Chronic Immune Thrombocytopenia in Children: Who Needs Splenectomy?

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In the field of emerging innovative therapies, such as thrombopoietin mimetics, the question of who needs splenectomy remains highly relevant. Removal of the spleen is an accepted and potentially curative treatment of immune thrombocytopenia (ITP) after decades with a favorable economical-effect ratio but with relevant morbidity particularly in the young patients. ITP is rare and splenectomy is performed in a minority of children, which makes its research almost impossible, resulting in a poor standardization of the procedure. Hence, in children, recommendation and decision for splenectomy is individually based and rests on expert opinions. Furthermore, local practice and availability of health products affect the frequency of splenectomy. Current guidelines agree on one point: splenectomy should be postponed for at least 12 months after the initial diagnosis of ITP, due to the high probability of improvement or even spontaneous remission. However, evidence-based data are lacking and splenectomy remains controversial. This article reviews the current literature and delineates controversies and complexities of splenectomy in children with ITP. There is an urgent need for consensus of this procedure in pediatric patients.
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In the early 1900s, Paul Kaznelson, a medical student in Prague, presumed that the excessive destruction of the platelets occurs in the spleen. He convinced his tutor to perform a splenectomy on a woman with chronic immune thrombocytopenia (ITP). The successful intervention represented the beginning of an established treatment for patients with ITP.

Splenectomy is an efficient and cost-effective procedure to overcome the premature destructions of platelets in chronic ITP. Long-term remission is achieved in more than two thirds of adults[1] and children,[2] with a probably low risk of short-and long-term severe adverse events as compared to splenectomy for other benign hematologic disorders.[3,4] However, in many pediatric cases the benefit of splenectomy does not overcome its disadvantages, because of the low risk of life-threatening bleeding in ITP, the potential of spontaneous improvement or even recovery in 26%–44% of chronic ITP cases,[5,6] the immediate risks of surgery, the long-term risks of overwhelming sepsis especially in the young, and the burden of splenectomized individuals, including administration of oral antibiotics, vaccinations, and medical interventions in case of fever. In a retrospective analysis of 270 children with chronic ITP, defined by a duration of more than >6 months, Bansal et al estimated predicted spontaneous remission rates of 30% and 44% at 5 and 10 years, respectively. The probability of remission was higher in children <8 years of age (51.2% at 10 years) and girls (39.6% at 5 years).[6]

Although bleedings are mostly benign,[7] the recommendations of restrictions in daily social activities represent a major problem. Severe bleedings are very rare[6,8]; still, the fear of serious hemorrhages can considerably disturb the quality of life of patients and their families, resulting in the strong desire for platelet-enhancing treatment.

There is no gold standard for the management of children with chronic and clinically severe or refractory ITP. Several guidelines are available with the aim to guide the physician as to when, how, and to whom to propose splenectomy. The therapy strategies (wait and see, immunosuppression, immunomodulation, and splenectomy) are often decided on an individual basis and on institutional experience. The Intercontinental Cooperative ITP Study Group (ICIS) developed a

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Table 1. National and International Guidelines for Splenctomy

ASH guidelines (1996)[30]	SE should be performed for children 3–12 years with disease duration >12 months who have bleeding symptoms and a PC of <10,000/μL. For children >8 years: PC of 10,000–30,000/ μL
ASH guidelines for children and adolescents (2011)[31]	SE should be performed in patients with chronic/ persistent ITP who have significant or persistent bleeding, and lack of responsiveness or intolerance of other therapies and/or who have a need for improved QOL. If possible it should be delayed for at least 12 months.
The British Society of Hematology (2003)[33]	SE is occasionally justified for life-threatening bleeding and for children with unremitting and severe ITP in whom the disease has been present for 12–24 months with demonstrable impairment of their QOL, but these children are rare, and should be referred to a specialist pediatric hematologist for individual consideration.
The International Guidelines (2010)[32]	SE is rarely recommended in children because the risk of death from ITP in childhood is extremely low (<0.5%). However the panel agrees that SE is an effective treatment for pediatric ITP

Abbreviations: SE, splenectomy; PC, platelet count, QOL, quality of life.

Splenectomy Registry in 1997 to observe and describe the management modalities of children with ITP in different institutions. The ICIS showed major differences in indication and management of splenectomy, reflecting the lack of evidence and consensus.[2]

Thus the question ''who needs splenectomy?'' remains unanswered and will be the focus of this review.

DEFINITIONS

According to the Vicenza Consensus Conference,[9] chronic ITP was defined by duration of more than 12 months and platelet count of $<100 \times 10^9$/L; persistent ITP corresponds to ITP of 3–12 months.

CURRENT RECOMMENDATIONS

In adults, splenectomy was for many years a cornerstone therapy for patients with chronic ITP and the sole therapy with proven long-lasting effect. In the last few years, thrombopoeitin-analogs (TPO-mimetics), eg, romiplostim and eltrombopag, showed relevant beneficial results regarding platelet count, bleeding events, and quality of life[10,11] along with favorable side effect profiles. Nevertheless, splenectomy will probably continue to maintain the status of an established therapy option for various reasons, including costs, compliance, long-term safety, and the potential to cure ITP. It should be noted that the indication criteria in the European Union stipulate that splenectomy must have been unsuccessful or is contraindicated to order one of these drugs. In the United States, the Food and Drug Administration is not as strict and recommends the therapy for patients with insufficient response to drugs or splenectomy.

The ICIS recommends that children with newly diagnosed ITP and without significant bleeding may not require therapy regardless of their platelet count. For the minority of patients with bleedings, the first-line therapy includes intravenous immunoglobulin (IVIG) or corticosteroids. Second-line therapy is not established and includes pulsed dexamethasone, rituximab, TPO-mimetics, and splenectomy. Current guidelines are presented in Table 1.

EFFICACY OF THE PROCEDURE

The rationale of splenectomy is the eradication of a major part of the mononuclear phagocytic system mediating destruction of platelets and a primary source of auto-antibody production. Unlike drug therapies it represents a curative procedure. The efficacy of splenectomy in children seems to be even superior to that in adults although there are no comparative prospective studies.[1,12]

The five major retrospective studies in childhood are listed in Table 2. An interpretation of these results in order to predict the individual outcome is difficult, given the heterogeneity of the population, the various indication criteria, the different institutional guidelines and the differences in terminology of chronic or severe ITP. No randomized study comparing splenectomy with other interventions for a defined population is available so far.

PREDICTION OF SPLENECTOMY RESPONSE

About one third of splenectomized patients suffer complications or non-response. There is a strong