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MANAGEMENT OF IMMUNE THROMBOCYTOPAENIA IN CHILDREN: A REVIEW
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MANAGEMENT OF IMMUNE THROMBOCYTOPAENIA IN CHILDREN: A REVIEW

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ABSTRACT

***Objective*: To provide an overview of the various treatment options available in the rational management of ITP in children.**
***Data source*: Published original research findings and reviews.**
***Data selection*: On-line searches for published data on immune thrombocytopaenia, idiopathic thrombocytopaenia, thrombocytopaenic purpura.**
***Data extraction*: Abstracts of selected articles were read and analysed to determine their relevance to this article.**
***Data synthesis*: All relevant articles were read in full and necessary contribution extracted for this review.**
***Conclusion*: Immune thrombocytopaenic purpura is a common disorder affecting children and adults. Ongoing research into the pathogenesis is providing the basis for future treatment options. Greater consensus as to appropriate treatment strategies is needed to improve outcomes.**

INTRODUCTION

Immune thrombocytopaenic purpura (ITP) is an autoimmune disorder characterised by a low platelet count and mucocutaneous bleeding. Classification is based on patient age (childhood vs adult), absence or presence of an underlying cause (primary vs secondary), and duration of the disorder (acute vs chronic). Typical presentation is that of an isolated thrombocytopaenia with normal bone marrow and the absence of other causes of thrombocytopaenia. It is the commonest cause of acute onset thrombocytopaenia in an otherwise well child (1-3).

Peak prevalence in children is at age two to five years, and in adults 20 to 50 years with a female to male ratio of 1:1 and 2-3:1 respectively (4). Incidence in childhood is 10-40 (Denmark, England) to 125 (Kuwait) cases per one million per year (average 50). Incidence in adults is 66 (USA) to 100 cases per one million persons per year (5, 6.) Onset is abrupt in children and gradual/insidious in adulthood.

There is a preceding (1 to 4 weeks) history of viral illness or live virus immunisation in 50-60% cases of childhood ITP. Virtually every common infectious virus has been described in association with ITP including Epstein Barr Virus (EBV) and HIV. HIV associated ITP is usually chronic as is ITP in children above the age of 10 years or under the age of one year.

Most patients have IgG antibodies against several specific platelet surface membrane glycoproteins such as GP IIb/IIIa, GP Ib/IX, and GP V complexes. Antibody coated platelets bind to antigen-presenting cells (macrophages or dendritic cells) through Fc γ receptors and are internalised and degraded. In childhood ITP, IgM antibodies directed against platelet antigens are frequently found. Since reticuloendothelial Fc receptors do not recognise IgM, it is assumed that some degree of IgM – mediated complement activation occurs to cause platelet destruction.

Spontaneous resolution occurs in 70-80% within six months with or without therapy. The child with ITP who presents with sudden severe thrombocytopaenia has approximately 90% chance of complete recovery. This is more likely where there is a clear history of viral illness with exanthem in the month prior to onset of ITP. Where there is a chronic history of easy bruising the probability of remission within three months was only 19% (7). Possibility of chronic ITP or that thrombocytopaenia is a manifestation of a systemic illness such as systemic lupus erythematosus (SLE), HIV, lymphoma is more likely in insidious onset ITP especially in an adolescent.

TREATMENT OF ACUTE ITP

The objective of early therapy is to induce a more rapid rise in platelet count to a safe level of more than 50×10^9/l, maintain a safe platelet count and thus prevent CNS bleeding (<1%) and reduce risk of prolonged bleeding, until spontaneous remission occurs.

Corticosteroids: Eighty per cent of patients remit on high dose corticosteroid therapy. Prednisolone 1-2 mg/kg/day (60-80mg maximum) for 2-3 weeks and then taper dose over 7-14 days is the usual initial therapy. The platelet count may fall during the time of the steroid taper unless the disease has already remitted; this is not a reason to reinstitute steroids. If the patient becomes severely thrombocytopaenic or has clinical haemorrhage an alternative form of therapy should be undertaken. Prolonged steroid therapy has been reported to suppress platelet production (8, 9).

IV pulse methylprednisolone (30mg/kg/day over 30-45 minutes for 3 days) leads to a more rapid rise in platelet count than does oral prednisolone (10, 11). The rate of response is equivalent to that of intravenous immunoglobulin G (IV IgG), and the cost is considerably less. It is recommended as initial therapy when platelet counts are below 20×10^9/l or when there is evidence of significant bleeding.

Corticosteroids increase vascular stability and ameliorate endothelial abnormalities associated with thrombocytopaenia (12-20). They also effect a decrease in production of antiplatelet antibodies and a decline in clearance of opsonised platelets (21-23). Side effects include growth retardation, osteoporosis, diabetes mellitus, hypertension, peptic ulceration, cushingoid features, cataracts, pseudotumour cerebri, fluid retention, acne and psychosis.

Intravenous Immunoglobulin: High-dose IV IgG (2g/kg given as 400mg/kg//day for five days or 1.0g/kg/day for 2 days) is able to produce a rapid rise in platelet count in the majority of patients (24-28). Over 80% children have a platelet rise to over 100 000 per mm^3. It is particularly useful in patients with life-threatening haemorrhage, in steroid refractory ITP, during pregnancy or prior to surgery. The mechanism of action may be blockage of Fc receptors on macrophages resulting in survival of opsonized platelets (29). The antiidiotypic antibodies in the pooled IgG preparations bind to circulating autoantibodies, rendering them ineffective as platelet opsonins. The antiidiotypic antibodies may also suppress the B cells that produce the offending auto antibodies since these cells express the same idiotype on their surface (30). The effect of IV IgG on platelet count lasts between two and six weeks.

Transient and minor side effects include fever, headache, nausea, vomiting, light headedness, vertigo. Paracetamol and slowing down the infusion rate is useful (31,32). More serious side effects of IV IgG include aseptic meningitis, anaphylaxis (32) – a life threatening allergic reaction, haemolytic anaemia (33, 34) – due to presence of erythrocyte alloantibodies in the preparation – and viral contamination (hepatitis C) (35, 36). Neither hepatitis B nor HIV infection has been reported to occur in recipients of IV IgG perhaps because ethanol fractionation and subsequent purification eliminate viral antigens (37-39). Most preparations probably contain anti-hepatitis B antibodies, so they impart immunity with the infusion.

Splenectomy: This operation is recommended in patients who have no response to initial therapy with IV IgG or with steroids and remain at risk for serious haemorrhage, in patients who have symptoms and low platelet counts ($<30\times10^9$/l) after three months of steroid therapy or who require toxic doses of steroids to maintain a safe platelet level. It is also indicated in life threatening haemorrhage and in patients with chronic ITP whose risk of haemorrhage precludes observation alone. It is a surprisingly safe procedure in the patient with ITP, with only one reported case of excessive haemorrhage (40, 41). The patient who responds to IV IgG or to steroid therapy should enter surgery with a normal platelet count if the procedure is elective. Regardless of the platelet count prophylactic platelet transfusion is unnecessary (42), although platelets should be readily available in case of excessive intra operative bleeding. Splenunculi must be removed otherwise subsequent relapse of ITP can occur.

The bulk of antiplatelet antibody is synthesised in the spleen (43-45). The splenic reticuloendothelial system clears most of the antibody coated platelets from the circulation. Consequently, 65-88% of ITP patients remit immediately after splenectomy often reaching a platelet count of 1000×10^9/l at the apex one to two weeks post operatively, before an equilibrium count is attained several months later (41, 46). This apparent thrombocytosis is not associated with an increased risk of thrombosis and needs no therapy (47).

If the peak platelet count achieved is more than $500\times I0^9$/l, permanent remission is likely (46). Even a partial remission may make further treatment unnecessary if the risk of serious haemorrhage is decreased. A relapse after an immediate response to splenectomy may be due to a transient decrease in platelet production after a viral infection in a patient who has a compensated thrombolytic state. If thrombocytopaenia persists, an accessory spleen should be considered. This tissue is usually visible under radionuclide imaging.

The major risk postsplenectomy is sepsis due to encapsulated organisms such as *Streptococcus*

pneumoniae, *Haemophilus influenzae* and *Neisseria meningitidis*. The risk is greatest in the under fives. Twenty three polyvalent polysaccharide pneumococcal vaccine, *Haemophilus influenzae* type b vaccine, Meningococcal ACWY vaccine should be administered at least two weeks prior to splenectomy. Prophylactic oral antibiotics such as penicillin V or monthly intramuscular injection of a long-acting penicillin such as benzathine penicillin can prevent 84% of the pneumococcal infections in children younger than five years. Educating the family on prompt management of infection is paramount.

Relapses after initial therapy: After an initial increase in platelet count coincident with IV IgG or steroid therapy, many patients may become thrombocytopaenic again after two or three weeks. Intermittent single booster doses (IV IgG, Ig per kg or IV methylprednisolone 30mg/kg) may be used to maintain a safe platelet count until spontaneous remission occurs. Where these modes of therapy cannot be used safely or effectively splenectomy or one of the second line therapies are indicated.

Platelet concentrates: These are beneficial in patients with acute life-threatening bleeding. Their benefit will only last a few hours since platelet autoantigens are public antigens, present on all normal platelets. Intermittent 2-4U/m^2 6-8 hourly or a continuous infusion of 0.5 to 1U/m^2 per hour platelet transfusions are recommended (48).

CHRONIC ITP

The patient in whom ITP persists for more than six months is considered to have chronic ITP. About 60% of children with acute ITP attain a complete remission within the first month of illness, whether they are treated or not. By six months after diagnosis, 80-90% will have resolved. There is a much smaller probability of spontaneous remission after six months, although children with ITP may experience recovery as long as 10 years after the initial diagnosis (7). The following management is recommended for chronic ITP and for cases of acute ITP that fail to respond to treatment with steroid, IV IgG and to splenectomy.

Anti-CD 20 monoclonal antibody, rituximab (375 mg/m^2 IV every week for four weeks) has been used, leading to responses within four to eight weeks after first infusion but response may occur as late as four months. Complete or partial remission is expected in 25% to 50% with many relapses responding to subsequent courses.

Anti-Rh(D) induces a slower rate of platelet rise than with IV IgG. It takes about 48 hours for the count to rise above 20×10^9/l. The effect of Anti-D on platelet count is also shorter than with IV IgG. Anti-Rh(D), when given to individuals with Rh (D) positive erythrocytes induces a transient mild haemolytic anaemia in the recipient. The RBC- antibody complexes bind to Fc receptors and interfere with platelet destruction thus causing a rise in platelet count. Anti – D is less able to block Fc receptors on reticuloendothelial cells outside the spleen because it is inefficient in complement fixation. Non-splectomised are therefore more likely to respond to IV anti – D.

Immunosuppressive drugs such as vinca alkaloids, cyclophosphamide, azathioprine, cyclosporine have been used. It is often necessary to combine two drugs (e.g. the androgen danazol and an immunosuppressive agent). Stem cell transplantation has cured some severe cases.

Vinca alkaloids: The doses recommended for weekly IV bolus treatment are 0.02 mg per kg (maximum 2 mg) for vincristine or 0.1 mg per kg (maximum 10 mg for vinblastine). The dose is repeated weekly for four weeks; if there has been no response after a month, further treatment is not indicated. In patients who respond, there is a prompt rise in platelet count, often to the normal range; in our experience, most children require repeated doses at two or three week intervals to maintain a safe platelet count. The rate of remission in children is not established, varying considerably in the reports to date (49-52). Appealing aspects of *Vinca* treatment are that it is quickly determined whether a patient will respond, and those patients who do respond are likely to attain a normal platelet count.

Danazol: The nonvirilising androgen danazol has been shown to increase the platelet count in many patients with refractory ITP. Schreiber and colleagues (53) have found that danazol treatment decreases the number of Fc receptors on circulating monocytes; presumably the same effect on reticuloendothelial macrophages is responsible for increased survival of platelets. Approximately half of patients with chronic ITP will have an effective response to danazol, usually with the platelet count increasing to a safer, but not normal, level.

The doses reported were 300 to 400 mg per m^2 per day taken orally for two to three months. One study reported that a smaller dose (50 mg per day = 25 mg per m^2 per day) was as effective and had fewer side effects (54). The responses are not likely to occur within the first month of treatment. Thrombocytopaenia has been observed as a side effect of danazol in four patients who were given danazol for conditions other than ITP (55).

Azathioprine: About half of the patients treated with azathioprine had a partial remission, although complete responses were uncommon. Doses used ranged from 1 to 4 mg per kg per day, which caused mild neutropenia. Three to six months of treatment

may be necessary before the maximal response is observed (56). The benefit of this drug over cyclophosphamide for children is a lower reported incidence of secondary malignancies. However, the smaller number of responsive patients and the longer treatment time before responses are seen make azathioprine impracticable for many patients.

Cyclophosphamide: The immunosuppressive agent cyclophosphamide has been used with variable success rates for ITP (57-61). An oral dose of 1 to 2 mg per kg per day has been recommended (56), although intermittent IV cyclophosphamide (300 to 600 mg per m^2 every 3 weeks) has also been reported (58). Responses occur in 2 to 10 weeks after initiating oral therapy (56).

The side effects of therapy with cyclophosphamide can be serious; bone marrow suppression is dose related, partial alopecia is typical. Patients must be monitored for hepatic toxicity and should be encouraged to take large volumes of fluids to reduce the risk of haemorrhagic cystitis. Long-term complications of this alkylating agent include an oncogenic potential, with development of leukemia most likely. This possibility makes cyclophosphamide particularly worrisome in the paediatric age group.

Cyclosporine: Cyclosporine is an active agent that suppresses the cellular arm of immunity. The serious side effects of cyclosporine make its widespread use unlikely in children with ITP.

CONCLUSION

ITP is a common disorder affecting children and adults. Ongoing research into the pathogenesis is providing the basis for future treatment options. Although only a small proportion of children progress to chronic refractory ITP, those who do may experience increased morbidity and even mortality. The search for effective therapy and greater consensus as to appropriate treatment strategies is needed to improve outcomes.

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