Initial management of immune thrombocytopenic purpura in children: Is supportive counseling without therapeutic intervention sufficient?

In this issue of The Journal, Dickerhoff and von Ruecker[1] describe their 7-year experience with 55 consecutive children presenting with a new diagnosis of immune thrombocytopenic purpura. The consistent management for all children was supportive care, beginning with a thorough discussion with the patient, parents, and teachers. Only 4 children received specific treatment—a 3-day course of prednisone only. The important conclusion of these observations is that the children did well; none had major bleeding, and there were no deaths.

Why is this important? Because, in spite of the simplicity and success of this approach, the management strategy of Dickerhoff and von Ruecker is very different from the usual practice in both the United States and the United Kingdom. In the United States over 85% of children[2] and in the United Kingdom 60% of children[3] with ITP are treated with intravenously administered immune globulin or steroids. Dickerhoff and von Ruecker began their study before the publication of the American Society of Hematology practice guidelines on ITP were published[4]; now, they state, their practice of only supportive care may be more difficult because the ASH ITP guidelines "have put many physicians under pressure to treat."[1] How did this dilemma evolve? How can it be resolved?

See related article, p 629.

Although I do not treat children with ITP, I have become immersed in the polarizing issue of their appropriate management. My experience is with the treatment of adults with ITP, in whom there is no controversy about initial treatment. In adults a spontaneous remission is not expected, and therefore initial treatment with glucocorticoids is universal when thrombocytopenia is severe and symptomatic. My involvement with the issues of ITP in children began 6 years ago when I accepted the responsibility of organizing a panel to develop a practice guideline on ITP for ASH. I felt comfortable with the topic of ITP; I knew nothing about practice guidelines. I did not appreciate what impact this document would have. The important conclusion of this project was to emphasize the lack of rigorous clinical trial data on which to base recommendations for the care of patients with ITP, affecting virtually every decision a clinician commonly encounters.[5] Having come to this realization, the panel resolved to describe the state of the literature, emphasizing the absence of evidence and the limitations of opinion-based recommendations, and to issue recommendations based on an explicit method of assessing opinion that clearly documented the strength and variance of opinion. Our document was published in 1996[4]; it has become one of *Blood*'s most cited articles, and it has been described as a model for guideline methodology.[6]

From this experience, I learned how polarized the opinions were regarding initial management of children with acute ITP. Although initial treatment of children was one of the very few areas in the ITP literature with evidence from excellent randomized clinical trials (eg, the study by Blanchette et al[7]), the opinions on the appropriateness of specific treatment ranged to both extremes. One panel member thought it was appropriate to offer no specific treatment for a child with a new diagnosis of ITP, a platelet count <10,000/μL, and minor purpura; 4 other panel members thought this practice was inappropriate. So striking was this discrepancy that I chose the panel votes on this question both to illustrate our method of objectively assessing opinion and to emphasize the extreme range of opinions on this clinical scenario. I hoped that this would temper the guideline recommendation that stated that these children should be treated with IVIG or glucocorticoid.

ASH	American Society for Hematology
ITP	Immune thrombocytopenic purpura
IVIG	Intravenously administered immune globulin

This recommendation triggered the most criticism of this document. The only letters published in response to the ITP guideline, from a respected group of American pediatric hematologists[8] and from a representative of the UK pediatric ITP guidelines,[9] strongly disagreed with this recommendation. The guidelines of the British Pediatric

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Hematology Group had previously recommended that "for children presenting with bruising only, without mucosal or more severe hemorrhage, no treatment at all is perfectly reasonable" regardless of the platelet count.[10]

Although randomized clinical trials have clearly demonstrated that the platelet count increases more rapidly with treatment (IVIG or glucocorticoid) than with no specific treatment,[7] the clinical importance of more rapidly increasing the platelet count remains unresolved. With treatment, is major bleeding prevented and survival increased? We do not know. Clinical outcomes of bleeding were not assessed in this[7] and similar studies. A review of 820 children in 13 clinical trials noted that the only death from bleeding occurred in a child who had been treated with IVIG.[11] Therefore although it is accepted that treatment causes more prompt recovery of the platelet count, a clinically important benefit of specific treatment remains unproven.

If specific treatment with steroids or IVIG causes the platelet count to increase more rapidly, then why not treat all children who have severe thrombocytopenia? The case for treatment was stated in an editorial in The Journal last year by Dr Diane Nugent[12]: the small but finite risk of intracerebral hemorrhage, anxiety of parents and referring physicians, and physician liability issues.

The case for no specific treatment, providing only counseling and supportive care, is supported not only by the results of Dickerhoff and von Ruecker[1] but also by the expense and complications of treatment. Many children treated with IVIG have headache and vomiting, often provoking alarm and diagnostic studies for intracerebral bleeding or meningitis.[7,13] Also, it is unclear whether treatment actually prevents the rare occurrence of major bleeding and death from bleeding. Children with severe bleeding may be those whose ITP is refractory to treatment.[11,14]

This issue, to treat or not to treat, has reached a position described as "clinical equipoise."[15] The benefits and harms on both sides of this debate appear to be balanced. Resolution can only be achieved by a randomized trial that measures clinical outcomes, as well as platelet count increments. Clinical outcomes must include quality-of-life measurements for parents, as well as for patients, in addition to objective assessment of bleeding. Quality of life may be better without treatment, avoiding complications of IVIG and steroids, or it may be better with treatment because of the comfort from doing everything possible to avoid catastrophic bleeding.

The outcome of a clinical trial with children randomly assigned to either a standard intervention (steroids or IVIG) or supportive care would have major implications for pediatric practice. If there were no differences in clinical outcomes with the 2 different management strategies, pediatricians would have strong support for withholding specific treatment. An advantage of this strategy, apparent from the experience of Dickerhoff and von Ruecker,[1] would be the emphasis on counseling and careful follow-up—an "intervention" not to be underestimated. Of course, this clinical trial would be difficult to design, manage, and support because there would be no incentive for corporate support, as there is in many intervention trials. But if there is support in the pediatric community, the issues of how to do such an important study can be solved.

Perhaps the ASH ITP guideline has helped to stimulate the reporting of opposing views[1,3,8,9,11] and has created the environment in which a clinical trial can provide a definitive resolution for this dilemma.

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