Personal Practice

Immune Thrombocytopenic Purpura

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Immune thrombocytopenic purpura (ITP) is a frequently encountered acquired hemorrhagic condition in day to day pediatric practice. It is characterized by an isolated thrombocytopenia (platelet count <100 x 10^9/L) resulting from shortened platelet survival. There is a concomitant increase in platelet production in the bone marrow and absence of other disease processes that could account for thrombocytopenia(l). The various controversies associated with the management of ITP are discussed in this communication.

Nomenclature

Although first described in 1735 by Werlhof as 'morbus maculosus hemorr\hagicus', antibody mediated destruction of platelets by reticuloendothelial cells as a pathogenetic mechanism, was proposed by Harrington in 1951(2). Most authorities, therefore, prefer to use the term 'immune' thrombocytopenia (TP) rather than idiopathic TP. A few hematologists designate it as 'ATP' to specifically imply an autoimmune basis. The association of acute ITP with antecedent viral infections has led to the suggestion that viral antigen-antibody complexes rather than platelet specific antibodies may be responsible for platelet sensitization and destruction. In addition, evidence for cell mediated platelet destruction has been demonstrated in a few cases of JTP(3).

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Types

ITP is classified as follows: *(a) Acute:* Platelet count returns to normal (>150 x 10^9/L) within 6 months of the onset of symptoms and relapse does not occur; *(b) Chronic:* Thrombocytopenia persists for more than 6 months; and *(c) Recurrent:* Platelet count decreases after having normalized for at least 8 to 12 weeks.

Nearly 80-85% of cases of ITP in children could be categorized as acute whilst the others pursue a chronic or recurrent course. In a referral hospital based practice, the proportions are biased towards chronic ITP which may constitute upto 45% of the cases registered.

Presentation and Natural History

The usual presentation is an acute onset of bruising, purpura and petechiae or less commonly mucosal bleeding from gums, nose or rectum in an otherwise normal child. Physical examination is unremarkable except for bleeds and blood counts show isolated thrombocytopenia.

Patients with acute ITP generally recover uneventfully. Platelet counts normalize within 6-8 weeks in 60% cases. The remainder recover in 2-6 months. It is

not possible to predict chronicity at the time of initial diagnosis. However, a chronic course should be anticipated in infants, in children >10 years old and in those presenting with an insidious onset bruising(4).

Mortality in acute ITP is almost exclusively associated with intracranial hemorrhage (ICH). The risk of ICH is minimal (0.1-l%)(5). Most instances of ICH have been reported within a few months of onset of the disease but the risk persists throughout the period of profound thrombocytopenia (<20 x 10^9/L). A higher incidence of ICH (3-8%) has been observed in referral institutions in India, probably as a consequence of accumulating the 'more serious' cases.

Diagnosis: Is Bone Marrow Aspiration Mandatory?

The presence of megakaryocytes in normal or increased numbers confirms that TP is destructive. The sole reason for a marrow examination in ITP is to exclude hypomegakaryocytic TP, *e.g.,* in acute leukemia and aplastic anemia. It has been shown in a number of studies that *isolated thrombocytopenia* is not a presenting feature of these conditions(6), which are virtually always associated with other abnormalities in history, physical examination or complete blood counts. Marrow aspiration need not be done in all children with classical ITP(7), but is recommended in the following situations: *(a)* If atypical features are present like age <1 yr or >10 yrs; history of chronic illness, weight loss, bone pains, anemia out of proportion to bleeds, associated lymphadenopathy or hepato-splen6megaly, CBC showing anemia, leukopenia or leukocytosis. *(b)* Before initiating steroid therapy as this could mask the signs and symptoms of leukemia, leading to delay in diagnosis and consequent poor prognosis; *(c)* If the patient is from a distant place, as the primary care physician could start steroids at a later date, without reconsultation; and *(d)* In all cases of chronic ITP.

Management

There is no 'curative' treatment available and hence a consensus on ideal therapy has not evolved. The literature is replete with reports of numerous drugs which have produced beneficial responses in a varied proportion of patients. The therapeutic options available are briefly reviewed.

Acute ITP

(a) Supportive

Treatments of acute ITP are primarily supportive and involve careful observation and follow up of the child. Physical activity should be restricted and contact sports should be avoided. All patients should avoid medications that could alter platelet function *(e.g.,* aspirin, NSAIDS).

Hospitalization is routinely not required in most patients. However, it is recommended for children who have significant mucosal bleeds, evidence of ICH or diagnostic uncertainty. The frequency with which platelet counts need to be monitored depends upon the severity of thrombocytopenia, the presence of hemorrhagic symptoms and an assessment of the rate of change in degree of the disease.

(b) Medical Treatment

There is considerable controversy regarding the need for specific pharmacologic intervention with steroid and/or intravenous immunoglobulin (IV IgG) in children with ITP. While neither treatment has been shown to alter the eventual course of the disease (4,6), either will increase the platelet count in the majority of patients.

This may, presumably, decrease the risk of serious hemorrhage. However, not all cases require medical therapy. The use of steroids or IV IgG should be restricted to cases presenting with: *(i)* Mucosal bleeds *(e.g.,* prolonged epistaxis, menorrhagia, hematuria or gastrointestinal bleeding), regardless of the platelet count; and/or *(ii)* Platelet count <20 x 10^9/L because of the higher risk of lCH.

Corticosteroids are the most commonly used agents in the treatment of acute ITP. Several controlled trials have shown that steroid therapy results in a more rapid rise in platelet count(8), whereas others indicate that they provide no measurable benefit(9).Steroids exert their beneficial effects by one or more of the following mechanisms: *(i)* Prolonging platelet survival by decreased clearance of opsonized platelets by mononuclear phagocytes; *(ii)* Decreasing the production of antiplatelet antibodies and their binding to antigens on platelet surface; and *(iii)* Increasing vascular stability. Numerous regimens for oral prednisolone have been advocated. It is generally used in a dose of 1-2 mg/kg/day. Some workers recommend a higher dose of 3-4 mg/kg/day whilst others have found I an extremely low dose (0.25 mg/kg/day) to be equally effective(l0). The drug should be discontinued after 2-3 weeks irrespective of whether an increment in platelet count has been attained or not. There is uniform agreement that long term steroids in childhood ITP are of little use and are, indeed, detrimental because of their serious side effects and suppression of platelet production. *The dictum is to treat the bleeding episodes rather than the number of platelets. Titrating the dose of steroids vis-a-vis the platelet count is a practice which must definitely be avoided. High dose intravenous methyl prednisolone* is an alternate way of administering steroids. A dose of 30 mg/kg intravenously over 20 minutes for 3-5 days produces significant increments in platelet counts in the majority of patients (ll). Alternately, methyl prednisolone, which has a bioavailability of 100%, could be given orally in a dose of 10-30 mg/kg/day for 5-7 days with equally gratifying results(12).

In a controlled randomized trial, methyl prednisolone produce a more rapid rise in platelet count than oral prednisone thereby decreasing the period of profound thrombocytopenia. The rapidity of response and the response rates were equivalent to IV IgG(13). It is, therefore, a cheaper alternative when a rapid increase in platelet count is desired; for example in life threatening hemorrhage or before surgery. The potential side effects of methyl prednisolone therapy include hypertension, hyperglycemia, hyperkalemia and circulatory complaints.

Intravenous bnmunoglobulin: Since 1981, IV IgG infusions have been increasingly used for treatment of acute ITP. The possible mechanisms of action are: *(i)* Blockade of Fc receptors on reticuloendothelial cells, resulting in survival of opsonized platelets; *(ii)* Inhibition of binding of antibodies to platelet antigen; and *(iii)* Decreased anti-body production by suppressing B cells(2).

Conventionally, a dose of 400 mg/kg/ day for 5 days as an IV infusion has been advocated(14). In recent times, it has been shown that a dose of 1 g/kg/day for 2 days is well tolerated and is equally effective(15). The decreased duration reduces costs of hospitalization significantly in the developed world. The response rates with IV IgG and oral steroids are similar(75-80%), but increments in platelet counts are observed faster with IV IgG(14,16). Platelet counts

increase within a few days of initiating therapy and elevations are usually sustained for 2 to 4 weeks. The cost of this form of therapy is, however, prohibitive in our circumstances. It is, therefore, used after methyl prednisolone has failed to generate a response in cases with active mucosal or intracranial bleeds or in those who require a surgical procedure. In addition, young children below the age of 5 years with severe thrombocytopenia or mucosal hemorrhage may be given IV IgG to postpone or avoid splenectomy(17).

Frequent side effects of IV IgG include fever, headache and nausea for which symptomatic management is sufficient. Anaphylaxis is the most serious side effect and transmission of hepatitis C is a potential hazard.

Platelet transfusions are not routinely indicated in ITP because the transfused platelets are liable to destruction by the basic immune process. They may, however, be used as a supportive measure in life-threatening hemorrhage. In such circumstances, emergency splenectomy and plasmapheresis have proved beneficial(l,2,4,6).

Chronic ITP

Investigations to exclude underlying diseases like systemic lupus erythematosus, acquired immunodeficiency (HIV) and lymphoma are warranted in cases where thrombocytopenia persists for more than 6 months. Patients with chronic ITP may still recover spontaneously years after diagnosis irrespective of treatment. *Treatment for a child with chronic ITP must be individualized* and the following factors should be considered: age, activity level, degree of bleeding manifestations and the resultant effects on the life style(6).

It must be realized that no therapeutic modality is uniformly successful with most agents producing transient increments in platelet counts, at best. *Therapy must, therefore, be restricted to a selected group of patients who have problematic mucosal bleeding manifestations. The physician must not, under any circumstance, fall into the trap of treating the platelet count, rather than the symptoms.*

The various therapeutic approaches available act through one or more of the following mechanisms: *(i)* Pharmacologic blockade or surgical removal of phagocytic cells which ingest antibody-coated platelets; *(ii)* Suppression of synthesis of offending antiplatelet antibody; and *(iii)* Removal of antiplatelet antibody from plasma.

Steroids

As long term daily steroids have unacceptable side effects, various alternatives have been tried. Pulses of high dose methylprednisolone (30 mg/kg/day for 3 days) are safe. Recently, pulses of high dose dexamethasone have been used in adults with resistant ITP(18). The latter approach offers a safe and cheaper alternative to methylprednisolone and IV IgG.

Intravenous Immunoglobulins

IV IgG in chronic ITP is mainly used as a means to postpone splenectomy(17) in a young child. It could, arguably, be considered the treatment of choice in life threatening bleeds such as ICH or severe gastrointestinal hemorrhage. In patients demonstrating significant elevations of platelet counts, booster doses (400 mg/kg/day x 2 days or a single dose of 800 mg/kg) may be recommended every 4-6 weeks.

Splenectomy

Removal of the spleen is the most effective form of therapy in the long term with a response rate of between 65-88%(2). Splenectomy removes the potential site of destruction of opsonized

platelets and also the major source of antiplatelet antibodies. Non-responders cannot be predicted prior to surgery. However, they seem to respond better to subsequent steroid and/or immuno-suppressive therapy. In case of relapse after an initial response, an accessory spleen should be excluded.

It should be remembered that there is a risk of overwhelming sepsis after splenectomy which is greatest in children less than 5 years(19). Splenectomy, therefore, should be considered only in severe cases of chronic ITP who fail to respond to steroids or have unacceptable side effects. It is best avoided in children below the age of 5 years.

IV IgG or steroids are usually given before surgery to raise platelet counts to the hemostatic range. However, this is not absolutely essential as, practically, hemostatic problems are seldom experienced per-operatively even in those with severe thrombocytopenia. Dramatic increments in platelet counts have been demonstrated as soon as the splenic pedicle is clamped. All patients should receive pneumococcal vaccine and prophylactic oral penicillin (for at least 5 years) to minimize the risk of post splenectomy sepsis.

The child with chronic ITP and problematic bleeds, who is too young for a splenectomy and cannot afford IV IgG, is a therapeutic challenge. A number of agents have been used, with varied success rates, in such patients. The choices may be 'unlimited' but responses are often frustrating for the relatives and the physicians. It is extremely important that therapy be initiated after proper counseling and without raising expectations to unrealistic proportions.

Vinca Alkaloids

These act by 'paralysing' phagocytic cells by inhibiting contractile proteins. Pulses and slow intravenous infusions (over 4 to 6 hours) of vincristine and vinblastine loaded platelets have been used. The results in children have not been very encouraging(2).

Colchicine

The action is similar to vinca alkaloids. It is used in a dose of 0.1-0.3 mg/day in divided doses for 2-6 months(20). The response rates vary from 30-40% in clinical trials incorporating small numbers of patients. Gastrointestinal side-effects need to be monitored.

Danazol

It is a non-virilizing androgen which has produced significant increases in platelet count in 30 to 50% cases of chronic ITP(21). The doses used are 300-400 mg/ m^2/day for 2-3 months. Some authors have used smaller doses (25-50 mg/m^2/day) with almost similar results(2). Responses are observed at least one month after initiating therapy. Side-effects are infrequent.

Azathioprine

Doses of 1-4 mg/kg/day have produced partial responses in about half of the patients after prolonged therapy(2). Experience in children is limited.

Cyclophosphamide

The response rates with cyclophosphamide are reportedly inferior to those obtained with azathioprine. The potential side effects of myelosuppression and malignancies preclude it from being recommended for use in childhood ITP.

Anti-D

It is a safe, effective and relatively inexpensive therapy for chronic ITP. Anti-D is effective only in patients who have Rh positive blood group. The major mechanism of action is blockade of Fc receptors of reticuloendothelial cells by anti

D coated erythrocytes. The response occurs 48-72 hours of initiating therapy and is seen in 70-90% of patients. The results are better in children and non-splenectomized patients(22).

Intravenous infusion of anti-D in a dose of 10-50 µg/kg over 30 minutes is recommended. Maintenance therapy every 3 weeks may be required. The major limitation in our country is the non-availability of the intravenous preparation. Intramuscular administration of anti-D in a dose of 15-25 µg/kg on alternate days for 5 days has also been found to be effective in some children with chronic ITP(23). Weekly boosters may be needed. Apart from mild hemolysis, no serious side effects have been observed.

Cyclosporine

Transient increase in platelet counts has been documented with cyclosporine(2). Serious side effects of this drug, however, limit its application in children with ITP.

Ascorbic acid

The response to high dose ascorbate (2 g as a single daily dose) in chronic ITP is extremely variable in adults(24). The mechanism of action is unclear. Its use in children has not been reported. We have had anecdotal successes with vitamin C in the Pediatric Hematology Clinic.

Monoclonal Anti Fc-receptor Antibody

This has shown transient responses in

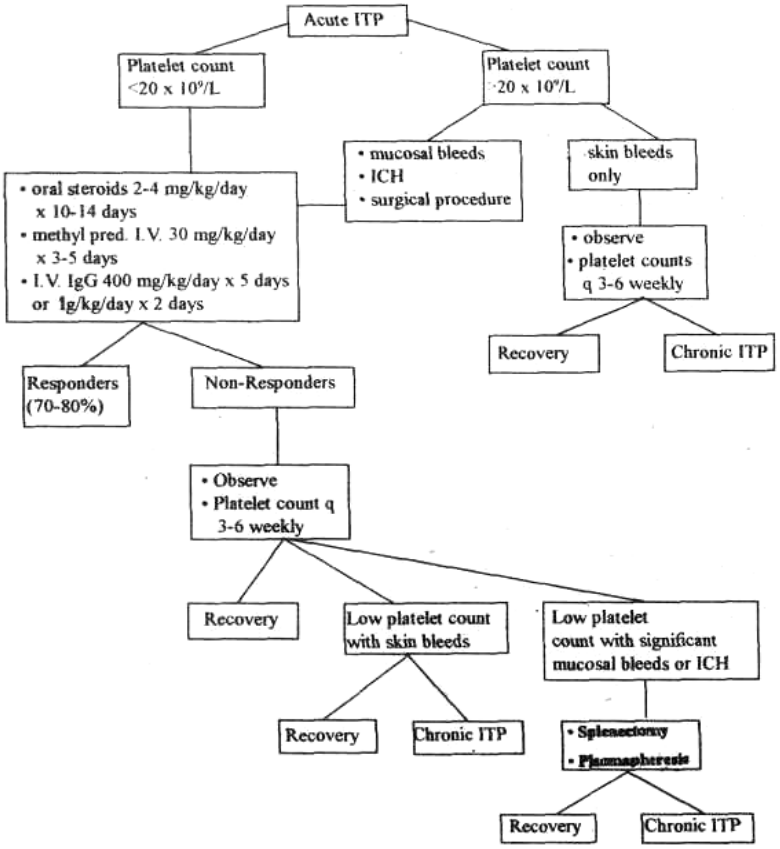

Fig. 1. Treatment plan in acute ITP.

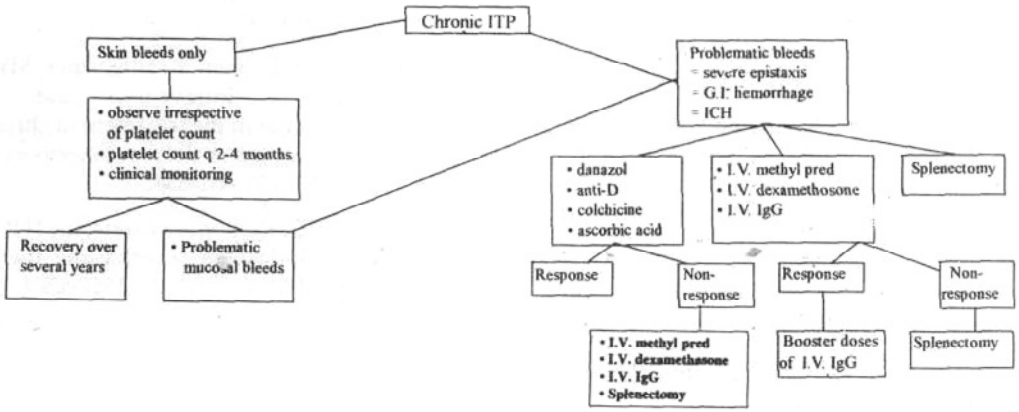

Fig. 2. Treatment plan in chronic ITP.

some adult patients(2) but its precise role is not yet clear.

Interferon α–2b

Doses of 2-3 million units given subcutaneously three times a week for 4 weeks have been recently reported to be effective in 60% of children(25). It is well tolerated and is less expensive than IV IgG. However, the rapidity of response is inferior to that obtained with IV IgG.

Concluding Comment

It is, thus, obvious that therapy in childhood ITP lacks consensus and this is reflected in the wide variety of agents used. Successes are difficult to evaluate in a disease wherein recovery can occur in the natural course of events. Although consensus is difficult, because of individual experiences and biases, it is worth following certain principles in selecting patients for treatment and also in choosing the appropriate modality of therapy. *Figures 1 & 2* provide guidelines for treatment in acute and chronic ITP, respectively. Each episode in recurrent ITP should be evaluated in the manner outlined for acute ITP.

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