Influence of the American Society of Hematology Guidelines on the Management of Newly Diagnosed Childhood Immune Thrombocytopenia

Corinna L. Schultz, MD, MSHP; Nandita Mitra, PhD; Marilyn M. Schapira, MD, MPH; Michele P. Lambert, MD, MTR

**IMPORTANCE** In 2011, the American Society of Hematology (ASH) published updated guidelines for the management of childhood immune thrombocytopenia (ITP) recommending management with observation alone when there are mild or no bleeding symptoms, regardless of platelet count. Little is known about practice patterns of newly diagnosed ITP in the United States.

**OBJECTIVE** To understand the impact of management recommendations on practice patterns.


**MAIN OUTCOMES AND MEASURES** Management type (observation alone vs pharmacotherapy) was determined via medical record review and electronic pharmacy data at diagnosis and within 6 months after diagnosis.

**RESULTS** Overall, 44.7% of patients were managed with observation alone at diagnosis, with a significant increase from 34.9% in 2007-2010 to 49.2% in 2011 (P < .02) and 71.1% in 2012 (P < .001). Of those treated, 99% were treated with intravenous immunoglobulin. In multivariable logistic regression, younger age (odds ratio, 0.92; 95% CI, 0.87-0.99), lower platelet count (odds ratio, 0.86; 95% CI, 0.83-0.89), and earlier period (2007-2010) of diagnosis (odds ratio, 0.17; 95% CI, 0.09-0.34) were significantly associated with increased odds of pharmacologic management. During 2010-2012, 20.8% of patients were also treated within 6 months after diagnosis. There was no significant difference by year or initial management type in those who received this later pharmacotherapy. Additionally, 19.6% of patients had documented bleeding symptoms beyond cutaneous bruising or petechiae at diagnosis. Intracranial hemorrhage at diagnosis was rare (0.6%).

**CONCLUSIONS AND RELEVANCE** We demonstrated a significant practice change in the management of newly diagnosed ITP at a pediatric care tertiary care hospital in the United States surrounding revision of the ASH management guidelines for childhood ITP. Our experience supports adoption of observation alone for a proportion of patients with newly diagnosed childhood ITP. This form of management did not lead to an increase in later treatment or an increase in delayed bleeding symptoms.
Immune thrombocytopenia (ITP) is an autoimmune disorder characterized by immunologic destruction of otherwise normal platelets affecting 1 in 20,000 children annually in the United States. The International Working Group defines ITP as a platelet count less than 100 ×10^9 per liter (to convert to ×10^3/μL, multiply by 1) in the absence of other causes. Immune thrombocytopenia is often considered a self-limited disease without significant medical complications but can rarely be associated with life-threatening bleeding including intracranial hemorrhage. Pharmacologic treatments may temporarily increase the platelet count but do not appear to decrease the time to resolution of ITP.

Treatment recommendations for childhood ITP have been the subject of debate. Although guidelines in the United Kingdom have long supported a watch and wait approach, the American Society of Hematology (ASH) did not universally adopt that approach until 2011. The ASH recommends that “children with no bleeding or mild bleeding (defined as skin manifestations only, such as bruising and petechiae) be managed with observation alone regardless of platelet count.”

Our objective was to understand the impact that the 2011 ASH guidelines had on practice patterns at the Children's Hospital of Philadelphia (CHOP), a large, urban, pediatric tertiary care hospital in the United States.

**Methods**

We conducted a retrospective cohort study. The initial cohort was developed by querying the hospital data system for patients ages 0 to 17 years seen in inpatient and outpatient locations at CHOP between January 1, 2007, and December 31, 2012, using the International Classification of Diseases, Ninth Revision (ICD-9) code for ITP (287.31). Manual medical record review was used to refine the cohort. The clinical data extracted included year of diagnosis, age and platelet count at diagnosis, sex, residence zip code, attending physician, and type of bleeding symptoms, and documented reason for pharmacotherapy as stated in the assessment and plan for the encounter. Bleeding symptoms included any subjective or objective documented bleeding symptoms aside from bruising or petechiae. Euclidian distance from the patient’s home zip code to the CHOP zip code was calculated in kilometers. Pharmacy data included all platelet-increasing therapy (intravenous immunoglobulin [IVIG], Rho[D] immune globulin, and corticosteroids) given at diagnosis or arranged for administration within 1 week. Blood bank data included any packed red blood cells or platelets given at the diagnosis encounter. Diagnosis encounter was determined by the presence of platelet count less than 100 ×10^9/μL in the absence of other causes, with physician documentation of new or likely ITP. For those diagnosed as having ITP between 2010 and 2012, we recorded bleeding symptoms and management during the 6 months postdiagnosis. This study was approved by the institutional review board of CHOP; informed consent was waived.

We compared clinical and demographic variables between patients receiving pharmacotherapy and observation. Additionally, we compared patients managed in the preguideline change period (2007-2010) and postguideline change period (2011-2012). Categorical variables were compared using the χ² test and continuous variables were compared using the t test or Wilcoxon rank-sum test for heavily skewed distributions.

We used multivariable logistic regression to assess the association between management type at diagnosis (pharmacotherapy vs observation alone) and age (years), platelet count (×10^9/μL), period of diagnosis (preguideline change vs postguideline change period), sex, and distance (kilometers). Odds ratios (ORs) and 95% CIs are presented. In secondary analyses, we used a generalized estimating equations approach to account for patient clustering by attending physician. Thirty attending physicians were represented, with 8 accounting for most study participants. Additionally, we evaluated interactions between period of diagnosis and age or platelet count by including multiplicative interaction terms in our models. The presence of bleeding symptoms correlated perfectly with receiving pharmacotherapy (ie, every patient who had documented bleeding symptoms received pharmacotherapy). Because of this, only 1 of the variables could be included in the regression models and, therefore, the presence of bleeding symptoms was excluded. The secondary outcome, management within 6 months after diagnosis, was analyzed via multivariable logistic regression accounting for clustering by attending physician and included management at diagnosis, age, platelet count, time of diagnosis, sex, and distance. All statistical tests were 2 sided and statistical significance was considered to be P < .05. Analyses were conducted using Stata 12.0 (Stata Corp).

**Results**

**Study Cohort Development**

An initial cohort of 502 patients was developed via ICD-9 code. Medical record review then excluded patients owing to treatment at another institution (n = 69), diagnosis prior to 2007 (n = 68), and alternative diagnosis (n = 41). Evan syndrome (n = 8), autoimmune lymphoproliferative syndrome (n = 5), and neonatal alloimmune thrombocytopenia (n = 3) were the most common alternative diagnoses. Twelve patients were excluded owing to age older than 17 years or diagnosis unable to be confirmed. The final cohort included 311 patients.

**Study Population Characteristics**

Distribution of age and platelet count were skewed toward younger age and lower platelet count. The mean (SD) age at diagnosis was 6.1 (5.1) years and the median age was 4 years (range, 0.1-17 years). The mean (SD) platelet count was 16.9 (18.7) ×10^9/μL and the median was 9 ×10^9/μL (range, 1-96 ×10^9/μL). Fifty-five percent of patients presented with a platelet count less than 10 ×10^9/μL. Forty-seven percent were male. Additionally, 19.6% had bleeding symptoms, all with a platelet count less than 23 ×10^9/μL and 80% with a platelet count less than 10 ×10^9/μL. The most common bleeding symptoms were epistaxis (n = 25), pet purpura (n = 20), gastrointestinal bleeding (n = 5), hematuria (n = 4), and menstrual bleeding (n = 4).
Intracranial hemorrhage at diagnosis was rare (n = 2, 0.6%), with 1 incidentally found on imaging.

New diagnoses ranged from 34 to 51 and 59 to 63 per year in 2007-2009 and 2010-2012, respectively. Overall, 55% of patients were managed with pharmacotherapy at diagnosis, with 98.8% of those receiving IVIG, 4.6% receiving glucocorticoids, 0.6% receiving Rho(D) immune globulin, and 3.5% receiving blood products. Every patient who received blood products also received another pharmacotherapy type. The proportion of patients managed with observation alone at diagnosis increased significantly during the study from 34% of patients in 2007-2010 to 49.2% in 2011 (P < .02) and 71% in 2012 (P < .001) (Figure).

Comparison by Management Type at Diagnosis

When compared based on management type (pharmacotherapy vs observation alone), there was a statistically significant difference in age, platelet count, and bleeding symptoms (Table 1). Sex and distance were not different between groups. Those receiving pharmacotherapy were significantly younger (mean [SD], 5.4 [5.5] years; median, 3 years) than those observed (mean [SD], 7.4 [5.5] years; median, 6 years) (P < .001). Additionally, those who received pharmacotherapy had significantly lower platelet counts (mean [SD], 7.9 [5.8] ×10³/μL; median, 6 ×10³/μL; range, 1-42 ×10³/μL) than those observed (mean [SD], 28.2 [22.7] ×10³/μL; median, 21 ×10³/μL; range, 1-96 ×10³/μL) (P < .001). Of those with a platelet count less than 10 ×10³/μL, 79% (n = 136) received pharmacotherapy. Additionally, every patient with bleeding symptoms received pharmacotherapy (P < .001).

Comparison by Period of Diagnosis

When looked at across periods (Table 2), patients were significantly younger in the postguideline change period (mean [SD], 5.2 [4.6] years; median, 3 years) than in the preguideline change period (mean [SD], 6.7 [5.3] years; median, 4 years) (P = .02). Similarly, patients lived further from the hospital in the postguideline change period (39.2 km) than in the preguideline change period (32.3 km) (P = .03). Neither age nor distance differed between management types in the postguideline change period. Platelet count and bleeding symptoms remained significantly different between management types during both periods. Most importantly, there was a significant change in the proportion of patients with a platelet count less than 10 ×10³/μL who were observed in the preguideline change period (9%) vs postguideline change period (41%) (P < .001).

Multivariable Model

Consistent with univariate analysis, younger age, lower platelet count, and preguideline change period were associated with increased odds of pharmacologic treatment (Table 3). In other words, for every 1-year increase in age, a patient has 8% lower odds of receiving pharmacotherapy (OR, 0.92; 95% CI, 0.87-0.99) and for every 1-×10³/μL increase in platelet count, a...
patient has 14% lower odds of receiving pharmacotherapy (OR, 0.86; 95% CI, 0.83-0.89). Additionally, as compared with the preguideline change period, those diagnosed as having ITP in the postguideline change period have 85% lower odds of receiving pharmacotherapy (OR, 0.17; 95% CI, 0.09-0.34). When variation based on attending physician was taken into account or period interaction terms were included, ORs were nearly identical.

Management Within 6 Months Postdiagnosis
During 2010 and 2012, 23% (27 of 119) of patients received pharmacotherapy within 6 months after diagnosis, with no significant difference by year or initial management type ($P = .54$). Of those receiving pharmacotherapy in the 6 months after diagnosis, 47% ($n = 7$) in 2010 and 42% ($n = 5$) in 2012 had also received pharmacotherapy at initial diagnosis. Despite this, the percentage of patients who were observed alone at diagnosis and who later received pharmacotherapy decreased from 40% to 16% from 2010 to 2012, respectively. Those receiving pharmacotherapy in the 6 months after diagnosis were treated, on average, 1.2 months after diagnosis (range, 0.25-5 months), with 68% within 1 month of diagnosis and no difference between 2010 and 2012. Age, platelet count, sex, and distance of those receiving later pharmacotherapy were consistent with the larger cohort.

In a multivariable logistic model, only older age was significantly associated with increased odds of pharmacologic treatment within 6 months after diagnosis when all other variables were held constant (OR, 1.08; 95% CI, 1.00-1.17; $P = .04$). Accounting for clustering by attending physician and including interaction terms produced nearly identical results.

**Documented Reasons for Pharmacotherapy**
Almost half who received pharmacotherapy at diagnosis had a reason documented for receiving pharmacotherapy, with the most common being epistaxis, activity level of the child, and wet purpura (Table 4). All children receiving pharmacotherapy within 6 months after diagnosis had a reason documented, with the most common being thrombocytopenia, brusing, activity level, or gastrointestinal bleeding. One child, initially treated with IVIG, presented with a small intracranial hemorrhage from direct head trauma 1.5 months after diagnosis. Overall, 35% of those treated at diagnosis and 31% of those treated within 6 months had potentially significant bleeding symptoms as the reason documented for pharmacotherapy.

<p>| Table 3. Predictors of Pharmacotherapy at Diagnosis |</p>
<table>
<thead>
<tr>
<th>Predictor</th>
<th>Odds Ratio (95% CI)</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postchange period$^a$</td>
<td>0.17 (0.09-0.34)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Age</td>
<td>0.92 (0.87-0.99)</td>
<td>.02</td>
</tr>
<tr>
<td>Platelet count</td>
<td>0.86 (0.83-0.89)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Male</td>
<td>0.73 (0.39-1.38)</td>
<td>.33</td>
</tr>
<tr>
<td>Distance</td>
<td>1.00 (0.99-1.01)</td>
<td>.37</td>
</tr>
</tbody>
</table>

$^a$ Postguideline change period (2011-2012) compared with preguideline change period (2007-2010).

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During the past 20 years, national and international groups have created practice guidelines for the management of

Discussion
Over the past 20 years, national and international groups have created practice guidelines for the management of

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childhood ITP. Despite these cooperative efforts, management practices vary, with the most notable difference between the United Kingdom and the United States. Starting in 1992 and reaffirmed in 2003, guidelines in the United Kingdom have supported a watch and wait approach, stating that treatment should be based on symptoms and not platelet count, opting for observation alone over pharmacotherapy when feasible.\(^6\)\(^7\) This contrasts with the 1996 recommendation by ASH that management be based on symptoms and platelet count because “current evidence is inadequate to recommend which groups of children with ITP can be safely managed without therapy.”\(^8\) The recommendations by ASH suggested, via opinion statement, that it may be appropriate to withhold treatment for those who are asymptomatic with platelet counts in the range of 20 to 30 \(\times 10^3/\mu\text{L}\). Although most of the recommendations from ASH were based on symptoms and platelet count, they did recommend that children younger than 3 years with a platelet count less than 20 \(\times 10^3/\mu\text{L}\), regardless of symptoms, undergo pharmacotherapy to increase the platelet count to a normal range.\(^8\)

Over time, there have been natural history studies of ITP indicating that most children do not experience significant bleeding at follow-up, regardless of the initial management.\(^2\)\(^5\)\(^9\)\(^12\) This led to guidelines, such as the 2010 International Consensus Report, which states that “the majority of children with newly diagnosed ITP lack significant bleeding symptoms and may be managed without therapy directed at raising platelet count.”\(^9\)\(^3\) and to the 2011 ASH guideline, which “moved away from recommendations for treatment based on platelet number”\(^10\)\(^14\)\(^19\)\(^9\) and now states that “children with no bleeding or mild bleeding (defined as skin manifestations only, such as bruising and petechiae) be managed with observation alone regardless of platelet count (grade IB).”\(^9\)

Without a national US registry, practice patterns of US physicians toward childhood ITP are not well described. Surveys of pediatric hematologists by the American Society for Pediatric Hematology/Oncology in 1997 and 2001 attempted to assess practice patterns. When given hypothetical patient situations, pediatric hematologists endorsed observation 16% of the time.\(^14\)\(^15\) This mirrored 2 single-center retrospective studies in Alabama and Indiana showing observation alone as first-line treatment used in 17% and 14% of patients older than 10 and 4 years, respectively.\(^16\)\(^17\) In 2008, an Italian group noted a 25% observation rate,\(^18\) while another large US tertiary care hospital observed 33% of patients over a similar period.\(^19\) The rates of observation alone have dramatically increased in the United Kingdom from 39% in 1995 to 62% in 2000 and 84% in 2009,\(^20\) where recommendations for watch and wait have been in place for nearly 20 years. In one survey done since the 2011 ASH guideline update, 5 of 12 (42%) Oklahoma pediatric hematologists endorsed observation alone for management when given a hypothetical situation.\(^21\) To our knowledge, there have been no studies looking at US trends after the publication of the 2011 ASH guidelines to date.

Using a single pediatric tertiary care institution, we described practice patterns in newly diagnosed childhood ITP surrounding guideline changes. We found a significant change in the use of observation alone at diagnosis of ITP at CHOP between 2007 and 2012, with its rate reaching 71% in 2012. Although we cannot prove causation, this significant change demonstrates a strong association with the timing of the 2011 ASH guidelines and the possible influence of the guidelines on practice. At CHOP, management decisions can be discussed at routine weekly divisional patient care conferences but ultimately remains at the discretion of the treating physician. While the hematology department has not had a written policy addressing management of newly diagnosed ITP, the ASH guidelines were presented at this meeting after publication. The relative influence of the 2011 ASH guidelines, clinical opinion leaders, treating physician, and patient preference has yet to be determined. Further research is also needed to investigate whether this increase in observation rate is unique to this large, research-based institution or whether observation rates have increased nationwide.

We demonstrated a significant difference in age, platelet count, and bleeding symptoms between those receiving pharmacotherapy and observation alone at diagnosis. In our multivariable analysis, children who are younger, with a lower platelet count, and presenting during the preguideline change period had increased odds of receiving pharmacotherapy. However, over time, age became less significant between the 2 management types despite an overall decreasing age.

When looking across periods, the most significant change was the increase in the use of observation alone among those with a platelet count less than 10 \(\times 10^3/\mu\text{L}\) because this is a platelet count often evoking fear of bleeding in parents and attending physicians. Although most of those who presented with bleeding symptoms had a platelet count less than 10 \(\times 10^3/\mu\text{L}\), there remains a substantial number of children with lower platelet count who continue to receive pharmacotherapy in the absence of bleeding symptoms. This represents a group that is potentially over treated and leaves room for improvement in management practices.

Additionally, cost savings from elimination of hospitalization, unnecessary medication administration, and evaluation of adverse effects of pharmacotherapy (ie, computed tomographic scan to evaluate headache post-IVIG) could be significant.\(^22\)\(^23\) Despite this, we anticipate that practice will continue to vary from guidelines owing to parent and referring physician’s expectations and managing hematologist’s decision-making approach.\(^23\)

Of concern was whether we delayed initial treatment of childhood ITP. Evaluating management within 6 months after diagnosis, we did not see an increase in the proportion of children receiving later pharmacotherapy or returning with bleeding symptoms after initial observation. Although the number of children receiving later pharmacotherapy was small, there was not a significant increase during our study. In fact, the percentage observed at diagnosis who received later pharmacotherapy decreased across time, representing perhaps an increased comfort with observation alone as first-line management in children with ITP.
This study had limitations. Because we conducted a retrospective medical record review at a single institution, our data and interpretation are only as robust as the quality of physician documentation. There were likely clinical and social factors that affected a physician’s management not easily ascertained via medical record review. This could have affected documentation of reason for management choice and bleeding symptoms. Bleeding symptom description may have been overemphasized or underemphasized in support of a management choice. No standardized bleeding scale was used at diagnosis or on medical record review. However, the percentage of bleeding symptoms (20% at diagnosis) was comparable with that from registry data (23%-24%). In prospective studies, use of a standardized bleeding scale at the time of decision making could help reduce any ambiguity.

Additionally, 37% of patients originally identified via ICD-9 code did not meet criteria for newly diagnosed ITP. With a greater shift to outpatient observation, inpatient databases, such as the Pediatric Health Information System and Kids’ Inpatient Database, could become skewed in regard to studying childhood ITP. Because of this, caution should be used in applying ICD-9 code to identify new diagnoses. Despite this, future studies should be able to identify changing trends in the inpatient management of childhood ITP across the United States as a study was published with pre-2011 Pediatric Health Information System data.

Conclusions
An increasing proportion of patients with newly diagnosed childhood ITP were managed with observation alone at our tertiary care academic medical center after publication of updated management guidelines. This occurred without an institutional policy change and without an increase in later treatment or delayed bleeding symptoms. Further investigation will determine whether practice change is sustained and widespread. We do not know how this change in practice is perceived by parents, caregivers, and referring physicians. We argue that as hematologists increase use of appropriate observation, parent and referring physician comfort will also increase. Further education of parents and referring physicians to the risks and benefits of management types is necessary for continued adoption of current guidelines, specifically observation, when appropriate.

To assure appropriate evaluation and follow-up, children with suspected ITP should be evaluated by a pediatric hematologist. However, we argue that initial hematologist evaluation may be done safely in the outpatient setting for children without bleeding symptoms, bypassing an emergency department encounter or hospitalization. Additionally, we have demonstrated that a significant practice change in the management of newly diagnosed ITP is possible within a small period and without apparent deleterious effects.

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REFERENCES


