Clinical Research of Idiopathic Thrombocytopenic Purpura ITP by the Intercontinental Childhood ITP Study Group ICIS

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ITP is not satisfactorily defined concerning etiology, pathogenesis, clinical presentation, natural history, management, quality of life and economical aspects. ITP is fearful for the child and the parents/family although the risk of lifethreatening bleeding is low and unpredictable.

The pathophysiology of ITP is characterized by (postinfectious) disturbed immune response with (auto-)antibodies against platelets. Platelet associated antibodies sensitize the monocytic phagocytic system and platelets are early removed from circulation eventually resulting in thrombocytopenic bleeding. ITP presents in an acute, transient form mostly in children, in a chronic form mostly in adults – arbitrarily defined by longer duration than 6 months – or in a recurrent form. Spontaneous recovery, rapid disappearance of bleeding and increase of platelet counts after treatment in responding patients, or treatment refractory ITP are observed. Prediction of the natural course is difficult. Only few controlled prospective clinical studies exist[1, 2, 3, 4].

Approaches for definition and guidelines have been published since 1992 by various groups[5, 6, 7, 8]. Surveys[9, 10, 11] and assessments[12, 13] underline the diversities in presentation and management. Validation of scoring systems and guidelines are necessary.

6 YEARS EXPERIENCE OF ICIS

The impetus for organizing ICIS were the above mentioned heterogeneity of ITP.

In 1997 an unrestricted grant to the author supported the formation of a prospective, cooperative registry for prospective studies in ITP. The aim was to achieve more evidence-based data regarding different aspects of ITP.

After 6 years of experience, ICIS is now well-established worldwide. The first project, Registry I, included 2031 children with newly diagnosed ITP and has been published in Lancet (2001) [14]. Registry I provided important confirmatory evidence of the presenting features of ITP and demonstrated the significant variability in initial management of children with thrombocytopenia. New findings were the higher rate of boys versus girls (54,8 % versus 45,2 %) with newly diagnosed ITP on all continents and chronic ITP has been observed in 31 % of children in equal numbers of girls and boys. Subsequent projects included the prospective Splenectomy Registry, which was designed to evaluate the appropriate timing and the perioperative management of children with ITP who undergo splenectomy. The study is still going on. To date 132 evaluable patients are enrolled and preliminary analysis of the first 5 years of follow-up has been done with an abstract recently submitted [15]. Longterm results after splenectomy are needed in this group of children. ICIS Registry II is an ongoing investigation of the frequency, location, timing and severity of bleeding in children with newly diagnosed ITP. A first analysis of 531 children (as of July 2003) was recently performed (abstract submitted) [16]

The current goals for ICIS include defining a long-term concept of its structure and ongoing projects. Plans include organization of an **expert panel** to develop new definitions of the different aspects of ITP. In addition to the ICIS advisory board, which has representatives from many different countries,

Table 1. Scheme of Staging* and Management of ITP

Stage/ Bleeding	History/Symptoms*/Platelet Count	Management
I None	- No bleeding Platelet count above 20 x 10^9/L	- No drug intervention
II Mild	- Bruising, petechiae of skin - Occasional epistaxis - Little or no interference with daily living - Platelet counts above 10-20 x 10^9/L	- Reach individual consensus with patient/parents for watchful observation - Aim: normal life style without drug treatment - Intervention/prevention with regard to sport, events, surgery etc.
III Moderate	- Bruising, petechiae of skin - Some mucosal lesions - Troublesome epistaxis and hemorrhagiae - Platelet counts above 10 x 10^9/L	- Drug treatment in the presence of active bleeding - Aim: reach stage I or II
IV Severe	- Bleeding: Epistaxis, melena and/or hemorrhagia requiring hospitalization and/or transfusion - Serious interference with quality of life - Platelet counts below 10 x 10^9/L and/ or hemoglobin decrease over 2g/dL	- Drug treatment and eventually substitution of thrombocytes and/or erythrocytes

(*modified from Bolton-Maggs P., Moon I. [12])

and the central operative office in Basel, an expert panel will meet to propose new definitions and treatment guidelines in ITP. Examples of issues that are controversial and could be considered by such an expert panel include classification of bleeding symptoms, as is currently being proposed by PHB Bolton-Maggs [12] and investigated by G. Buchanan [16]. A summary of such a classification, together with related platelet counts and management guidelines is suggested in Table 1.

Other issues – provided by an international expert group - are

- the accurate definition when chronic ITP starts
- the exact rate of secondary ITP and of treatment refractory ITP
- the risk of severe bleeding
- prognostic factors (e.g. polimorphism)
- cultural and environmental/economical aspects worldwide
- patients and families quality of life
- evaluation of new treatment form

Another aim is the **cooperation of hematologists for adults and children** concerning chronic ITP. ICIS is planning a prospective database on both pediatric and adult patients with chronic ITP with long-term follow-up, named PARC-ITP Study. Since chronic ITP shows similarities in children and adults, a common database may be useful. The hypothesis of the PARC study is to find new selection criteria for future clinical trials concerning diagnosis, pathogenesis, severity, management and prognosis.The PARC study is designed for worldwide cooperation of investigators willing to register patients anonymously and to report data by the registry procedure similar to the Registry I [14].

To continue the prospective clinical investigation and registries using the current ICIS structure, new independent **financial support** has to be identified. **Rules** for participation in ICIS need to be adapted constantly and the cooperation must be regulated to maintain the integrity and quality of the data collected. Lessons learned from the Intercontinental Childhood ITP Study Group (ICIS) may provide a **basis for other similar organizations** for disorders which are relatively uncommon and for which clinical management is based primarily on anecdotal evidence, such as Thrombocytopenia absent radius syndrome (TAR), Wiskott-Aldrich Syndrome, Schönlein-Henoch Purpura and others.

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Note: Part of this article will be published in JPHO, Supplement of the State-of-the-Art Expert Meeeting onf ITP