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Matzdorff, Alex; Neufeld, Ellis J.; Roganović, Jelena

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To Treat or Not To Treat—From Guidelines to Individualized Patient Management

Axel Matzdorff,[a] Ellis J. Neufeld,[b] and Jelena Roganovic[c]

Immune thrombocytopenia (ITP) is a rare disorder. Evidence-based guidelines provide important information for hematologists, as well as diagnostic and therapeutic recommendations to other physicians with limited expertise in the field. However, guidelines in pediatric and adult ITP do not answer some imperative questions: which patient is at risk of severe bleeding and requires pharmacologic treatment? Who will recover spontaneously? Is splenectomy still an appropriate second-line treatment for all chronic or persistent ITP patients? This review summarizes the current approach to these important issues, the patients' perspective, and how we can improve individual patient management.
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Immune thrombocytopenia (ITP) is rare with an incidence ranging from 1.6-3.9 per 100,000 persons per year.[1] The average pediatrician or internal medicine doctor will see only a handful of cases during the professional lifetime. Therefore, personal experience with ITP care is often limited. To address the need for more information and recommendations, the American Society of Hematology (ASH) established an expert panel in 1994 and eventually published the 1996 ASH practice guideline.[2] Although since that time there have been important publications on standardizing the terminology and definitions of ITP, as well as on the investigation and the treatment of the disease, this guideline is still one of the most cited articles in the field.

The need for more information was not limited to physicians. In 1995 the ITP Support Association was founded in the United Kingdom by Shirley Watson whose son had ITP. The Platelet Disorder Support Association (PDSA) started in the United States in 1997 as an internet platform to exchange information among patients. In 2003 the first patient representative coauthored the British ITP guideline.[3] Patient-reported outcomes (PROs) started to provide information from the patient's perspective. Health-related quality of life (HRQoL) measures as the most commonly assessed PRO in clinical research thus became very useful components for evaluating and understanding the effects of disease and medications from the patients' perspective.

The advent of rituximab at the end of the 1990s and thrombopoietin receptor agonists in the last decade generated interest in the clinical community and changed the situation. The high costs of these drugs threatened to limit financial resources either of the individual patient or the public health care systems. At the same time, introduction of new drugs prompted activities to revise existing recommendations. During the last years several updates have been published, the most relevant being the international consensus report on the investigation and management of primary ITP in 2010[4] and the new ASH 2011 evidence-based practice guideline for ITP.[5] Many patients feel that these publications primarily address clinicians' needs and do not reflect the impact of the disease and treatments on their daily life. This is perceived as a growing gap between academic medicine and treatment reality. There is an unmet need for a more individualized patient approach. Which patient is really at risk of severe bleeding and requires pharmacologic treatment? Who will recover spontaneously and could be treated with observation alone? Is splenectomy still a proper second-line treatment for all chronic patients unresponsive to initial measures?

[a]Caritasclinic Saarbruecken, Saarbruecken, Germany.
[b]Division of Hematology/Oncology, Boston Children's Hospital and Harvard Medical School, Boston, MA.
[c]Department of Hematology and Oncology, University Children's Hospital Rijeka, Rijeka, Croatia.
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Address correspondence to Axel Matzdorff, MD, PhD, Caritasclinic Saarbruecken, Rheinstrasse 2, 66113 Saarbruecken, Germany. E-mail: a.matzdorff@caritasklinikum.de
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Table 1. Eight Countries With Experts Present at the Subgroup Meeting on Individualized Management Approaches in ITP

- Argentina
- Croatia
- Germany
- Israel
- Italy
- Netherlands
- Patient Support Group (PDSA–US)
- United States (Brooklyn, Boston, Augusta, Dallas)

In September 2012 a group of ITP specialists from nearly 20 different countries came together at the 4th International Cooperative ITP Study Group (ICIS) Expert Meeting in Montreux, Switzerland. A subgroup representing eight countries discussed ''individualized patient care'' (Table 1). The group discussed different subjects from basic science to daily care, relating to the questions posed above, as well as variations in treatment practice from center to center (Table 2). This article provides a summary from the symposium on individualized patient management.

THERE ARE MORE THINGS IN HEAVEN AND EARTH THAN CAN BE DREAMT OF—SPONTANEOUS RECOVERY IN ITP

A newly diagnosed ITP patient with significant bleeding is a clear indication for first-line treatment. But what about the patient with a very low platelet count and absent or only minor bleeding? One third of adult ITP patients are completely asymptomatic and diagnosed by chance during a work-up for other medical problems.[6] Only 3% of children with ITP have clinically significant manifestations such as severe epistaxis or gastrointestinal bleeding.[7] Can one wait for spontaneous remission in asymptomatic or oligosymptomatic patient?

The first-line treatment has never been shown to avert the development of chronic ITP or reduce morbidity during follow-up. Nevertheless, to date most newly diagnosed ITP patients receive treatment with corticosteroids or intravenous immunoglobulins (IVIg) irrespective of severity of hemorrhage and only because their platelet counts are low. The approaches to an asymptomatic or oligosymptomatic child and adult vary from country to country, among institutions within a country, and sometimes even among experts in one institution. Moreover, the same clinician can make different decisions depending on the day of the week, with a higher likelihood to treat a patient on weekends when experienced senior physicians are not ''right

Table 2. Subjects Discussed at the Subgroup Meeting

Given the available data and published guidelines:
- What do we actually do for our patients?
- What should we do?
- What do our patients want?

Initial management:
- Corticosteroids for all?
- What considerations should be taken into account in deciding upon initial therapy?

Strategies when the initial management is not working:
- Which second-line agent?
- Is ''observation only'' an option?

What should a next round of guidelines address?
- What necessary studies remain undone?
- What shortcomings arise in strict adherence to evidence-based guidelines?
- When there are no data on certain clinical problems, should guidelines refrain from giving recommendations or are opinional statements appropriate?
- What is the future role of patient support groups in guideline writing?
- What is the future role of physicians: stewards of their patients or of healthcare resources?

What are the best ways forward?
- Collaborations/consortia working in parallel
- Will standardized clinical assessment and management plans (SCAMPs) prove to be a helpful tool?

next door.'' Fear of litigation may also influence these decisions in some healthcare systems. Children with ITP have an excellent prognosis, with 80% of patients recovering completely within 6 months. The remission in pediatric ITP correlates with sudden onset of disease and younger age, and is not correlated with the treatment.[8] Spontaneous remissions in adults with ITP do occur too, although they are much less common compared with children. The true remission rate is not known, because most adult patients are promptly treated with glucocorticoids. There is evidence that a great proportion of ITP adults achieve remission even without splenectomy, 30% of them within the first 6 months increasing up to 53% three years after diagnosis.[9] The 2011 ASH guideline recommends longer courses of corticosteroids over shorter courses or IVIg as first-line treatment based on the results of one study.[5,10] Considering adverse effects of long-term corticosteroids, it would be extremely helpful to have some easily accessible criteria to identify patients who will recover spontaneously and spare them unnecessary toxicities.

COME, YOU SPIRITS! MAKE THICK MY BLOOD!—WHICH PATIENT IS AT RISK OF BLEEDING?

The primary anxiety of all ITP patients, parents, and treaters, is severe bleeding, with intracranial hemorrhage being the most feared complication. Platelet count is widely used as a surrogate marker for bleeding risk because the risk for severe bleeding increases when the platelet count drops below 10,000/μL.[11] Several bleeding scores have been designed for objective quantification of bleeding symptoms, mostly for pediatric patients.[12-15] They were never commonly integrated in clinical practice for various reasons, including complexity and time required for completion. Risk factors for intracerebral bleeding in children with severe ITP include head trauma and concomitant use of medications that adversely affect platelet function. It still remains questionable whether the severity of mucocutaneous bleeding really predicts the risk for life-threatening bleeding. In adults, intracranial hemorrhage may be a more common complication of ITP than previously appreciated, with the cumulative incidence being 2.67% in recent large cohort study.[16] Increasing age, low platelet count, and certain medical co-morbidities but not mucocutaneous bleeding could be correlated with severe bleeds.[17,18]

The 1996 ASH guideline panel considered it inappropriate to withhold treatment even at the patient's request if the platelet count was $<20{,}000/\mu L$. This was a fairly strong statement considering the absence of any evidence. Not a few patients ended up with high-dose corticosteroids for very long time according to this recommendation. The 2009 International Consensus Statement[4] acknowledged this, conceding that it would be acceptable to live with low platelet counts foregoing further toxic treatments as long as patients have no or only very mild bleeding and near normal quality of life. Then the 2011 ASH guideline authors had only minor changes from 1996, reintroducing the platelet count in treatment decisions, because the ''majority of clinicians use threshold of $<30{,}000$ as a trigger for treatment, and they find no evidence to contradict this practice.''[5] Can we do better? There is an urgent need to identify patients at risk of severe bleeding and spare all others corticosteroid-related toxicities.[19]

TRUE APOTHECARY. THY DRUGS ARE QUICK.—TOO MUCH STEROIDS FOR TOO LONG TIME

William Osler wrote: the desire to take medicine is perhaps the greatest feature which distinguishes man from animals. Osler may have been wrong. ITP patients do not like their medications and particularly dislike corticosteroids. Despite this aversion, between 90% and 100% of adult patients have received or receive corticosteroids during the course of their disease, many for prolonged periods.[20–22] The 2011 ASH guideline supports prolonged use of corticosteroids as first-line treatment over shorter courses. Treatment guidelines discuss side effects but put much emphasis on hypertension, hyperglycemia, cataracts, and osteoporosis. Instead, the side effects most bothersome to patients receiving prednisone and dexamethasone are weight gain, increased appetite, changes in personality, mood or emotions, ''moon face'' or puffy cheeks, bloating, swelling, and sleep disturbances. Children often experience hyperactivity. Patients rank treatment-bother with corticosteroids higher than with any other ITP therapy.[23,24] There is no treatment for moon face. It is not surprising that in one survey many patients stated that they had feeling their doctors did not know enough about ITP and its impact on their quality of life.[25] In another study, 59% of patients responded that they felt their physicians often paid an appropriate amount of attention to their corticosteroid side effects. However, the differences between patients' and hematologists' perception of the number and severity of corticosteroid side effects experienced by ITP patients suggest that communication may be improved.[26] Almost 50% of patients are not satisfied with traditional therapy and turn to complementary and alternative medicines (CAMs).[19,22]

THE PEACE IS THEIRS THAT LIFT THEIR SWORDS!—SPLENECTOMY

The first report of a successful therapy for ITP was in 1916, when a young Polish medical student, Paul Kaznelson, described a female patient responding to splenectomy. Splenectomy remained up-front treatment until the introduction of corticosteroids in the 1950s. It was the standard second-line treatment in the 1996 ASH guideline and in 2011 still receives a strong recommendation for patients who have failed initial therapy. But in contrast to expert recommendations, most patients do not undergo splenectomy. Most of them who accept it perceive their disease as having a negative impact on their quality of life, whereas patients who refuse it feel their situation is not severe enough to warrant surgery. Studies on new thrombopoetin receptor agonists in chronic ITP show that to date only about 30% of patients had undergone splenectomy. Considering a sustained response rate of approximately 70% with splenectomy, physicians might perceive patients' fear as irrational. What it really reflects is that all ITP patients have been told from the first day to avoid activities where injuries are likely if they don't want to ''bleed to death.'' It is therefore coherent that they try to avoid any invasive procedure, including splenectomy. With the availability of new effective agents and in the light of the one-third long-term failure rate of splenectomy, the desire to postpone or even avoid it becomes understandable. We urgently need guidance on which patients have a clear indication for splenectomy and which not.[27]

ET TU, BRUTE?—THE CHARACTER OF MEDICINE HAS CHANGED

With the advent of rituximab and thrombopoietin receptor agonists, many chronic ITP patients voiced the legitimate desire to use these new agents before splenectomy. In the absence of randomized studies this was supported by opinioned statements of many experts in the field.[28-31] However, it did not affect licensure status. Rituximab is still off-label. Sustained remission rates with rituximab are disappointing. Thrombopoietin receptor agonists are restricted to adult patients at risk of bleeding who relapse after splenectomy or have a contraindication to splenectomy and have failed another therapy. The high response rates have been reported in randomized trials of refractory post-splenectomy patients treated with thrombopoetin mimetics. How could we provide clinical data for a more logical treatment algorithm? The persistent support for splenectomy as second-line treatment in the International Consensus Statement and the 2011 ASH guideline has the smack that cost may have influenced this decision. Splenectomy is much cheaper than thrombopoetin receptor agonists. The authors of the International Consensus Report openly admitted that their recommendations were influenced by cost considerations.[4] Although high costs of modern drugs could limit their availability, it seems like physicians have accepted their role as stewards of the healthcare system. It is not surprising that self-support groups have become very attractive for ITP patients.

THE HEART OF HEARTS—WHAT NEEDS TO BE ADDRESSED IN FUTURE GUIDELINES

The foundation of self support groups in the 1990s in the United Kingdom and the United States, and thereafter in many other countries, reflects the growing gap between academic medicine and treatment reality. Many patients turn to CAMs outside the system of traditional and school medicine. Surveys show that almost half of the patients try CAMs at some time during their course of disease.[20–22] Besides bleeding risk, splenectomy and limited access to new agents, there are more problems confronted by our patients: fatigue; effect of the disease on occupation, lifestyle activities, and families; and health insurance problems. None of these has been addressed in the current guidelines. The absence of data should not justify the absence of expert opinion. It is a legitimate request of our patients to get answers to these pressing questions.[32] Each expert has his personal approach to these problems. Larger institutions have an opportunity to combine their experience using SCAMPs, which are flexible, outcomes-based practice guidelines that allow for variation from written management strategies, but clinicians must explain their reasons for variation, and iteratively the management plans can be changed.[33]

ITP has a very long history. The first reports date back to the 16th and 17th centuries. It was German physician and poet Paul Gottlieb Werlhof who wrote in 1735 the most complete initial report of purpura of ITP.[34] More than 50 years ago Jeanne Lusher, the doyenne of pediatric ITP, wrote that we should treat the patient, not the platelet count.[35] Has anybody listened? We still treat patients who may not need treatment with medications they dislike to achieve goals that do not mean very much. A wide variety of controversial studies and review articles are being published. We can do better. The following articles on splenectomy,[27] bleeding risk,[19] and spontaneous recovery[36] will highlight current knowledge and how we can improve. If in 10 years a new expert panel convenes again to provide consensus-based recommendations on ITP, then it should address the

perspectives of all involved in the field, including physicians, the healthcare system, and patients.

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