

Guideline

Newly Diagnosed Immune Thrombocytopenia (ND-ITP) in children

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Purpose

This guideline provides clinical practice guidelines to guide clinicians in the evaluation and management of children with newly diagnosed Immune Thrombocytopenia (ND-ITP)

Scope

This guideline relates to staff involved in the care and management of children with ND-ITP.

Related documents

Forms and templates

- Immune Thrombocytopenia Patient Information Sheet

Guideline

Introduction and definitions

Newly diagnosed Immune Thrombocytopenia (ND-ITP) is an acquired isolated thrombocytopenia due to immune-mediated destruction of otherwise normal platelets at a rate that exceeds production. ND-ITP is defined as patients who are within 3 months of initial diagnosis. It can often occur in the absence of identifiable and specific precipitants (Primary ITP) or may occur in conjunction with other defined autoimmune disorders or immunodeficiency (e.g. systemic lupus erythematosus or common variable immunodeficiency).

ND-ITP is uncommon overall affecting 1-3 in every 10,000 children.

Children with ND-ITP present with bleeding symptoms, most commonly petechiae or bruising. Other bleeding symptoms may include mucosal bleeding such as epistaxis or menorrhagia, and ND-ITP can rarely cause more serious bleeding problems in children such as intracranial haemorrhage (ICH, 0.1- 1.0%) (1,3,4).

The majority of children with ND-ITP will resolve spontaneously within 12 months from diagnosis, however 20% will have thrombocytopenia at 12 months, and are termed chronic ITP at this point (1,2).

Clinical Assessment

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ITP is a diagnosis of exclusion – patients with ND-ITP should have:

- **Normal history and examination (aside from bleeding symptoms), AND**
- **Normal FBC and other investigations (aside from thrombocytopenia)**

There is no single laboratory investigation for ITP, thus it is important that patients have a thorough assessment to exclude signs or symptoms which may indicate an alternate cause of thrombocytopenia. Differential diagnosis includes but is not limited to, bone marrow pathology (leukaemia, aplastic anaemia), consumption (disseminated intravascular coagulation (DIC), haemolytic uremic syndrome (HUS)), familial thrombocytopenia, infection and medications.

Initial assessment of suspected ND-ITP may be made by a senior ED physician, however any child with suspected ND-ITP should be referred to the **on-call Consultant General Paediatrician** prior to discharge so that appropriate further investigation, education and follow up can be arranged (see below).

- **At QCH, the general paediatric team on call should review the patient in ED. Children seen in DEM who live outside of the catchment will need ongoing care to be arranged with the General Paediatrician in that catchment.**
- For regional centres, the local general paediatric team should be consulted, and ideally should see the patient prior to discharge to arrange local General Paediatric follow up.

Clinical features of ND-ITP in children include:

- Abrupt onset
- Platelet type bleeding - bruising, petechiae +/- mucosal involvement. Adequate assessment of bleeding is important and may guide management (see Management below)
- Child is otherwise clinically well with no associated fevers or infective symptoms
- Normal history and examination with no **significant** lymphadenopathy, hepatosplenomegaly or other concerning signs or symptoms (e.g. bone pain, night sweats, weight loss, bloody diarrhoea, jaundice etc).

Investigations

Children with suspected ND-ITP should have baseline bloods completed. These include:

- Full blood count (FBC)
 - Platelet count $<100 \times 10^9/L$, with no other abnormality on the FBC are suggestive of ND-ITP
- Blood film should always be requested

- An isolated low platelet count, may be due to a clotted sample, thus the blood film needs to be examined for platelet clumps, and repeat sample should always be considered to ensure an accurate result.
- Alternate causes such as leukaemia, disseminated intravascular coagulation (DIC), and haemolytic uremic syndrome (HUS) can be screened for on blood film examination.
- Coagulation studies
 - To exclude DIC, and other causes for bleeding/bruising (e.g. clotting factor deficiency)

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ITP is defined as an isolated thrombocytopenia, thus any other abnormalities on the FBC, blood film or an unusual clinical history or examination should raise the possibility of alternate diagnosis.

Other testing which **may** be considered include:

- Chem20 – Liver disease, HUS can often be associated with thrombocytopenia
- Viral serology/studies – viral mediated thrombocytopenia is common with EBV, CMV and HHV6 infections. These may be considered in patients with signs or symptoms of infection
- Autoimmune screen - antinuclear antibodies (ANA) and other investigations for secondary causes of ITP are **not necessary** in the evaluation of children and adolescents with new diagnosis ITP unless there are positive features of autoimmune disease (5).
- Imaging – in patients with thrombocytopenia and symptoms suggestive of bleeding (headache, vomiting, decreased consciousness, melaena) imaging may be considered to define haemorrhage.

Platelet antibody studies have high false positive and false negative rates and offer little information in suspected ITP. Bone marrow examination is not warranted in children with typical features of ND-ITP, however can be considered in consultation with haematology if there are other concerning features. (5)

Management

Most paediatric patients with ND-ITP, without significant bleeding, can be safely managed as an outpatient. If there is significant bleeding or the diagnosis is unclear, the child should be admitted for further investigation and management.

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These are “Guidelines” and do not take into account all relevant patient related factors. The decision to treat a paediatric patient with ND-ITP may be multifactorial.

Without treatment, most paediatric patients with ND-ITP will recover a normal platelet count within six to twelve months. Therapy has not been shown to change the natural history of this recovery, nor has it been shown to reduce the risk of serious haemorrhage (1,2,7). Platelet count in paediatric patients with ND-ITP has not been reliably shown to be associated with risk of serious bleeding, although most reports of ICH have occurred in patients with platelet counts below $20 \times 10^9/L$ (1,2).

Both the American Society of Haematology (ASH) and an International Working Group (IWG) recommend **observation without drug therapy** in paediatric patients with ND-ITP who do not have severe bleeding, regardless of platelet count (5).

Any management decision should involve a detailed discussion with the family regarding potential benefits and toxicity expected from therapy, education regarding the low rate of serious haemorrhage in paediatric patients with ND-ITP, and the natural history of the disorder. It is also important to consider patient and family situation in any treatment decisions.

In situations where follow up cannot be assured, for patients living in remote locations, or where there are pending surgical procedures which cannot be safely rescheduled, a lower threshold for therapy may be considered.

Severity scoring of bleeding in patients with ITP:

Treatment decisions should be based on bleeding at diagnosis rather than platelet count. The table below has been used in a prospective trial in paediatric patients with ND-ITP (6) and can be used to guide therapy decisions:

Bleeding Grade	Bleeding risk	Description	Treatment recommendation
0	None	No new haemorrhage of any kind	No treatment usually required
1	Minor	Few petechiae (≤ 100 total) and /or ≤ 5 small bruises (≤ 3 cm diameter), no mucosal bleeding	
2	Mild	Many petechiae (> 100 total) and /or > 5 large bruises (> 3 cm diameter)	
3A	Low risk moderate	Blood crusting in nares, painless oral purpura, oral/palatal petechiae, buccal purpura along molars only, mild epistaxis ≤ 5 min	Treatment usually indicated
3B	High risk moderate	Epistaxis > 5 min, haematuria, haematochezia, painful oral purpura, significant menorrhagia	
4	Severe	Mucosal bleeding or suspected internal haemorrhage (brain, lung, muscle, joint etc.) that requires immediate medical attention or intervention	
5	Life threatening / fatal	Documented intracranial haemorrhage or life-threatening or fatal haemorrhage at any site	

Treatment of patients with Life-Threatening Bleeding (Bleeding Grade 5):

- Severe or life-threatening bleeding may include:
 - Intracranial haemorrhage
 - Any bleeding in a patient with ND-ITP with haemodynamic compromise (severe tachycardia, hypotension).



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Goal of treatment is to stop active bleeding, NOT to normalise platelet count.

- Urgently contact the on-call haematologist at Queensland Children's Hospital through the hospital switch board (30681111)
- Management of severe life-threatening bleeding often involves **a combination of:**
 - Intravenous Immunoglobulin (IVIg)
 - Dose of 2 g/kg
 - Application for IVIg needs to be made through Bloodstar.

- Phone authorisation for Emergency requests can be made by contacting 07 3838 9223 (business hours), 07 3838 9010 (after hours) – please confirm these numbers through the Bloodstar website (<https://www.bloodstar.blood.gov.au>)
- The link to the procedure for IVIg ordering can be found here (Blood and Blood products: Intravenous Immunoglobulin. CHQ-PROC-02910).
- Corticosteroids
 - Often intravenous methylprednisolone (30mg/kg/dose up to 1000mg max) or dexamethasone (0.6mg/kg/dose up to 40mg max)
- Platelet transfusion(s)
 - Dose of 20 mL/kg, up to one unit per transfusion.
 - Platelet transfusion should ideally be given after IVIg/corticosteroids, however in the event of life-threatening bleeding it may be given prior.
 - **Repeated platelet transfusions to maintain a platelet count above $50 \times 10^9/L$ will often be required in addition to medical management.**
- Tranexamic acid IV
 - Dose of 15mg/kg
- Surgical intervention to stop bleeding where appropriate
 - Urgent surgical referral depending on site of haemorrhage is indicated (e.g. neurosurgical referral for intracranial haemorrhage)
 - Urgent splenectomy is only indicated in serious, life-threatening bleeding where medical and initial surgical management has not resolved the haemorrhage.
- Other supportive care and consultations should be considered based on site of bleeding.
- Intramuscular injections should be avoided.

Treatment of patients with high risk or severe bleeding (Bleeding Grades 3b and 4)

- The goal of therapy in patients with ND-ITP is to increase platelet count to a haemostatic level (usually $>20 \times 10^9/L$), and ensure **cessation of bleeding**, rather than to restore a normal platelet count.
- First line treatment includes corticosteroids **or** IVIg.
 - Corticosteroids
 - Prednisolone 4mg/kg (maximum of 120mg) daily for four days
 - High dose steroids can increase the platelet count as rapidly as IVIG (i.e. within 48-72 hours) (8, 9).
 - **In uncomplicated ND-ITP, prolonged courses of corticosteroids should be avoided.**
 - Intravenous Immunoglobulin (IVIg)
 - A single dose of 1g/kg is usually sufficient and will often raise the platelet count within 48-72 hours of administration.
 - An application for IVIg must be made through BloodStar (<https://www.bloodstar.blood.gov.au>).
 - The link to the procedure for IVIg ordering can be found here (Blood and Blood products: Intravenous Immunoglobulin. CHQ-PROC-02910).
- Involve appropriate team if surgical repair or intervention is needed (such as ENT in patients with epistaxis, gynaecology in patients with menorrhagia etc.)
- Tranexamic acid orally (25mg/kg TDS to a maximum of 1500mg per dose), should also be considered.
 - Oral tranexamic acid is available in 500mg tablets only. The dose should be rounded to the nearest 250mg. Tablets can be crushed and mixed with water.
- Do not repeat FBC for at least 48hours after treatment has been completed unless clinically indicated for monitoring of anaemia etc.
- There is no role for platelet transfusion outside of acute life-threatening bleeds.

NOTE: Therapy with IVIg or prednisolone often has a short-term increase in platelet count, and it is not unusual for thrombocytopenia to recur on cessation of therapy. The goal of therapy is to manage haemorrhage rather than long term normalisation of platelet count.

Treatment of patients without life threatening bleeding

Bleeding Grade 0 to 3A (none to low/moderate risk of serious bleeding):

- This is defined as skin manifestations or a history of mucosal bleeding which on assessment has stopped.
 - These patients can be managed with close observation and education alone without the need for pharmacological therapy, regardless of the platelet count.
 - It is important that patients and families of patients with ND-ITP are given adequate education prior to discharge (see Discharge Management below), and that they are referred to the General Paediatric team of the hospital to ensure adequate followed up.

Discharge Management

Prior to discharge it is important that education of the family be given with respect to:

- Signs and symptoms of serious bleeding which would require urgent presentation to hospital:
 - Signs of intracranial haemorrhage – persistent or severe headache, irritability, lethargy, decreased consciousness, vomiting.
 - Epistaxis which is not resolved after 30 minutes with adequate pressure on nares.
 - Malena or haematuria.
- Parents should be told to avoid anti-platelet medications including aspirin and NSAIDs (such as ibuprofen), and to avoid certain over-the counter and herbal remedies which may also have anti-platelet effects.
- Head injury advice should be given to the family
 - See Head injury care after discharge fact sheet (CHQ Intranet) and Head injury: Emergency Management in Children (CHQ Guideline 00708)
- Activity restriction needs to be conveyed:
 - No contact sports or sports with significant risk of injury e.g. rugby, AFL, martial arts.
 - Limit the risk of head injury by not allowing children to climb great heights, supervision of children and infants on change tables, beds etc.

On discharge it is important that children with ITP are closely monitored and followed up by a General Paediatrician – **please ensure that the On-Call General Paediatrician has been consulted by the DEM staff and appropriate follow up has been arranged prior to discharge.**

- Patients should be seen within 1 week of discharge, with repeat FBC regardless of therapy received. Repeat education to families (as above) should again be provided at follow up.
 - **At QCH, the general paediatric team on call should review the patient in ED. Children seen in DEM who live outside of the catchment will need ongoing care to be arranged with the General Paediatrician in that catchment.**
- Future blood tests and clinic reviews are determined on the basis of patient and family knowledge of the disease (especially when to present for medical assessment), bleeding symptoms and platelet count. This is at the discretion of the General Paediatrician caring for the patient.
 - Weekly clinical reviews and FBC may be considered initially, however it is not unreasonable to review the patient, with a FBC at monthly intervals if they are stable and have no or minimal bleeding symptoms.

- Patients over 10 years of age and those that have required significant therapy for bleeding are more likely to have complications and early referral from the General Paediatric team to Haematology should be considered.

Please provide the ITP Factsheet to parents, along with contact details of treating teams prior to discharge.

Consultation

Key stakeholders who reviewed this version:

- Consultant Haematologist, Queensland Children's Hospital
- General Paediatrician, Queensland Children's Hospital
- Emergency Physician, Queensland Children's Hospital
- Senior Medical Pharmacist, Queensland Children's Hospital

References and suggested reading

1. ITP Factsheet (CHQ)
2. Head injury care after discharge fact sheet (CHQ Intranet)
3. Head injury: Emergency Management in Children (CHQ Guideline 00708)
4. Blood and Blood products: Intravenous Immunoglobulin. CHQ-PROC-02910.

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NSQHS Standards (1-8): Standards 4, 5 and 7

Appendix 1 – Immune Thrombocytopenia (ITP) in children Factsheet

What is Immune Thrombocytopenia?

Immune Thrombocytopenia (ITP) is a bleeding disorder that is caused by a shortage of platelets in the blood. Platelets are small cells in the blood that form a plug to help stop bleeding and bruising when a blood vessel is damaged.

Children with ITP do not have enough platelets to plug the source of bleeding.

What causes ITP?

The exact cause of ITP is unclear, but it involves activation of the immune system. Once activated the body produces antibodies which leads to the destruction of platelets in the spleen and elsewhere. This is known as an “autoimmune” disorder. Possible triggers may include viral infections.

How common is ITP?

Newly diagnosed ITP is relatively uncommon in children, affecting 1-3 in every 10,000 children.

What are the symptoms of ITP?

Common minor symptoms include:

- Easy bruising
- Red pinpoint spots on the skin (known as petechiae)
- Nose bleeds or mouth bleeding
- Excessive bleeding/bruising with injuries
- Prolonged menstrual bleeding in young women

Serious bleeding in children with ITP, such as bleeding into the brain and other internal bleeding, is rare.

How is ITP diagnosed?

ITP is diagnosed by combination of the child's history, physical examination findings and blood tests showing a low number of platelets, without any other abnormality. In typical cases, the diagnosis can be made on these findings alone without the need for further investigations.

What is the treatment of ITP?

The majority of children with ITP will get better by themselves usually within 12 months of diagnosis. The management of ITP is not focused on the platelet number but treating any serious bleeding symptoms your child has.

It is important to note that treatments used in ITP may have side effects, and although they may increase the platelet count while your child is being treated, they do not alter their recovery from ITP.

Children with no or only minor bleeding or bruising may not require any treatment. These children still need to be monitored by their treating doctor, to ensure there is no bleeding which may require treatment.

For children who develop more serious bleeding, there are treatment options available to increase their platelet numbers which will help stop bleeding. The main treatment options include corticosteroids (such as prednisone) and intravenous immunoglobulin (IVIg, Intragam).

What happens when I go home?

After discharge home, your child will need to come back to see your treating doctor. The time between visits depends on your child's symptoms. Please discuss this with your treating doctor.

Children with ITP should be able to participate in most activities and attend school. They will need to avoid activities that pose a risk of serious bleeding or head injury, such as climbing equipment, contact sports such as rugby or AFL and martial arts. These activities need to be avoided until the platelet count improves and can be discussed with your treating doctor.

If your child has a small cut or graze, apply normal first aid measures such as pressure and a band aid to stop the bleeding. This may take longer than usual.

Certain medications can interfere with how platelets work and should be avoided while the platelet count is low. These include:

- aspirin
- non-steroidal anti-inflammatory medications (NSAIDs), such as ibuprofen (Nurofen)

Some over the counter medications and herbal supplements/remedies also contain compounds which can stop platelets working correctly. Please seek medical advice before giving any of these substances to your child.

In a small number of children, the platelet count does not return to normal after 12 months. This is known as chronic ITP and may require further investigation. Many children with chronic ITP will still recover a normal platelet count over time and may not require specific therapy.

When should I seek medical attention?

You should seek medical attention if any of the below occur:

- Head injury
- Persistent or severe headache
- Vomiting or drowsiness
- Nose bleed lasting more than 15minutes and not improving with pinching the nose
- Prolonged bleeding from mouth, gums or throat
- Blood in the stool or urine
- Coughing up blood
- If you are worried your child is seriously unwell