hospital's location.

Statistical Analysis

We organized institutions into geographic regions based on US Census divisions. We described the entire

population of ITP admissions during the study period. We reported percentages and confidence intervals for categorical data. For count data, we generated a median and range. We then compared the following among geographic regions: median age, therapy usage, median length of stay, rate of readmission within 60 days, and total charges per day. Finally, we compared the following among ITP treatment groups: median length of stay, rate of readmission within 60 days, and total charges. Statistical analyses included χ^2 tests for categorical outcomes and Kruskal-Wallis tests for ordinal outcomes such as length of stay and total charges. All analyses were conducted by using Stata 11.0 (Stata Corporation, College Station, TX).

RESULTS

Over the 3-year period between January 2008 and December 2010, we identified 2314 unique patients meeting the study diagnosis of newly diagnosed ITP (Table 1). Male patients accounted for 52.4% of discharges, and patients between the ages of 1 and 3 years accounted for 35.8% of discharges. The median age was 6.0 years old. Noncutaneous bleeding occurred in 12.0% of patients, with epistaxis as the most commonly reported symptom. Intracranial hemorrhage was rare, even in our hospitalized population, occurring in only 0.6% of patients. Bleeding incidence increased with age (Table 2).

Almost all patients (99.0%) were discharged, and 0.1% died. The remaining 0.9% either left against medical advice or were transferred. Overall, 72.2% of patients received IVIG as a solitary therapy, and 9.4% patients were admitted to the hospital with ITP but received none of the medications included in our search. Total charges per day averaged $8984, with a median stay of 2.0 days. Pharmacy charges accounted for 50% of charges.

We identified significant variation ($P < .05$) by geographic region in all examined parameters except median patient age (treatment strategies, length of stay, hospital charges, and likelihood of readmission in 60 days; Table 3). In all regions, IVIG was the most used therapy for newly diagnosed ITP, and anti-D was the least used therapy. The use of IVIG as a solitary therapy ranged from 66.2% of patients in Pacific states to 85.0% of patients in the West North Central region (MN, MO, KS). Use of corticosteroids as solitary therapy ranged from 3.5% of admissions in the Mountain region to 11% in the West South Central (AR, LA, TX) region. The median length of stay was 1.0 to 2.0 days in all regions, and the rate of readmission within 60 days varied between 5.5% and 14.4%. There was a wide range in median total charges per day, with New England/Mid-Atlantic the lowest at $7194, and West South Central (AR, LA, TX) the highest at $11 409. The category of patients receiving no identified drug therapy for ITP had the lowest charges per day and shortest median length of stay (Table 4). Median length of stay again was 2 days among all patients who received ITP therapy. Differences in rates of readmission were not statistically significant among treatment groups.

TABLE 1 Clinical Characteristics of 2314 Hospitalized Pediatric Patients With Newly Diagnosed ITP, Pediatric Health Information System, 2008–2010

Population Description	(%)
Male	52.4
Age	
1–3 y	35.8
4–12 y	42.1
13–18 y	22.1
Noncutaneous bleeding	
Epistaxis	7.9
Menorrhagia	2.3
Gastrointestinal hemorrhage	2.3
Intracranial hemorrhage	0.6
Admissions with any noncutaneous bleeding	12.0
Medication use	
IVIG	72.2
Steroids alone	7.8
Anti-D alone	4.8
IVIG and anti-D	5.8
No ITP treatment identified	9.4
Length of stay (d), mean, median, range (n = 2250)	2.2, 2.0, 1–14
Readmissions within 60 d	10.1

DISCUSSION

Although recent evidence-based practice guidelines for the management of ITP recommend a more conservative, observation-based approach for newly diagnosed pediatric ITP, current practice patterns with regard to hospitalization and treatment strategies among pediatric hematologists in the United States are not well known. In a report from the Intercontinental Cooperative ITP Study Group of 1784 children presenting from 2004 through 2009, only 20% of children received no treatment, and the most common therapy was IVIG.[7] In the United Kingdom, however, current practice has shown a continued reduction in the number of children receiving treatment.[8] The proportion of children in the United Kingdom receiving platelet-raising treatment has decreased from 61% in 1995% to 38% in 2000% to 16% in 2009.

Our analysis of the PHIS provides insight into the current inpatient treatment patterns at US children's hospitals. We found that newly diagnosed ITP is not an uncommon reason for hospitalization, with ~800 admissions occurring per year. This is a fairly large number given that the number of new pediatric ITP cases in the United States is estimated to be ~3000 to 4000 annually,[9] and our data source does not represent all children's hospitals or any community hospitals. It appears that the majority of children admitted for newly diagnosed ITP do not have active noncutaneous bleeding during these admissions, with only 12% of admissions including a diagnostic code consistent with the most common bleeding events seen in patients with ITP.

TABLE 2 Incidence of Bleeding by Age Group

Age (y)	Bleeding Incidence (%)	95% CI	Most Common Bleeding Symptom (%)
1–3	8.0	6.2–10.0	Epistaxis (6.1)
4–12	12.1	10.1–14.2	Epistaxis (10.4)
13–18	18.5	15.3–22.1	Menorrhagia (8.8)

Difference in age groups significant at $P < .0001$. CI, confidence interval.

Our results also demonstrate that among children with newly diagnosed ITP who are admitted to a children's hospital, the majority receive ITP-directed therapy during the admission. Corticosteroids, IVIG, and anti-D are all considered first-line therapies for newly diagnosed ITP, with similar efficacy in increasing platelet counts.[10] The costs of these therapies are substantially different, however, with IVIG having the highest wholesale cost among first-line agents.[11] We found that IVIG was by far the most commonly used treatment strategy in US children's hospitals, with >78% of patients receiving this medication alone or in combination with other ITP-therapies. Among the 10% of admissions that did not receive ITP therapy, it is possible that these patients were admitted for observation alone. However, we cannot exclude the possibility that some of these admissions represent patients with ITP who were admitted to the hospital for a non-ITP indication.

We also identified geographic variability in the use of ITP therapies and costs of care for children hospitalized with newly diagnosed ITP in US children's hospitals. For example, hematologists in the Mountain and Pacific regions appear more likely to admit new ITP patients for observation only, with ~20% of patients not receiving an identified ITP therapy. Although IVIG was consistently the most commonly used therapy, geographic variations in the percentages of admissions receiving each of the first-line therapies was statistically significantly different. Even when adjusting costs for differences in cost of living between geographic areas, we still found differences of up to $4000 per day in hospital charges.

Our findings should be interpreted in light of the strengths and limitations of our data source and study design. As a large database providing ample ITP cases from multiple, geographically diverse children's hospitals, PHIS is a powerful data source and represents the majority of discharges from tertiary care US children's hospitals. Unlike other national hospital databases, the unique patient identifiers in PHIS allowed us to ensure that each ITP admission reported represents a unique patient. However, our analysis is only an indirect measure of all hematology practice patterns across the United States and may not be representative of ITP management at smaller children's hospitals, at community hospitals, or in rural settings.

One major limitation is that PHIS represents only inpatient care. We cannot report the percentage of total newly diagnosed ITP cases that receive inpatient care or treatment patterns for newly diagnosed ITP patients seen only in the outpatient or emergency department (ED) setting. Because our analysis was limited to inpatient care, it is not surprising that the majority of admissions received IVIG, because this medication requires prolonged infusion and observation. Although we cannot discern the physician decision making behind these ITP admissions, one could assume that if the patient was admitted to the hospital, then the managing physician's preference was to treat the ITP, and a rapid rise of platelet count was the desired effect.

Although our results suggest that hematologists are admitting large numbers of ITP patients without

TABLE 3 Regional Variability in Age, Therapy Choice, Rates of Readmission, LOS, and Charges per Day

	Total (N = 2314)	New England/ Mid-Atlantic (n = 347)	South Atlantic (n = 344)	East North Central (n = 347)	East South Central (n = 162)	West North Central (n = 167)	West South Central (n = 338)	Mountain (n = 115)	Pacific (n = 494)
Age	6.0	6.0	5.0	5.0	5.0	6.0	6.0	8.0	5.0
Steroids alone (%)[a]	7.8	6.3	7.6	7.5	9.3	4.8	11.2	3.5	8.3
IVIG (%)[a]	72.2	75.2	79.1	81.3	75.3	85.0	74.6	67.8	66.2
Anti-D (%)[a]	7.8	6.9	10.2	5.8	4.9	8.4	13.3	7.8	5.3
IVIG + anti-D (%)[a]	5.8	5.8	7.3	6.6	4.9	9.0	4.7	6.1	4.3
No ITP treatment identified (%)[a]	9.4	11.5	3.2	5.5	10.5	1.8	0.9	20.9	20.3
Readmission within 60 d (%)[a]	10.1	10.7	10.5	5.5	8.0	14.4	12.4	9.6	10.3
LOS (median)[a]	2.0	2.0	2.0	1.0	1.0	2.0	2.0	2.0	1.5
Total charges/d (median)[a]	$8984	$7194	$8902	$7921	$8690	$8206	$11 409	$8226	$9862

LOS, length of stay.

[a] Difference among regions significant at $P < .05$.

TABLE 4 LOS, Total Charges, and Readmission Rates by Treatment

	Median LOS	Total Charges[a]	Readmission (%)
Steroids (n = 180)	2.0	$18 313	11.7
IVIG (n = 1671)	2.0	$16 814	10.1
Anti-D (n = 111)	2.0	$16 373	9.9
IVIG + anti-D (n = 135)	2.0	$16 919	6.7
No ITP treatment identified (n = 217)	2.0	$13 050	11.1

LOS, length of stay.

[a] Treatment groups significantly different, $P < .05$.

clinically significant bleeding, it is possible that some of these patients did experience bleeding at home or in the ED before admission. Despite our best efforts in study design, it is also likely not all of the included patients were truly de novo cases of ITP. Some may have failed outpatient management, some may have been chronic ITP patients with infrequent hospitalizations. Finally, our work is subject to the limitations inherent in any analysis of administrative data. Medical conditions were identified on the basis of ICD-9-CM diagnosis codes that, if recorded inaccurately or not at all, may have caused some patients and events to be misidentified.

To investigate the magnitude of some of these known limitations, we performed a mini-validation study by linking the 106 PHIS patients from our own institution (Nationwide Children's Hospital) with data from our electronic medical records. We were able to match 98 patients between the 2 data sources. Of these 98 patients, 72 had inpatient medical records available for review, and 26 had only ED medical records for review (our current inpatient electronic medical records system was initiated in late 2008, after the start of our study period). From this cohort, we could determine that 95.9% of our Nationwide Children's Hospital PHIS patients did in fact have a diagnosis of ITP, and 75.5% had a diagnosis of newly diagnosed ITP. We reviewed emergency and inpatient records searching for evidence of bleeding symptoms. According to our review, the percentages of patients with symptoms of bleeding before admission to the hospital (n = 98) were as follows: 43.9% oral petechiae or purpura, 35.4% epistaxis, 16.3% gum bleeding, 6.1% gastrointestinal bleeding, 2.0% heavy menstrual bleeding, 0% intracranial hemorrhage, and 7.3% other bleeding. The severity of these bleeding symptoms could not be accurately determined through a chart review.

The percentage of patients with bleeding symptoms/signs noted during their hospitalization (n = 72) were as follows: 8.2% oral petechiae or purpura, 6.9% gum bleeding, 11.1% epistaxis, 0% heavy menstrual bleeding, 1.4% gastrointestinal bleeding, 0% intracranial hemorrhage, and 8.3% other bleeding. Because of the small numbers, we only calculated the sensitivity and specificity of PHIS at detecting epistaxis in our cohort (sensitivity 100, specificity 98.4). There is not an ICD-9 code that distinguishes oral petechiae/purpura from cutaneous petechiae/purpura.

It is difficult to draw firm conclusions from this mini-validation study, which represents <5% of our total study population. However, it appears that our search strategy was accurate at identifying patients with ITP in PHIS, but less accurate at identifying newly diagnosed cases. The prevalence of in-hospital bleeding was similar between our chart review and PHIS analysis, with an excellent sensitivity/specificity profile for epistaxis, the most common bleeding symptom. However, we found that bleeding was more likely to be reported in the ED record than the inpatient record. The use of administrative data to perform research will always be limited by the reliance on billing codes for diagnoses and procedures. However, ongoing work in this field is working to enhance the capabilities of secondary data methodology. Although traditionally an inpatient data source, PHIS has data on select outpatient (ED, ambulatory surgery) encounters and is working to expand these capabilities. Although the existing PHIS data set does not include the results of laboratory or radiologic studies, the ongoing PHIS+ project will augment PHIS with laboratory and radiology results data for children seen in the ambulatory and inpatient departments of 6 participating hospitals.[12] In addition, researchers have linked PHIS data to electronic medical records or other data sources to maximize the amount of clinical data that can be extracted. For example, Aplenc et al recently merged data from the Children's Oncology Group and PHIS to monitor toxicity in patients enrolled on a phase III Children's Oncology Group trial for de novo acute myeloid leukemia.[13]

What could be done to decrease the number of ITP admissions? Our findings suggest that factors other than bleeding symptoms are driving admission decisions. The expectations of referring pediatricians with regard to the aggressiveness of ITP management may influence decision making. Also, if treatment decisions are being driven by efforts to improve quality of life and general well-being, as opposed to reducing the risk of serious bleeding, practice patterns may be unlikely to change.[14,15] Our mini-validation study using our institutional data suggest that oral symptoms (oral petechiae, oral purpura, gum bleeding) and epistaxis are common in patients

ultimately hospitalized with ITP, but it is not known how these symptoms drive admission decision-making on a national level. At our institution during the study period, the great majority of newly diagnosed ITP patients with platelets <20 000 seen in our ED were admitted to the hospital for intravenous therapy, regardless of symptoms.

According to the American Society of Hematology guidelines, the decision to manage ITP with observation alone requires a detailed discussion with the family about health-related quality of life, medication side effects and efficacy, and anticipatory guidance about preventing and monitoring for bleeding.[6] Treatment may also be appropriate if follow-up cannot be ensured, the family lives a great distance from the hospital and does not have means to travel, or there are concerns attributed to a patient's activity level and risk of bleeding. Such detailed discussions require hematologic expertise and are not well suited to the ED setting. Encouraging primary care providers to contact their local hematologist when there is concern for ITP but no active bleeding, rather than referring the patient to the ED, would be an initial method of promoting outpatient management of this disease. For such a strategy to work, however, hematology clinics need to have the capability of evaluating a patient with suspected ITP within the same or next business day to meet the needs of the family and referring physician.

CONCLUSIONS

Our analysis provides a snapshot of ITP admissions and inpatient therapy at the time period when evidence-based international guidelines were first published (October 2009 and February 2011) recommending a more conservative approach to ITP management. We found that brief hospitalizations (mean length of stay 2 days) still commonly occur for newly diagnosed pediatric ITP in the United States. It also appears that the majority of children admitted for newly diagnosed ITP do not have active noncutaneous bleeding during these admissions. Future studies will be able to identify if the number of ITP admissions, costs of care, and geographic variability decrease with the dissemination and implementation of recently published evidence-based practice guidelines.

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