

CURRENT TOPIC

Guidelines for management of idiopathic thrombocytopenic purpura

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Children with idiopathic (immune) thrombocytopenic purpura (ITP) are almost invariably admitted to hospital for diagnosis. The usual presentation is an acute onset of bruising, purpura and petechiae or, less commonly, with mucosal bleeding from gums, nose, or rectum. Serious mucosal bleeding is unusual in uncomplicated ITP and should provoke a search for other causes. The majority of patients (80%) will provide a history of some infection, usually viral, within the preceding three weeks. The peripheral blood normally shows simple thrombocytopenia without other abnormality, although some individuals have a modest relative or absolute lymphocytosis. In 75% of cases the platelet count returns to normal within 3 months (90% by 9-12 weeks), but a history of bruising for one to two weeks before diagnosis often suggests a more chronic course is likely.¹⁻³

Should bone marrow aspiration be done?

The presence of associated symptoms or signs such as pallor, lassitude, pain (particularly in the abdomen or limbs), a limp, lymphadenopathy, or hepatosplenomegaly should lead to the suspicion of more serious pathology, and in such circumstances bone marrow aspiration is obviously essential. But the majority of patients present just with a short history of bruising, petechiae, or bleeding without other symptoms or signs. They show no pancytopenia and have a blood picture which does not suggest marrow infiltration or aplasia. For such children, provided no treatment is contemplated, urgent marrow examination is probably not necessary, but despite this some clinicians and parents still feel happier if infiltration and aplasia are immediately and absolutely excluded and so perform the procedure on all patients. A legitimate alternative approach is observation without treatment or investigation, especially if the platelet count is above $30 \times 10^9/l$, and only to perform a bone marrow examination if a child fails to remit within two to three weeks or if treatment, especially with steroids, is contemplated.

Other recommended investigations

Childhood ITP is only rarely associated with other immunological disorders. Immunoglobulin concentrations (especially IgA and IgG) are worth measuring, and viral serology can occasionally be informative. Cytomegalovirus

infection should be considered in infants under 1 year old (perinatally acquired infection) and infectious mononucleosis in older children. Immune thrombocytopenia has been reported as the first manifestation of HIV infection in vertically transmitted and blood product associated infection. Clinical pointers from the history should alert the clinician to the necessity for exclusion of this cause of ITP and routine investigation of all patients is clearly not required.

There is probably no need regularly to perform a Coombs's test or coagulation screen or to look for antinuclear factor (ANF) and DNA antibodies. ITP as a feature of systemic lupus erythematosus (SLE) is reported more commonly in adolescent girls and is usually associated with other stigmata of the disease. It is sometimes informative to check patients with chronic disease for these other autoimmune disorders.

Finally, platelet antibody tests are surprisingly unhelpful for either diagnosis or management, certainly in acute ITP. They may be more useful if the disease progresses to chronicity (defined as lasting for more than six months). Platelet associated immunoglobulin assay is more helpful; but the test is impossible with very low platelet counts and not readily available.

Should children with ITP stay in hospital?

Once the diagnosis is confirmed there is usually no justification for keeping a patient in hospital until the platelet count rises. Exceptions depend on bleeding problems or social circumstances, and (to a lesser extent) whether the parents will be able to prevent fights or vigorous knockabout games. The risk of serious bleeding, in particular intracranial haemorrhage, is probably as small at home as in hospital. Confining children to bed or putting severe restrictions on their activity is difficult to achieve, of no proved benefit, and produces boredom in the patient and anxiety in the parents. The risk of intracranial haemorrhage, based on published series, is under 1%, but that risk persists throughout the time of profound thrombocytopenia (platelet count $< 10 \times 10^9/l$).

Treatment—steroids or not?

Only small randomised studies testing steroids compared with no treatment have ever been

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possible in ITP. The evidence, such as it is, suggests that those receiving steroids recover their platelet counts slightly faster than those receiving no treatment.^{4,5} The essential natural history of the condition does not appear to be influenced by steroids and there is no evidence that steroids reduce the vanishingly low mortality rate.

Low doses of prednisolone (0.25 mg/kg/day) appear to be as effective as higher doses.⁶ In order to prevent troublesome side effects, doses over 2 mg/kg/day should definitely be avoided, and the drug should be discontinued after two to three weeks irrespective of the platelet count. For children presenting with bruising only, without mucosal or more severe haemorrhage, no treatment at all is perfectly reasonable. The patient's condition rather than the number of platelets should determine the management. Patients with counts above $30 \times 10^9/l$ very rarely need any treatment.

Continuation of steroids in full dosage beyond two weeks is unlikely to increase the chance of response if none has been achieved in that first fortnight. A reasonable compromise is to give full dosage for one week only with a gradual reduction in the second week. Cessation of treatment after two weeks is sometimes associated with a dip in platelet count when there has been a good initial response, but usually not to the initial low levels.

The mode of action of steroids principally operative in ITP appears to be inhibition of phagocytosis of sensitised platelets. In the rare patient with very severe persistent thrombocytopenia and symptomatic thrombocytopenia unresponsive to steroids, some believe there may be benefit from low dose treatment (5 mg) on alternate days. This is based on the theory that steroids can stabilise capillary endothelium and may reduce cutaneous bruising. However a decision to continue such treatment long term should not be taken lightly. The most frequent instance of mismanagement in ITP is the use of prolonged courses of steroids, and patients with persistent problems require careful evaluation for other treatment. Long term steroids can impair growth and produce all the well known cushingoid problems, and of course can generate immunosuppression with subsequent major risk from infections such as measles.

Intravenous immunoglobulin

Latterly there has been a vogue for the rapid and liberal use of intravenous high dose human pooled immunoglobulin in children with newly diagnosed ITP.⁷ It is hard to justify such an approach. To date there has been only one multicentre trial comparing no treatment, steroids, and intravenous immunoglobulin.⁸ In that study immunoglobulin appeared to be slightly better than steroids in shortening the period of profound thrombocytopenia but this was not clinically important. Both appeared to allow a rise in platelet count faster than no treatment. As with steroids there is no evidence at all that immunoglobulin reduces the low mortality of this condition. Recommended doses have been reduced in recent times, but the material is

very expensive, requires the patient to stay in hospital for its infusion, and there is still some lingering anxiety about the transmission of non-A non-B hepatitis.¹ A few cases of transient encephalopathic symptoms have also been reported.

For the present it seems reasonable that immunoglobulin should be reserved for: (i) emergency treatment of patients who do not remit or respond to steroids and who present with active bleeding and (ii) if cover is required to enable essential operations or emergency dental extractions to be performed.

Non-remitters and chronic ITP

Chronic ITP is defined as thrombocytopenia persisting beyond six months, and it will arise in 10–20% of patients.^{1–3} Such children may still recover spontaneously years after diagnosis irrespective of treatment.^{1,3} There is a regrettable tendency to treat platelet counts rather than symptoms, and it should be understood that chronic thrombocytopenia is compatible with normal activity and longevity.^{3,9} Most patients and their families simply require reassurance together with avoidance of aspirin and contact sports.³ If other treatment is considered prior discussion with, or referral to, the regional paediatric haematology team is recommended. The only patients with chronic ITP who need treatment are (a) those with profound thrombocytopenia and repeated mucosal bleeding (particularly epistaxes), (b) older children with menorrhagia, (c) victims of accidental or other trauma, (d) those needing elective surgery, and (e) (obviously) those who develop any acute neurological signs. Profoundly thrombocytopenic patients who develop persistent or recurrent headache should be investigated and, if appropriate, treated aggressively (see below). Chronic ITP patients are the group who warrant investigation for other autoimmune disorders (for example SLE).

As long term steroids have unacceptable side effects, alternative treatments have to be considered in the few children with chronic ITP who need treatment. Pulses of high dose methyl prednisolone (30 mg/kg daily for three days) appear safe and can often temporarily raise platelet counts to cover emergencies.¹⁰ This approach offers a perhaps safer and cheaper alternative to intravenous immunoglobulin which can be used in similar circumstances.

Splenectomy has been used for many years and about two thirds of chronic sufferers will derive permanent benefit,^{9,11,12} but it should be remembered that there is a mortality from postsplenectomy infection.¹³ The risk of overwhelming sepsis is real, and while greatest in young children (under 5 years),¹⁴ probably persists for life.¹⁵ The mortality from infection after ITP splenectomy is estimated to be 1.4% by Singer,¹⁶ but Eraklis and Filler reported seven deaths out of 262 patients (2.7%).¹⁷ Bearing this in mind, splenectomy should not be considered before at least six months and preferably 12 months from time of diagnosis, unless there are very major problems (see

below). Before splenectomy all patients should receive pneumococcal vaccine and commence life long prophylactic penicillin.

Other alternative treatments are legion, but none has yet been shown to be universally effective and/or safe.

Cytotoxic drugs, especially vincristine¹⁸ and azathioprine¹⁹ have been used but cannot be recommended for routine practice. Toxicity may be severe and life threatening.²⁰ High dose vitamin C,²¹ anti-D immunoglobulin,²² and danazol²³ have recently been tried, primarily in adults. Although it is perhaps premature to comment on their efficacy, preliminary results are not encouraging in children. Toxicity appears acceptable.

Life threatening haemorrhage

The extremely small risk of intracranial haemorrhage (less than 1% in most published series⁸⁻¹¹) persists throughout the period of profound thrombocytopenia and does not diminish. The presence of severe headache with neurological signs in any patient with a very low platelet count should be treated as an emergency and computed tomography should be performed urgently. Major bleeds need not be fatal. Massive doses of allogenic platelets (20 or more donor units) along with high dose methylprednisolone and intravenous immunoglobulin can be given. Such life threatening haemorrhage is the only indication for platelet infusions in ITP. Simultaneous emergency splenectomy and craniotomy under the same anaesthetic can be carried out. The mortality using such an aggressive approach is under 50% with minimal long term sequelae, but the response with treatment has to be rapid.^{13 24}

Late sequelae

Follow up of an acute episode of ITP for a period of six to 12 months is recommended to ensure that the patient does not have the chronic or relapsing variety. There is no evidence that chronic multisystem autoimmune disease or other pathology is likely to ensue in later life, but mothers who have had ITP in the past can give birth to thrombocytopenic babies even if they themselves no longer have reduced platelet counts. Haematologists and obstetricians need to be aware of this.

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