## Idiopathic thrombocytopenic purpura: an old disease revisited in the era of evidence-based medicine

In 1735 P. G. Werlhof[1] first described, under the name of *Morbus Maculosus Hemorrhagicus,* a new disorder now identified as idiopathic thrombocytopenic purpura (ITP). This condition, often also known as immune thrombocytopenic purpura, is a primary, acquired disease of adults and children, characterized by a transient, self-limited (acute form) or persistent (chronic form) decrease of platelet count (less than $150\times10^9$/L), caused by autoantibody-mediated platelet destruction.[2] In some cases, a defective platelet production has also been demonstrated.[3,4]

The study of the pathophysiology of this disease started 50 years ago with the historical experiments by Harrington,[5] showing that a humoral factor in the patient's plasma transfused into a normal subject was able to cause a drop in platelet count. Despite this long history of investigation, the diagnosis remains one of exclusion and the clinical management of ITP is still largely based on anecdotal evidence, descriptions of series of patients and a very few controlled studies, mostly concerning initial treatment of children. As a consequence, many guidelines, such as those of the *American Society of Hematology* (ASH)[6] and of the *British Committee for Standards in Haematology* (BCSH), have been produced largely based on expert opinion.[7]

*Pathogenesis*

Autoantibodies are certainly involved in the pathogenesis of ITP as anticipated by the pioneering work of Harrington[1] and Shulman's identification[8] that the causative agent in the plasma of patients as a 7S IgG (immuneglobulin G) fraction. When Dixon developed his assay for the measurement of platelet-associated Ig, high values of platelet-associated autoantibodies were found in ITP patients.[9] Later, Van Leeuwen, working with platelets congenitally lacking membrane glycoprotein (GP) IIb/IIIa (obtained from a patient with Glanzman's thrombasthenia), demonstrated that most autoantibodies were directed against this platelet GP complex.[10] Recent techniques are available to measure antibodies, both platelet-associated and free in the plasma, with specificity for GP IIb/IIIa and Ib/IX, IV and V.[2,11]

Very recent molecular studies are revealing that inherited polymorphisms of platelet-membrane GP genes may be associated with alterations of their antigenicity, by regulating their expression level and modulating their functional expression.[12] In addition, an association of ITP with some HLA polymorphisms, such as HLA-DRw2 and DRB1*0410 alleles has been described in certain ethnic populations,[13] suggesting the crucial role of the antigen-presenting T-lymphocytes, which in turn regulate cells for antibody production by B-lymphocytes. However, despite much recent progress, the events initiating ITP still remain unsettled.

*Epidemiology*

No firm data are available on the incidence and prevalence of ITP. An incidence ranging from 1 to 12 cases/100,000/year, including both children and adults, can be extrapolated from case series.[14-17] The incidence of ITP was estimated from an exhaustive direct examination of all in- and out-patients in a well-defined health care region of a Danish county during a 22-year period. The survey purporting to capture all symptomatic and also asymptomatic cases seen by general practitioners.[18] An annual standardized incidence rate of 2.64 (CI 2.29-2.98) per 100,000 persons (platelet count less than $100\times10^9$/L) and 2.25 (CI 1.92-2.57) per 100,000 persons (platelet count less than $50\times10^9$/L) was calculated, with a female/male ratio of 1.7 and an increasing annual incidence rate with age up to 4.6 per 100,000 in subjects aged 60 years or more. These accurate estimations largely confirm the results of previous studies, although a very recent population-based investigation[20 bis] suggests that the absolute incidence of ITP is similar in males and females.[19,20]

*Natural history*

In children, ITP manifests typically with an acute, abrupt onset, often following a viral illness. The platelet count at presentation is less than $50\times10^9$/L in most patients.[21,22] The majority of these children (80%) do not require specific treatment, and will reach a spontaneous remission within 6 months.[6,23] Some 10%-20% of cases develop a chronic form[24,25] persisting after six months, with a later remission, during the next years in one third of cases.[24,26-29] The incidence of intracranial hemorrhage is estimated to be about 0.5-1%, with a fatal evolution in 50% of these cases, but only limited observational data are available.[6,27,30,31]

In adults, ITP often has an insidious onset, with a mean platelet count between $30\times10^9$/L and $130\times10^9$/L at diagnosis and a typical evolution into

a chronic form, lasting more than 6 months,[32-34] and indeed often lifelong. Less than 10% of cases present with an overt hemorrhagic picture and a platelet count less than 5–10×10$^9$/L requiring hospitalization and immediate treatment.[35,36] Very few cases, less than 5%, are unresponsive to first line treatments including splenectomy,[37] whereas about 10-15%[38] of chronic cases develop a disease which is refractory to second-line therapy. The clinical relevance of refractory ITP was recently evaluated by a meta-analysis[39] which pooled 17 studies including 1,817 refractory patients with a platelet count less than 30×10$^9$/L. A total of 49 fatal hemorrhages were recorded, with a rate of 0.0162 and 0.0389 cases per patient-year (not age-adjusted). In 9/17 studies reporting age at the time of event, the risk of hemorrhage increased from 0.4% per year in patients younger than 40 to 13% per year in patients older than 60, confirming the results of a previous study.[36] The mortality rate at 5 years was 2.2% in young patients and 47.8% in older patients. In another retrospective study on a cohort of 138 patients,[37] the relative risk of mortality from hemorrhage in refractory ITP patients was significatively higher than that observed in the general population, the RR being 4.2 (1.7-10). Interestingly, 2 years after diagnosis 5% of 138 patients were still under treatment to maintain a platelet count >30×10$^9$/L, with an ITP-related hospital admission rate 5 times higher that of mild, untreated thrombocytopenic patients. The mortality rate in splenectomized patients, estimated from these retrospective studies, was recently confirmed by a prospective analysis of patients with ITP refractory to splenectomy,[37bis] showing a hemorrhagic death rate of 1.6%. Hemorrhagic fatalities occurred only in patients who did not achieve platelet counts higher than 10×10$^9$/L, in spite of various treatments after splenectomy had failed. Sadly, in addition to hemorrhagic deaths, a large proportion of fatal bacterial infections (14%) favored by the various immunosuppressive treatment[37] or fulminant sepsis in splenectomized patients was reported.[40,41]

*Diagnosis*

The diagnosis of ITP requires the exclusion of any recognizable underlying disease at presentation. The concomitant presence of isolated lupus anticoagulant, antiphospholipid antibodies, antinuclear antibodies or Coombs' test positivity does not cause any change in the management. Testing for antiplatelet antibodies with the various available techniques is not necessary. They lack sufficient sensitivity and specificity and have no prognostic value. About half of patients manifest some muco-cutaneous bleeding, without systemic symptoms. The finding of thrombocytopenia should always be confirmed by direct microscopic examination of a peripheral blood smear, to exclude pseudo-thrombocytopenia or inherited disorders with giant platelets such as Bernard-Soulier syndrome.

The guidelines of the ASH[6] and BCSH[7] are concordant in advising a diagnosis of ITP based on history, physical examination, blood count and peripheral blood film examination (Table 1), to exclude secondary causes of thrombocytopenia. Further

**Table 1. Aspects that need to be investigated in a patient with suspected ITP.**

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| History |
| • Family history of thrombocytopenia |
| • Previous viral illness |
| • Drug or alcohol intake |
| • Systemic symptoms such as fever or weight loss |
| • History of hemorrhage |
| • Risk factors for bleeding, such as hypertension, gastrointestinal disease, surgery |
| • Pregnancy (exclude gestational thrombocytopenia) |
| Physical examination |
| • Spleen, liver, lymph nodes |
| • Skin rash, arthralgias, evidence of thrombosis |
| • Type and localization of mucocutaneous bleeding |
| Peripheral blood smear examination |
| • Pseudo-thrombocytopenia |
| • Red cell shape abnormalities |
| • Evidence for myelodysplasia, e.g. Pelger-Huet anomaly, immature white blood cells |
| Bone marrow examination (see text) |

**Table 2. Laboratory tests suggested to complete the clinical assessment in a patient with suspected or confirmed ITP.**

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| • Anti-platelet antibodies. Testing not required: low sensitivity and specificity. Their assay may be of some value in case of associated bone marrow failure and ITP, in refractory forms or drug-dependent thrombocytopenia. |
| • Platelet survival time: not required. |
| • Coagulation profile: necessary during pregnancy. |
| • Reticulated platelets: higher concentrations in ITP in comparison than in other causes of thrombocytopenia, but their assay has not yet been validated in a clinical setting. |
| • Autoimmune markers, if autoimmune disease is suspected. |
| • *Helicobacter pylori* infection: in case of a refractory form |
| • Urinalysis, liver function tests, hemolysis markers and arterial hypertension monitoring during pregnancy to exclude obstetric causes of thrombocytopenia. |

investigations (Table 2) are not required in typical cases. Bone marrow examination is recommended in adults with atypical features at diagnosis or in those over the age of 60, after a relapse following complete remission and before splenectomy. However, consensus on this policy is far from unanimous and we continue to consider bone marrow a valuable investigation in most cases. In children, marrow examination is required in the presence of atypical features and recommended before therapy with corticosteroids or in case of no response to immune globulin administration.

*Treatment*

Many recent reviews[42-45] and guidelines[6,7] have addressed the management of ITP and the reader is invited to refer to them for detailed analysis of the different aspects. Specific references will be provided here only when appropriate to focus on particular aspects.

*Hospitalization and emergency treatment*

Hospitalization is rarely mandatory, apart from in cases with active severe or life-threatening bleeding. In these cases, in addition to emergency treatment, immediate transfusion with platelet concentrates is appropriate. In other cases, including children and adults with extensive purpura, sub-conjunctival hemorrhage or mucosal hemorrhagic bullae of the oral cavity, patients with overt bleeding (hematuria, epistaxis, etc.) or women with menorrhagia, hospitalization is appropriate and may be required for a sake of prudence, especially if the platelet count is less than 20-30×$10^9$/L. These cases are at higher risk of acute intracerebral bleeding (1-5%)[46,47] than are less symptomatic patients, those younger than 60 years or those with a higher platelet count (less than 1%).[36] The fatality rate is around 50% when intracerebral hemorrhage occurs.

Emergency treatment includes intravenous methylprednisolone (1 g/day for 3 days in adults or 30 mg/kg/day in children). Administration of high dose intravenous immune globulins (IVIg) (1 g/kg/day for 2 days in adults or 1 g/kg/day for 1 day in children) is also recommended.[43]

*Initial treatment*

Clinical criteria for selecting patients in whom initial treatment could be safely deferred have not been properly investigated. In general, in adult patients, even if asymptomatic, treatment is advised when the platelet count is less than 20-30×$10^9$/L, or when significant mucous-cutaneous bleeding is present, regardless of the platelet count. Other cases in which initial treatment is appropriate include patients at higher risk of hemorrhage, such as those with hypertension, peptic ulcer, recent surgery, head trauma and a platelet count less than 50×$10^9$/L. These criteria could be relaxed in children, who have a high percentage of spontaneous remission within a few weeks. Indeed, in the young the aim of therapy is mainly to increase the platelet count in risky situations, i.e. in the presence of severe bleeding symptoms or an extremely reduced platelet count (less than 10×$10^9$/L). In order to allow children to maintain their life-style we prefer to treat them with a short course of corticosteroids when the platelet count is less than 20-30×$10^9$/L.

Initial therapy includes oral corticosteroids, IVIg and splenectomy. Up to 80% of adults will respond to prednisone 1 mg/kg/day for 2-4 weeks. Tapering of prednisone should be prolonged over several weeks. However, most patients frequently relapse within 6 months when the dose is tapered.[7,32,48] Two randomized trials showed no difference between low (0.25-0.5 mg/kg/day) and high (1-2 mg/kg/day) doses.[49,50] Long-term remission is seen in only 10-20% of cases.[32,37,48] In a very recent not-randomized and not controlled study,[51 bis] a 4-day course of high-dose dexamethasone (40 mg/day) was tested as initial therapy for adults with ITP and platelet count less than 20×$10^9$/L or less than 50×$10^9$/L in the presence of bleeding manifestations. After a median follow-up period of 30.5 months, 106/125 patients had a good initial response, with 53/125 (42%) of patients showing a sustained response after a single course. If these impressive data are confirmed in controlled trials, this cheap regimen might be a safer and more effective alternative to the conventional prednisone treatment.[51ter] In children, the dosage of oral corticosteroids is usually higher than in adults (1.5-2 mg/kg/day for 3 weeks[51] or 4 mg/kg/day for 1 week) with tapering over 2 weeks.

IVIg are very effective in the treatment of ITP, inducing a substantial increase or normalization of platelet count in almost all untreated patients. However, the response is invariably transient, lasting for no more than 2 to 4 weeks.[52,53] IVIg are indicated only in patients with very low platelet counts and severe bleeding. A single, randomized study showed no difference between a dose of 400 mg/kg/day for 5 days and 1 g/kg/day for 1 day.[54] Another randomized clinical trial found no difference between the use of corticosteroids and IVIg (as single agents or in association) in preventing evolution into chronic ITP.[33] Their use is not always devoid of significant side effects including renal impairment or failure.[55,56] In children, IVIg infusion is appropriate as first-line therapy in cases of severe bleeding and/or a platelet count less than 10×$10^9$/L or in cases of bleeding and a platelet count less than 20×$10^9$/L. Limited evidence suggests that repeated IVIg infusions in children might be useful in order to postpone or possibly avoid splenectomy. In non-splenectomized Rhesus (D)-positive patients anti-D IgG treatment at a dose of 75 µg/kg/day is

similarly effective and less expensive than IVIg which is not without problems such as intravascular hemolysis.[57]

In two-thirds of adult patients with ITP, splenectomy will be curative[6,7,42,43] producing a complete and sustained remission without requiring additional therapy. This intervention is indicated in the case of no response after first line therapy with oral corticosteroids (6 weeks after diagnosis in asymptomatic patients with platelet count less than $10\times10^9$/L; 3 months after diagnosis in symptomatic or asympomatic patients with a platelet count less than $30\times10^9$/L) or when a response is obtained only with long-term corticosteroid treatment at a dosage higher than 0.15-0.20 mg/kg/day.[43,44] Our policy is to try to postpone splenectomy until at least six months after diagnosis, since late remissions may occur. Splenectomy is rarely indicated in children. It seems appropriate in cases of chronic severe ITP (platelet count less than $10\times10^9$/L or major bleeding) unresponsive to corticosteroids or IVIg 12-24 months after diagnosis or in the presence of life-threatening hemorrhage.[7] Patients should be given prophylactic vaccination with pneumococcal, meningococcal C and *Haemophilus influenzae* vaccines, preferably 2 weeks prior to splenectomy[58] and advised on the conduct to be observed in the case of fever. They should also be provided with broad spectrum antibiotics for immediate treatment of any suspected infection.

During pregnancy, asymptomatic women with a platelet count exceeding $20\text{-}30\times10^9$/L do not need treatment during the first and second trimesters. During the third trimester, specific treatment is warranted to maintain a peripheral platelet count above $50\times10^9$/L. IVIg are indicated as first line therapy in the case of severe thrombocytopenia (platelet count less than $10\times10^9$/L) during the third trimester, or in the case of failure to respond to oral corticosteroids treatment. It is appropriate to plan splenectomy during the second trimester in women with platelet counts less than $10\times10^9$/L who are refractory to moderate doses of corticosteroids and IVIg.

*Second-line therapy*

Second-line treatments are reserved for patients with refractory ITP, defined as the persistence of thrombocytopenia after initial therapy including splenectomy, with the need for active treatment to maintain a safe platelet count.[59] The identification of a safe platelet count should take into account the patient's life style and preferences but is usually defined as a platelet count not associated with significant bleeding symptoms including purpura and a count higher than $10\times10^9$/L.[38] In refractory patients, the need to obtain a hemostatic level of platelets is counterbalanced by the risk of severe side-effects of the drugs.[6,37,38] Indeed, the morbidity and mortality in these patients is often associated with iatrogenic side effects, including fatal infections in immune-suppressed patients. This is particularly the case in older patients and the risk of overtreatment must be seriously considered.[38] In the series of 138 patients described by Portiejlie,[37] of the four deaths occurring during the first two years, one was due to hemorrhage and three to infections.

The first-line therapy (corticosteroids and IVIg) should be reconsidered, reducing corticosteroids to the lowest effective dose, taking into account their chronic use. High-dose steroids, such as 40 mg of dexamethasone daily for 4 days, repeated every 28 days for six cycles, has been proposed[60] but initially reported favorable results were not confirmed. Ultimately most patients become refractory to IVIg and cannot tolerate prolonged administration of corticosteroids. Vinca alkaloids (vincristine, 1 mg, occasionally 2 mg, single dose) are effective in producing a briefly-sustained platelet increase in up 50% of splenectomized patients and might be the agents of choice in cases requiring rapid correction of the platelet count.[7] Immunosuppressive treatments with cyclophosphamide (1-2 mg/kg /day) and azathioprine (150 mg/day) produce a sustained response in about 25% of cases, but are associated with a significant risk of developing a secondary neoplasia.[43] These treatments should be reserved for the management of acute bleeding or for prophylaxis of risky situations. Cyclosporin A, alone or with prednisolone (3-5 mg/kg /day), has been shown to increase the platelet count in 55% of patients, but with significant side effects in up to 30% of patients.[61,62] Danazol,[63,64] an attenuated androgen, should be tried in male patients or in females aged more than 50, at a dose of 200 mg 2-4 times daily. At least two months of treatment are required to assess the response. A variety of drugs including interferon,[65] dapsone,[66] ascorbic acid,[67] colchicine,[68] and protein A immunoadsorption[69] have been used in small case series with minor and transient responses. Most of these disappointing results discouraged the planning of controlled trials with these agents.

In patients with *Helicobacter pylori* infection, microbial eradication with antibiotic therapy was associated with a substantial increase in platelet count in some series of patients with refractory ITP,[70-73] with a median remission of 8.3 months.[71] In this issue of Haematologica, Franchini and Veneri[71bis] in their editorial, report that eradication therapy is accompanied by a platelet increase in 55% of eradicated cases. They appropriately suggest the need for placebo-controlled trials on larger number of patients, since most data are still uncontrolled and anecdotal.

*Innovative and experimental therapy*

In recent years, autologous peripheral blood stem

cell transplantation (PBSCT) has been used as salvage therapy in severe unresponsive autoimmune diseases, including ITP.[74] The risk of early and late toxicity with a high transplant-related mortality and the lack of clear evidence of long-term effectiveness suggest that this option should be considered only in the setting of controlled clinical trials.

In a small group of refractory ITP patients, mycophenolate mofetil, a drug licensed for prophylaxis of acute rejection of solid organ transplants, has been shown to induce sustained remission (5/6).[75] Its use is attractive since this agent is devoid of nephrotoxicity and is able to inhibit both T- and B-lymphocytes. Larger studies are needed to confirm its value.

An emerging role for biological treatment based on chimeric humanized monoclonal antibodies against membrane receptors of specific lymphocyte subsets is apparent from recent literature and ongoing trials. Anti-CD20 antibody was used at a dosage of 375 mg/m$^2$ weekly for 4 weeks (as for the treatment of lymphomas) in a single study[76] in 25 ITP patients. A total of 13/25 (52%) patients showed a complete or partial response, maintained for 6 months in 7 of them (28%). No increase of infection was recorded. Similar results were obtained in other studies.[77,78]

Campath-1H, an anti CD52 humanized antibody against B- and T-lymphocytes, was used by Lim[79] in 6 patients with refractory ITP; four of them showed a response which lasted more than 4-9 months in three of them. Willis[80] treated 21 patients with a variety of cytopenias at a dosage of 10 mg/day for 10 days. A response was obtained in 15 and maintained in 6 patients but at the expense of significant side effects. Finally, anti-CD25 antibody, against interleukin-2 receptor, impairing the activated T-lymphocyte, is being tested in an ongoing clinical trial at the *Warren G. Magnuson Clinical Center* in Bethesda (USA), in ITP patients not responding to corticosteroids treatment. So far no successful results have been obtained with the use subcutaneous human recombinant thrombopoietin, which was associated in some cases with *de novo* production of autoantibodies against the natural hormone[80] with a potential to worsen the thrombocytopenia.

### *Conclusions*

Because of the lack of controlled clinical trials on which to establish recommendations for decision-making, the management of ITP remains largely guided by expert opinion based on retrospective analyses of limited series of patients, often producing unconfirmed results. Local practices may vary and expose patients to the risks of over or undertreatment, a situation which demands rapid correction. Considering the very low incidence of mortality and major morbidity of this condition, prospective trials will require the enrollment of thousands of patient to demonstrate the superiority of a particular agent or management protocol. Accordingly, the definition of appropriate surrogate endpoints agreed on by the scientific community would be a major step forward. Further pathophysiologic studies are needed to produce a better understanding of the mechanisms of this disease and its initiating mechanisms and to offer highly specific and sensitive confirmatory laboratory tests.

In the light of these considerations, the co-operative prospective data register made available by the *Intercontinental Childhood ITP Study Group*, which has enrolled 2,073 children with newly diagnosed ITP in three years[24] represents an admirable effort to approach the problems of ITP in the right direction. We hope that this register will stimulate similar initiatives to investigate pathophysiology, diagnosis, clinical course, short- and long-term efficacy and safety of therapy also in adult patients with ITP5-such as the Working Group on Thrombocytopenias recently formed within the European Hematology Association.

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## *Helicobacter pylori* infection and immune thrombocytopenic purpura

*Helicobacter pylori* is a recently re-discovered Gram-negative bacterium which has revolutionized the understanding of the pathogenesis of peptic ulcer disease and hence its treatment.[1] *H. pylori* is etiologically related to many digestive tract diseases including peptic ulcer disease, chronic active gastritis, primary low-grade B cell gastric lymphoma and gastric carcinoma.[2,3] The seroprevalence of *H. pylori* has also been investigated in many other diseases and a positive correlation has been found in an increasing number of conditions outside the digestive tract, such as cardiovascular, respiratory, neurological, skin and autoimmune disorders.[4,5] These last include rheumatoid arthritis, autoimmune thyroiditis and autoimmune neutropenia. The interaction between *H. Pylori* and the immune system was also confirmed by recent studies that reported an association between *H. pylori* infection and idiopathic thrombocytopenic purpura (ITP) and, in many cases, a significant increase in platelet count after bacterial eradication.[6,8] The relationship between infection with *H. pylori* and the development of ITP opens a new exciting and controversial area of investigation with important implications for both pathogenesis and patients' management. However, the data reported in literature are limited[9-24] and mostly regard single case reports or small series of patients so that the evi-