The Child With Immune Thrombocytopenic Purpura: Is Pharmacotherapy or Watchful Waiting the Best Initial Management?

A Panel Discussion From the 2002 Meeting of the American Society of Pediatric Hematology/Oncology

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Abstract: The initial management of immune thrombocytopenic purpura is a topic of debate among pediatric hematologists. The decision whether to start a patient on pharmacotherapy or to employ an approach of watchful waiting and patient education is problematic for this group of physicians. A wide variety of research studies and review articles have been published on either side of this debate. Here, the proceedings from a panel discussion, held at the 2002 American Society of Pediatric Hematology/Oncology meeting, are presented. The panel, composed of experts on both sides of the debate, presented the rationale, benefits, and risks of both pharmacotherapy and the watchful waiting strategy.

Key Words: idiopathic (immune) thrombocytopenic purpura, anti-D, immune globulin, intracranial hemorrhage, platelets

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Immune thrombocytopenic purpura (ITP) is one of the most common bleeding disorders among children. The community of pediatricians and hematologists has divergent opinions on the management of a child with newly diagnosed ITP. At the 2002 Annual Meeting of the American Society of Pediatric Hematology/Oncology, a panel discussed the pharmacotherapeutic approaches and weighed them against watchful waiting. This article describes the proceedings from this symposium.

The format for the symposium included presentations by four faculty members to review the natural history of the disease, when and if treatment might be needed, and the advantages and potential adverse effects of the available forms of pharmacotherapy. In addition, the presenters explored clinical assessment and management of bleeding problems and impact on quality of life, as well as the economic impact and cost-effectiveness of alternative management strategies. To encourage audience participation in the discussion, the faculty presented brief case studies, and the audience was invited to answer polling questions designed to solicit their input on these issues. Immediate graphic displays of the audience responses were shown.

In this summary, the major discussion points of the four faculty presentations will be reviewed by describing each case presentation, with a relevant polling question and results from the audience participation. The audience consisted of pediatric hematologists who see a range of patients with ITP, with about 40% of them treating 10 to 20 patients a year.

CASE 1

Paula Bolton-Maggs described the case of an 11-year-old girl who presented with clinically mild ITP symptoms, including some bruising and epistaxis (Fig. 1). Although the patient had a low platelet count, Dr. Bolton-Maggs chose the watch-and-wait strategy. When polled, 58% of the audience agreed with her recommendation. She reported that, indeed, the patient remitted after 4 months, continuing a normal lifestyle with no additional bleeding problems.

Rationale

Dr. Bolton-Maggs reviewed her rationale for using reassurance and watchful waiting rather than pharmacotherapy in

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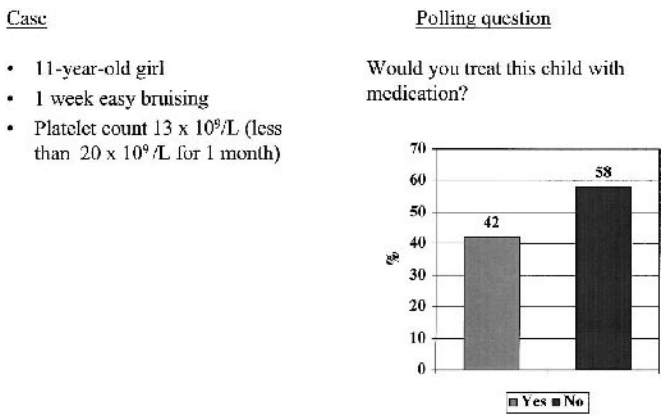

FIGURE 1. Polling question: Initial treatment of an 11-year-old girl with purpura and a platelet count of 13 $\times$ 10^9/L.

this case. She feels that treatment to raise the platelet count can be reserved for the small minority of patients who have significant bleeding.

In two surveys of pediatricians and hematologists, conducted in the United Kingdom, the signs and symptoms in children who were diagnosed with acute ITP were reported.[1,2] These surveys indicated that the most commonly observed symptoms in children presenting with ITP are minor. For instance, 70% to 90% of patients had bruising and purpura, while less than 20% had nose and mouth bleeds, of which most were trivial. ITP cases were classified by severity of symptoms (mild, moderate, or severe), ignoring the platelet count. Mild symptoms consisted of bruising and petechiae along with occasional minor epistaxis, with little interference with daily living. Moderate symptoms were classified by more severe skin manifestations, with some mucosal lesions and more troublesome epistaxis or menorrhagia. Severe symptoms included bleeding episodes requiring hospital admission, blood transfusions, or both, that seriously interfere with the quality of life.

These surveys showed that regardless of the platelet count, the majority of children classified exhibited only mild symptoms, similar to the case presented by Dr. Bolton-Maggs. Less than 5% of children had severe bleeding. The patient in this case was monitored, without pharmacotherapeutic intervention, and achieved normal platelet counts without further bleeding problems.

Dr. Bolton-Maggs concluded that the watch-and-wait strategy, in which the treatment includes reassurance, education, and monitoring rather than pharmacotherapy, is a safe alternative. In fact, 50% of 163 children observed in one study reached platelet counts of more than 50 $\times$ 10^9/L within 2 to 3 weeks using the watch-and-wait strategy.[2]

In addition, Dr. Bolton-Maggs argued that it may be less risky to watch mild symptoms such as bruising and purpura than to treat, due to the side effect profiles for the common treatments.[3] For instance, with the use of steroids, such side effects as behavior problems, weight gain, infection, hypertension, and gastrointestinal hemorrhage are observed. Some common side effects in patients treated with IVIG include headache, malaise, and febrile reactions. In rare cases, hepatitis C transmission has been reported. Side effects of anti-D include headache, fever, chills, and hemolysis.[4]

Conclusions

Dr. Bolton-Maggs' position is that the watch-and-wait strategy is a valid and effective course of action. She stresses that treatment must be targeted toward the individual child's symptoms, taking into consideration that the treatment may be worse than the disease itself. She reports that in the United Kingdom, 63% of pediatricians and hematologists caring for children with ITP do not treat all children who are initially diagnosed with ITP with pharmacotherapy, but generally now reserve treatment for those with significant bleeding.

CASE 2

Michael D. Tarantino, M.D., presented a case in which a 4-year-old boy developed a sudden rash. Upon examination, the pediatrician found extensive purpura and a platelet count of 10 $\times$ 10^9/L (Fig. 2). In addition, Dr. Tarantino pointed out that in many cases other quality-of-life and cost issues may come into play when considering pharmacotherapy. For instance, in this scenario, the parent was a single mother who had to take time off from work to take the child to the pediatrician.

When polled regarding their course of action for initial management of this child's ITP, a slight majority of the audience chose some form of pharmacotherapy (55%) versus the watch-and-wait strategy (45%). Of those who chose drug treatment, 32% chose anti-D therapy. Dr. Tarantino agreed with the latter course of management, recommending pharmacothera-

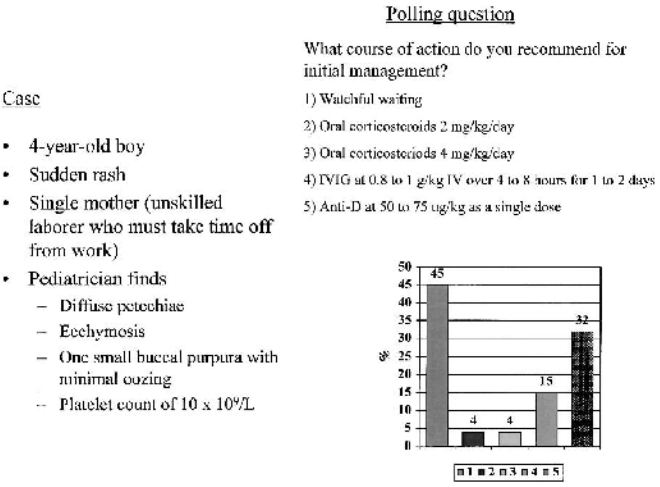

FIGURE 2. Polling question: A 4-year-old boy with diffuse petechiae and a platelet count of 10 $\times$ 10^9/L.

peutic intervention as the best course of treatment in this case, citing the American Society of Hematology practice guidelines on ITP.[5]

Rationale

Dr. Tarantino's rationale was that pharmacotherapy prevents life-threatening hemorrhage. He cited data indicating that pharmacotherapy increases the rate at which platelet counts rise[6–9]; in turn, increasing the rate at which the platelet count rises may decrease the risk of morbidity and mortality.

Dr. Tarantino then focused on the cost benefits of treatment by stating, "the cost of one intracerebral hemorrhage from ITP is far greater than the cost of treating every child with a platelet count less than 20×10^9/L." To support his hypothesis, Dr. Tarantino compared the cost of Ig treatment (IVIG or anti-D) versus reassurance without drug therapy. He reviewed his analysis of data collected in the Nationwide Inpatient Sample (NIS),[10] which was developed by the Healthcare Cost and Utilization Project (HCUP), sponsored by the Agency for Healthcare Research and Quality (AHRQ). The NIS database, containing information regarding 7 million hospital admissions from 1987 to 1997, was assembled based on outcomes from diagnostic coding. Analysis of the NIS database indicated that of almost 5,000 patients with a primary diagnosis of ITP, those treated with either anti-D or IVIG had a significantly lower frequency of intracerebral hemorrhage (ICH; 0% vs. 0.5%) and other major bleeding episodes, decreased lengths of hospital stay, and lower hospital charges versus the group who received reassurance without drug therapy or who received oral corticosteroids.[10]

Thus, although pharmacotherapy may be perceived as costly, if it can reduce the number of patients who experience ICH, it saves money compared with the costly treatment necessary when a patient has an ICH. Using the data from the NIS sample and assuming a 5-year-old patient lived to age 75 by avoiding a fatal ICH, the estimated cost per potential year of life saved was calculated to be $4,792 or $4,982 (for using one dose of IVIG, 0.8 g/kg, or anti-D, 50 μg/kg, respectively).[10] These estimates are well within the range of socially acceptable cost-effective therapies. The limitations of the database, however, include the potential for diagnosis and procedure coding errors and the limitation of the data to hospitalized patients. Over the past decade, a substantial number of children with ITP have been treated or observed as outpatients. Including outpatients with uncomplicated ITP in this analysis would decrease the frequency of ICH, perhaps by 30% to 40%, still short of obviating the apparent cost-effectiveness of Ig treatment.

Conclusions

Dr. Tarantino concluded that considering the cost of short- and long-term ICH treatment, litigation, and lost productivity, it is more cost-effective to treat children with ITP than to withhold pharmacotherapy. Of the pharmacotherapies available, the most cost-effective treatments are low-dose IVIG and anti-D.[10]

CASE 3

The case study chosen by George R. Buchanan, M.D., involved a 10-year-old boy who had an upper respiratory infection 10 days prior to the onset of mild symptoms of ITP (Fig. 3). The patient's platelet count was 5×10^9/L. In exploring the treatment recommendations for this case, Dr. Buchanan focused on the idea that one should "treat the child, not the platelet count." He stressed that the risks and benefits of an initial management plan must be weighed for the individual patient and his or her family before a course of action is taken.

Rationale

To address the risk/benefit issue, Dr. Buchanan presented several treatment scenarios for this patient. The treatment regimens were reassurance, education, and observation without drug therapy; oral prednisone therapy; IVIG treatment; and anti-D immunoglobulin treatment. When asked whether the potential benefits of drug therapy usually outweigh the risks, 55% of the audience responded yes and 45% responded no.

In each of these treatment schemes, it was assumed that the patient eventually entered a remission. In this case, the reassurance and observation scenario was adopted and indeed, 1 week later, the platelet count was up to 8×10^9/L and fewer new bruises and petechiae were present. Within 2 months the platelet count had returned to over 200×10^9/L. Had pharmacotherapy been used, the outcome would have been essentially the same, except that bruising and petechiae may have resolved slightly faster.[8]

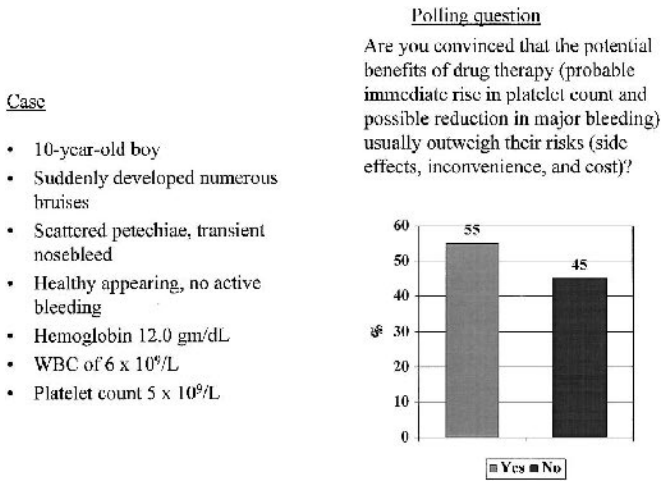

FIGURE 3. Polling question: Do potential benefits of drug therapy usually outweigh their risks?

Although the outcomes of different treatment strategies are often similar, Dr. Buchanan draws attention to the fact that when the reassurance and observation approach is used, the patient is not exposed to the risks of the side effects associated with the various pharmacotherapies. For example, when oral prednisone is chosen as the course of treatment, patients commonly experience one or more side effects such as irritability, hyperactivity, insomnia, hyperphagia, abdominal pain, and in rare cases diabetes, gastric ulceration, and hypertension with encephalopathy.

When IVIG is administered, the child must deal with quality-of-life issues, such as spending 2 days in the hospital or outpatient clinic. In addition, common side effects include nausea, vomiting, and severe headache, as well as the more rarely seen anaphylaxis, renal failure, and thrombosis. Similarly, with the administration of anti-D, patients commonly experience chills, nausea, vomiting, fever, and back pain, and in rare cases intravascular hemolysis, renal failure, and even death.[11]

Other risks and disadvantages of drug therapies include the discomfort and inconvenience of administering the drug, the high cost of treatment, and the eventual recurrence of thrombocytopenia. It is also possible that quality of life could be diminished (e.g., due to inconvenience and side effects) and that life-threatening or fatal complications may result.

Despite these side effect profiles, certain benefits of pharmacotherapies must be considered when making the decision whether to use drug therapy. For instance, it has been demonstrated that drug therapy transiently increases the platelet count. Pharmacotherapies may also potentially prevent serious hemorrhage, thereby improving the quality of life for the patient by allowing the parents peace of mind regarding the condition and course of treatment.

Conclusions

Overall, Dr. Buchanan stressed the importance of treating the patient and not the platelet count. In his opinion, for most children diagnosed with ITP, the risks associated with drug therapy outweigh the potential benefits. He is therefore in favor of the reassurance, education, and observation without drug therapy strategy in most patients.

CASE 4

James B. Bussel, M.D., did not present a single case; rather, he presented data collected from a survey of ICH patients to better understand the typical ICH case and what factors may help physicians to discriminate between patients at high risk and at low risk for ICH. A summary of the preliminary data analysis from this survey (described below) is presented in Figure 4. The audience poll demonstrated that 71% of the attendees had experience involving a child with ITP who had an ICH, and 61% of those said this occurrence influenced their treatment of subsequent patients. This supported the need for a survey to identify patients at risk for ICH.

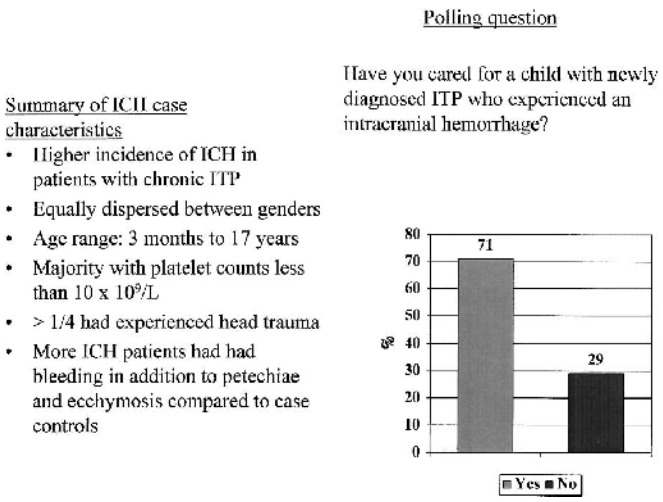

FIGURE 4. Polling question: Have you cared for a child with newly diagnosed ITP who experienced an intracranial hemorrhage?

Rationale

ICH is rare, but because it is the most important cause of mortality in children with ITP, it is important to be able to identify children who are at risk for ICH. To date, it has been difficult to identify predictors, modifying variables, and outcomes of ICH because cases fortunately do not occur commonly and therefore are scattered among different centers. The specific goals of the ICH study were designed to reliably identify those at risk. These goals were to explore ICH cases of pediatric ITP to determine the clinical characteristics of the population at risk; to determine whether patients at "high risk" of ICH can be distinguished from patients at "low risk" of ICH by use of a control group; and to examine the outcomes of ICH patients and what factors determine their outcome. Data collection in this survey consisted of mailings and phone calls to physicians in the ASPH/O and ASH directories during the years 1997 to 2001. For each patient with ITP who experienced ICH, two case controls were collected consisting of non-ICH patients with platelet counts less than 20×10^9/L.

The results in 39 patients are reported in the list of ICH case characteristics in Figure 4. Some of the notable trends observed included the relatively higher incidence of ICH in chronic than in acute ITP patients. In addition, more than 70% of the patients with ICH had platelet counts less than 10×10^9/L, and a number had experienced head trauma. Importantly, more than two thirds of the ICH patients had had bleeding symptoms beyond petechiae and ecchymoses, including wet purpura, epistaxis, hematuria, and heavy menses. Head trauma was reported in approximately 20% of the cases with ICH but in only one of the case controls.

Other interesting findings of the study were that there were no arteriovenous malformations confirmed in either the ICH or control group, and few patients were using nonsteroidal anti-inflammatory agents. The majority of patients reported having been treated with IVIG, steroids, or splenectomy prior to the occurrence of ICH. Of the 39 ICH patients, 17 died or experienced neurologic sequelae.

The study provides physicians with a starting point for identifying high- versus low-risk cases and determining which patients should be candidates for drug therapy that may prevent ICH. These patients would have bleeding in addition to petechiae and ecchymoses or a clear history of head trauma. Based on the results in this survey, approximately 90% of the ICH patients would have been identified using these two criteria and approximately 30% to 40% of the controls would have been thought to be at high risk. From the perspective of ITP treatment, these results are crucial in helping to identify the patients for whom pharmacotherapy should be encouraged, and the patients for whom it should be pursued vigorously.

Dr. Bussel then pointed out that newer treatments for ITP may alter the management of chronic ITP, citing a study using rituximab to control platelet levels in adults. Dr. Bussel showed data compiled from more than 50 adults with chronic ITP on rituximab therapy. Of the responders, whose platelet counts reached 50 to 150 × 10^9 but not the normal range, the majority relapsed by 6 to 12 months. However, of the 18 patients who reached platelet counts above 150 × 10^9, 16 were still in remission more than 1 year after their initial treatment.

Conclusions

From these trends, Dr. Bussel assembled a potential treatment algorithm for management of ITP. He recommends an initial evaluation to discriminate between high- and low-risk cases for ICH. Once a patient is determined to be at high risk, Dr. Bussel suggests aggressive treatment, including possibly a combination of drug therapies including IVIG, anti-D, and oral steroids to rapidly increase the platelet count. For lower-risk patients, the decision to treat with pharmacotherapy should be made on an individual basis.

DISCUSSION

Following are the highlights from the audience and panel discussion portion of the symposium after the faculty presentations.

Is bone marrow aspiration mandatory prior to treatment? Dr. Buchanan stated that if the patient was to be treated with steroids, the majority of experts still recommend a bone marrow aspiration prior to beginning treatment.[3] If steroids are not to be used and the symptoms, signs, and blood counts, including analysis of the peripheral blood smear, are characteristic for ITP, then a bone marrow aspiration is not necessary. Dr. Bolton-Maggs agreed and stated that the bone marrow aspiration does not confirm the diagnosis but only excludes other causes. An audience member added that although these are sufficient guidelines for hematologists/oncologists to follow, pediatricians who are not as experienced in this specialty and are less likely to recognize subtleties of the differential diagnosis between ITP and acute lymphoblastic leukemia should still consider a bone marrow aspiration.

A member of the audience raised the issue of informed consent related to management strategy. He stressed the utmost importance of informing parents about the controversy in choosing whether to treat ITP with pharmacotherapy and providing them with information regarding side effects prior to deciding on the treatment course. Dr. Bolton-Maggs was in absolute agreement and added that because of the complicated nature of the decision, the person who discusses these issues with the parents should be a senior staff member who knows how to properly present the information and educate them, rather than a junior doctor.

The panel debated the issue of steroid doses and regimens, comparing a long course of treatment with low-dose steroids, which is generally undesirable, to higher-dose steroids (e.g., 3–4 mg/kg prednisone) for a short duration (3–4 days). Dr. Buchanan uses a higher-dose regimen (4 mg/kg for 4–7 days) when he believes that treatment is indicated and finds that the platelet count seems to rise more rapidly.[12] However, he often observes rebound thrombocytopenia after treatment is discontinued. In general, due to the lack of comparative studies between the varying doses of prednisone, it has not been conclusively determined whether one regimen is more effective than another.

An audience member asked if it is possible to predict some of the patients who will be at risk for excessive bleeding by investigating whether patients have underlying platelet disorders (e.g., von Willebrand disease) or a history of other mild bleeding or coagulation disorders. Dr. Buchanan stated he believes that children with ITP may have other subtle abnormalities, either genetic or acquired, that may influence the extent of bleeding. However, he suggested that a more practical clinical tool to address this might be the use of a bleeding scoring system, based on the extent of a hemorrhage from the skin, nose, mouth, and other sites. This type of system would measure grades of hemorrhage in a manner analogous to the measurement of a toxicity grade for an oncology patient.[13] Dr. Bussel pointed out that none of the ICH cases had any history of other bleeding tendencies identified that might have contributed to their ICH.

Audience feedback was an excellent indicator of the current opinions about management of ITP at diagnosis. For instance, when polled, 95% of the attendees said that when considering management options for a child with newly diagnosed ITP, the platelet count (and not the degree of clinical bleeding) was the most important variable in their decision-making. More than 80% of the audience said they would find a semi-quantitative bleeding score system useful in assessing hemor-

rhage, independent of the platelet count. Overall, the majority (65%) of the audience felt that drug treatment reduces the possibility of ICH.

CONCLUSIONS

Throughout the discussion, audience members expressed their interest in and concern about the decision to treat with pharmacotherapy or use patient education and monitoring. To get a general idea whether the audience members were affected by the presentations and debate that took place, the results of a poll regarding an identical case presented at the beginning and again at the end of the program were compared. At both times, the majority of the attendees chose pharmacotherapy (70% at start of program and 58% at close of program) rather than the strategy of watch and wait with education and monitoring for this child. However, at the close of the program more attendees chose education and monitoring without pharmacotherapy (42%) than at the beginning (30%) (Fig. 5).

This informative discussion emphasized the need for clinical trials comparing different management strategies, with endpoints measuring the frequency of mortality and morbidity from bleeding and the frequency of side effects from treatment. Such a study would require instruments that can quantitatively assess bleeding outcomes and quality of life of the child and the parents.[13]

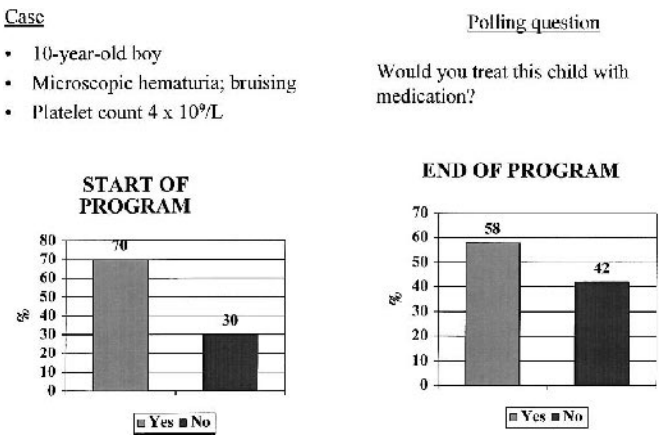

FIGURE 5. Polling question: Initial management of a 10-year-old boy with purpura and a platelet count of 4×10^9/L; comparison of votes at the start and end of the program.

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