Australia and New Zealand Consensus Guidelines for Paediatric Newly Diagnosed Immune Thrombocytopenia (ITP)

by

ANZCHOG

Australian & New Zealand Childrens Haematology/Oncology Group

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POSITION PAPER

Australian and New Zealand consensus guideline for paediatric newly diagnosed immune thrombocytopaenia endorsed by Australian New Zealand Children's Haematology and Oncology Group

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In children, the majority of cases are self-limiting and thus many paediatric patients can be managed conservatively with minimal complications. This varies considerably compared to adult newly diagnosed immune thrombocytopaenia (NDITP) where, in most cases, thrombocytopaenia persists with higher risk of moderate to severe bleeding complications. In the past decade, local and international guidelines have emerged to support approaches to the investigation and management of NDITP, with a focus primarily on adult immune thrombocytopaenia (ITP). International consen- sus guidelines on paediatric NDITP have been developed, however gaps remain, and approaches vary between North American, Asia, Europe and the UK. There are no current Australian or New Zealand paediatric ITP guidelines readily available, rather differing guidelines for each state, territory or island. These inconsistencies cause uncertainty for patients, families and physicians managing cases. Subsequently, physicians, including paediat- ric haematologists and general paediatricians, have come together to provide a consensus approach guideline specific to paediatric NDITP for Australian or New Zealand. Persistent or chronic paediatric ITP remains a complex and separate entity and are not discussed here.

Keywords: bleedingrisk;immunethrombocytopaenia;management;paediatrics;treatment.

Immune thrombocytopaenia (ITP) is a common cause of thrombocytopaenia in childhood occurring in 4–10 per 100 000 children a year caused by immune-mediated platelet destruction.[1–5] The majority of paediatric patients with newly diagnosed ITP (NDITP) will present with cutaneous and mucosal bleeding, however, may initially present with more significant bleeding, including gastrointestinal bleeding or intracranial haemorrhage (ICH). ICH secondary to ITP is rare, with an incidence of 0.5–1%, however, has potential devastating consequences and mortality rates as high as 25%.[1,2,6–8]

The unpredictability of ICH in NDITP can contribute to patient, parent and physician anxiety, which is compounded by the fact that there is no strong evidence showing therapy reduces the risk of ICH.[6,8–10] This anxiety often leads to overtreatment in paediatric NDITP with therapies that can potentially have significant toxicities. The development of consensus guidelines for management and treatment of ITP were established for adult patients due to the higher rates of severe bleeding. In 1996, the American Society of Hematology (ASH) published the first guidelines for the management of ITP, later updated in 2011 and 2019.[11] The international consensus guidelines (ICGs) were most recently updated in 2019.[9] Chinese, British and Italian guidelines were also reviewed last updated in 2021 and 2008, respectively.[12–14] Although all the guidelines commented on paediatric management of NDITP, not all were paediatric-specific.

Aim

This article aims to summarise paediatric NDITP and give clini- cians in ANZ guidance on investigation and management. How- ever, it is important to acknowledge that paediatric patients with

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NDITP will vary significantly in their presentations, social and geographical situation, and the decision on management should be individualised after discussion with the family around the ben- efits and possible risks of treatment.

Methods

This paper has reviewed local and international evidence statements, recommendations and any best practice guidance made with respect to the ANZ setting. When sufficient supporting evidence was found a recommendation for the local setting was made with a GRADE level applied (Table 1). When there was insufficient quality evidence, best practice statement guidance was made based on the consensus opinion on the guideline writ- ing group which includes general paediatricians or paediatric haematologists from each state, territory or island.

ITP was classified based on the current nomenclature proposed in 2009 by members of the International Working Group[18] as time from diagnosis to 3 months as NDITP, Persistent ITP (3–12 months from diagnosis) and chronic ITP (greater than 12months from diagnosis). As the management of persistent or chronic ITP varies, this consensus statement will only discuss the investigation and management of paediatric NDITP.

Diagnosis

The diagnosis of NDITP requires careful consideration, with a thorough history, examination and investigations. Paediatric NDITP presentations differ from the typical adult presentation of NDITP (Table 2). The typical paediatric presentation is of a well child with no significant prior medical history who has an increase in bruising and/or bleeding symptoms over a relatively short period (hours to days). ITP is a diagnosis of exclusion, with a broad differential diagnosis (Table 3).

NDITP in children most commonly presents between the ages of 2 and 10 years.[2,4,5,9,19] Infants and adolescents (under 1 and

Table1 GRADEsystemusedforrecommendations[15–17]

Strength of recommendation		
1	Strong	Whenthedesirableeffectsofanintervention clearly outweigh the undesirable effects
2	Weak	Whenthedesirableeffectsofanintervention clearly do not outweigh the undesirable effects
Levels of evidence		
A	High	Furtherresearchisveryunlikelytochangeour confidence in the estimate of effect (several high-quality studies with consistent results)
B	Moderate	Furtherresearchislikelytohaveanimportant impact on our confidence in the estimate of effect and may change the estimate (one high quality studies; or several studies with some limitations)
C	Low	Furtherresearchisverylikelytohaveanimportant impact on our confidence in the estimate of effect and is likely to change the estimate (one or more studies with severe limitations)
D	VeryLow	Anyestimateofeffectisveryuncertain(expert opinion; no direct research evidence; one or more studies with very severe limitations)

Table2 Typicalfeaturesversusatypicalfeaturesofnewlydiagnosed paediatric immune thrombocytopaenia

Typicalfeatures	Atypicalfeatures
Age2–10years	Familyhistoryofthrombocytopaenia
Isolatedthrombocytopaenia	Atypicalbloodfilmfeatures
Respondswelltosteroids/ IVIg	Olderage(adolescents)
Unremarkableexamination	Moderatethrombocytopaeniaonfirst presentation
Predisposingevent(i.e.viral infection)	Noresponsetofirst-linetreatment
	Previous recurrent infections

Table3 Differentialdiagnosisofimmunethrombocytopaenia

Congenital	Thrombocytopaeniaabsentradiussyndrome, Wiskott-Aldrich syndrome, MYH9-related disease (May-Hegglin anomaly, Epstein syndrome, Fechtner syndrome, Sebastian syndrome), radioulnar synostosis, congenital amegakaryocytic thrombocytopaenia, Bernard-Soulier syndrome, X-linked thrombocytopaenia, amegakaryocytic thrombocytopaenia, velocardiofacial syndrome, benign Mediterranean macrothrombocytopaenia, gray platelet syndrome, Jacobsen syndrome, familial platelet disorder/acute myeloid leukaemia
Infection	Sepsis,viralcauses(EpsteinBarr,varicella, influenza, rubella, cytomegalovirus, human immunodeficiency virus, hepatitis), tuberculosis
Impaired thrombopoiesis	Aplasticanaemia,bonemarrowpathology (malignancy/clonaldisorders–leukaemia, myelodysplastic syndromes, solid tumours; inherited bone marrow failure syndromes, e.g. Fanconi anaemia, dyskeratosis congenita; myelofibrsosi) paroxysmal nocturnal haematuria, cyclic thrombocytopaenia
Platelet sequestration	Hypersplenism(lysosomalstoragedisease,portal veinthrombosis,ALPS),sarcoidosis
Drugs	Sodiumvalproate,chloramphenicol,quinidine, indomethacin, rifampin
Consumption	DIC,thromboticthrombocytopenicpurpura, haemolytic uraemic syndrome, vasculitis, envenomation, type 2B von Willebrand disease.
Immune	Commonvariableimmunodeficiency,systemic lupus erythematosis, ALPS, recent vaccinations (MMR)
Other	Liverdisease,ETDA-inducedplateletclumping

ALPS, autoimmune lymphoproliferative syndrome; MMR, measles-mumps-r ubella.

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over 10 years) may develop ITP however minimal data is avail- able for those less than 2 years of age[4,14,18,20] and adolescents are more likely to progress to chronic ITP or an alternate diagnosis.[11,20,21] Neonatal thrombocytopaenia remains a separate entity and will not be discussed here.

Any constitutional signs or symptoms are atypical for an NDITP diagnosis and warrant further investigation (Table 2).[4,9] A detailed physical examination in a child with suspected NDITP is required as any associated congenital anomalies may indicate an alternative diagnosis. Inherited thrombocytopaenia should be considered in all patients with chronic thrombocytopaenia, a family history or failure to respond to therapy.[9,14]

Investigations

There is currently no specific diagnostic test for NDITP. Investigations are indicated to exclude alternate diagnoses (Table 3) and ancillary investigations are often only helpful in those patients with atypical presentations.

Evaluation of the full blood count and blood film by an experi- enced morphologist is required. A typical full blood count shows isolated thrombocytopaenia with normal platelet morphology.

Anaemia and signs of anaemia are not often present in ITP unless there has been significant acute bleeding. Anaemia in this instance is like to be normochromic and normocytic.

Coagulation studies are an optional investigation and are not routinely required for the diagnosis of NDITP (Fig. 1) and should be normal. They may be indicated if it remains unclear whether bleeding symptoms are mucocutaneous versus coagulopathic bleeding.

Testing for specific autoimmune or immune dysregulation disorders, such a common variable immunodeficiency or systemic lupus erythematosis, is not routinely advised in paediatric patients with typical NDITP.[4] The 2019 ICG made a low level recommendation in regards quantitative immunoglobulin level testing and direct antiglobulin test in that it may be useful in excluding immunodeficiency and autoimmune disease only prior to treatment with intravenous immunoglobulin (IVIg).[9,22] Immunoglobulin G, A and M levels may be a useful test prior to IVIg treatment as a baseline investigation and to provide addi- tional information into immunodeficiency syndromes or chronic inflammatory disorders.[9,22]

Local guidance

Routine immunoglobulin testing is not advised in a child with an uncomplicated presentation of ITP. Testing may be considered prior to treatment with IVIg (GRADE2C)

There remains inconclusive and conflicting evidence regarding Helicobacter pylori eradication and the improvement of platelet count following treatment.[4,9,14,22] Testing for H. pylori infection is recommended in certain geographical regions (i.e. Japan) with higher prevalence rates and CagA-positive strains, which are considered to be more pathogenic in ITP.[9]

Local guidance

Routine testing for H. pylori in NDITP is not advised in children in ANZ with NDITP (GRADE 2C).

Bone marrow analysis is not recommended in paediatric patients with typical presentations of NDITP in most centres[9–11,14,22,23] (GRADE 2C). It is suggested prior to corticosteroid treatment in NDITP in China and Italy despite the lack of strong evidence.[12,20] Typically, the bone marrow evaluation in a child with NDITP demonstrates normal trilineage haematopoiesis. It may be appropriate in those not responding to initial treatment, where splenectomy is considered, or if other abnormalities are detected in the blood count or morphology (GRADE C).

Local guidance

Bone marrow analysis is not advised in those with typical presentations of NDITP.

Assessment of Bleeding Risk

The assessment of severity of bleeding is difficult due to the lack of specific laboratory markers or validated assessment tools. Most cases of serious bleeding complications in patients with NDITP were associated with platelet counts <20 $\times 10^9$/L; however, this has little predictive value for severe bleeding.[24]

Notably, there is a lack of a consistent universal bleeding assessment tool in the literature. The ICGs use a grading system from 1–4 to determine severity whereas ASH and CPS use a terminology-based approach. The most widely used clinical bleeding assessment tool has been developed by Buchanan et al.[25] and Bolton-Maggs et al.[3] (Table 4) with some modifications.

The standardised clinical assessment and management plan is the modified Buchanan score (Table 4).[26] The standardised clinical assessment and management plan has been used in some local Australian guidelines, including Queensland and Western Australia.[26]

Local guidance

For consistency, we advise the modified Buchanan and Adix bleeding score for the assessment of bleeding risk for ANZ paediatric NDITP.

Mucosal bleeding, or 'wet purpura', has been long recognised as a risk factor for severe bleeding, although no direct correlation has been established.[6] Quantification for treatment of haematuria is not specified in the modified Buchanan and Adix Bleeding score and there is little evidence to suggest is associated with more significant bleeding (GRADE D).

Local guidance

We advise there is no role for routine urinalysis testing in asymptomatic children with NDITP. However, suggest clinical discretion for testing and treatment of microscopic haematuria (GRADE 2C).

Risk Stratification of Severe Bleeding

Goals of management for paediatric patients with NDITP are to minimise significant haemorrhage and maintain quality of life whilst avoiding unnecessary treatment. As most children with platelet counts <20 $\times 10^9$/L do not suffer significant bleeding, there is no clinical indication to treat based solely on platelet count (GRADE 2D).[9,22,23] Although treatment may increase

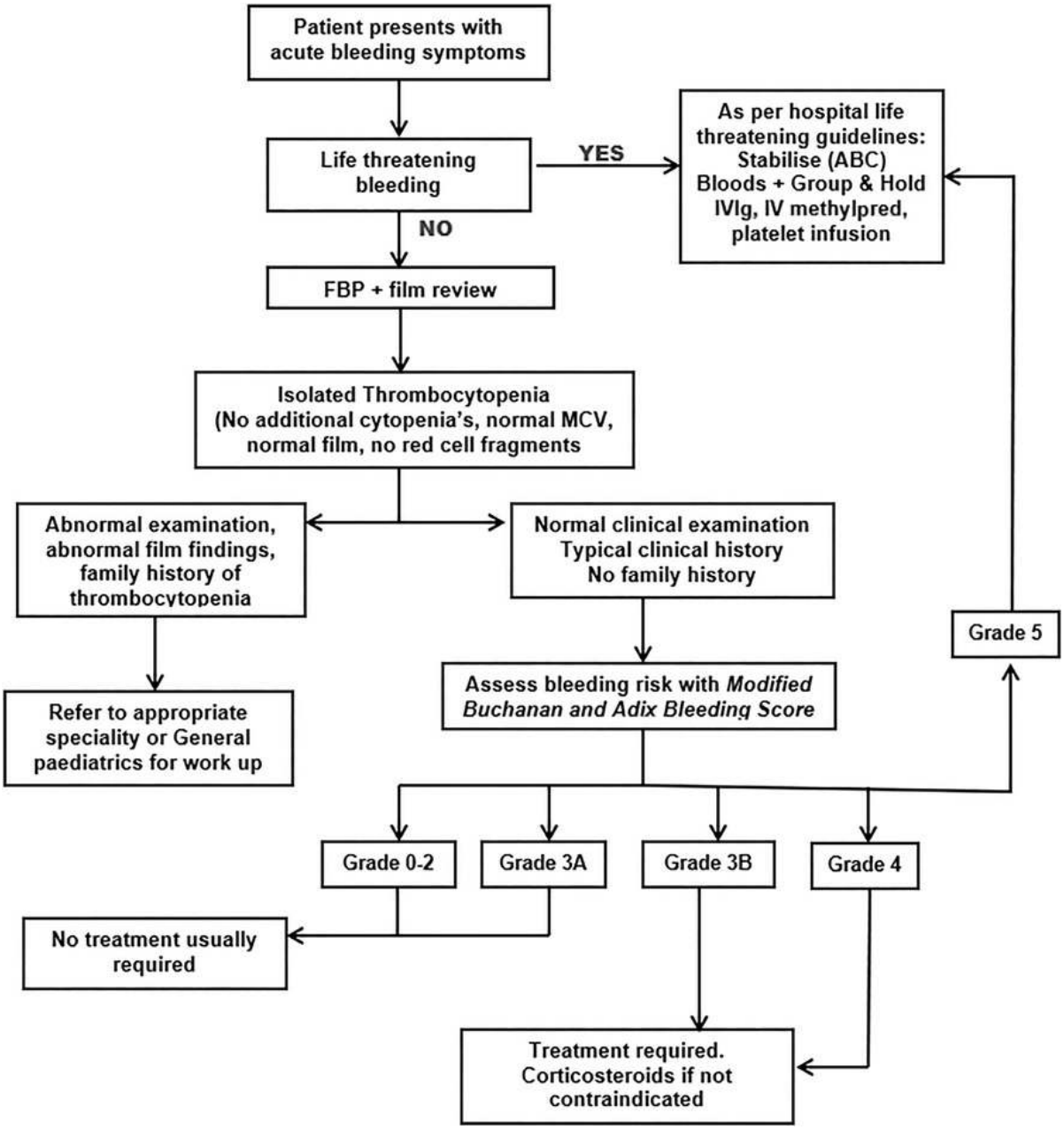

Fig. 1 Suggested approach to diagnosis and management of paediatric newly diagnosed immune thrombocytopaenia.

platelet numbers in the short term, there is no current evidence that treatment prevents or affects the risk of life-threatening bleeding complications or alters the natural history of ITP in childhood.[9,20,22,23]

Local guidance

We advise the decision to treat be based on bleeding presentation or risk of future bleeding not dependent solely on platelet count.

Risk factors associated with serious bleeding are not well definedbutincludelowplateletcount(<20 ^{9}10 /L), head trauma, and other signs of bleeding.[1,22] Severity of bleeding must include assessment of volume, duration and number of bleeding sites. Despite low platelet counts in both cohorts groups, those with bleeding at more than one site were more likely to have life-threatening bleeding.[7]

Considerations of treatment should be based on a bleeding assessment, age of the child and activity levels, risk of head injury, social considerations, accessibility to 24-h medical services and outcomes of parental discussions with the platelet count act- ing as a guide rather than the sole indicator for treatment (GRADE 1C).

We recommend a conservative 'watch and wait' approach in children with NDITP with no to mild bleeding (Score 3A or less – Table 4),[9] aligning with ICG, ASH, UK and CPS guidelines[10,23,27]

Table 4 Modified Buchanan and Adix bleeding score [24,25]

GRADE		
0	None	None whaemorrhage of any kind
1	Minor	Few petechiae (<100 total) and/or ≤5 bruises (≤3 cm diameter), no mucosal bleeding
2	Mild	Many petechiae (>100 in 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
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	Documented intracranial haemorrhage or life threatening or fatal haemorrhage at any site

(GRADE 2C). All patients managed conservatively should be provided with education around ITP and given clear instructions on potential bleeding complications, when to present for medical care. Follow-up with ongoing clinical evaluation and platelet monitoring is recommended by a General Paediatrician and/or Paediatric haematologist [9,11,14,22] (GRADE 2D).

For patients with significant bleeding (Table 4 – Grade 3B and above) therapy is usually required. In these cases, the actual therapeutic agent(s) used should be based on the severity, urgency and location of bleeding.

Management of Paediatric NDITP

First-line adjuncts

First aid and topical therapy is paramount with any bleeding symptom. Direct pressure, topical vasoconstriction agents or nasal packing devices may be used alone or in conjunction with alternative agents.[28] Supportive therapy with tranexamic acid for mucosal bleeding is a safe, cheap and often effective and can be used alone or as an adjunct. Tranexamic acid is contraindicated in patients with haematuria because of the risk of bladder clot formation.[4]

Cor ticosteroids

Randomised controlled trials comparing corticosteroid use in preventing bleeding to placebo (no treatment) have found no difference in the clinical outcome and platelet count recovery, however, play a role in cessation of acute bleeding complications.[29] For patients requiring treatment (non-severe), corticosteroids are recommended first-line therapy [9,10,14,22] (GRADE 1B).

Various corticosteroid regimens have shown to be effective with each guideline differing in their approach. Dose recommendations for prednisolone range from 2 to 4 mg/kg/day in divided doses for a duration of 4–14 days.[9,10,12,14,27] There has been no direct comparison between low-dose (2 mg/kg/day) and high-dose (4 mg/kg/day) prednisolone therapy.[9,14] Longer-term (>1–3 week course) corticosteroids should be avoided in children due to potential side-effects.[9,10,14,22,27] It is advised that corticosteroids be weaned or stopped once bleeding has ceased, a safe platelet count has been established or when treatment has not been successful.

Local guidance

We advise a short course of prednisolone at 2–4 mg/kg for a total of 4–5 days with a maximum dose of 100 mg/day (GRADE 2C).

Intravenous immunoglobulin

IVIg has been recommended as alternative first-line therapy in most guidelines.[9,10,14,22] IVIg at recommended guideline doses 0.8–1.0 g/kg has not been shown to lead to persistently elevated platelet counts or effect clinical outcome in paediatric NDITP.[9,14,20,30,31] However, is expensive, requires intravenous administration in hospital and potentially exposes the child to multiple donors. Side effects include headaches, flushing, fever, haemolytic anaemia, thrombosis and aseptic meningitis.[32]

Beck et al. showed that children receiving corticosteroid therapy for NDITP were 26% less likely to achieve a platelet count >20 109/L at 48 h after treatment compared to those with IVIg (independent of type of steroid or dosage of either therapy).[31] These outcomes were based on platelet count and noted no significant differences between ICH or any clinical relevant outcomes.[31]

Local guidance

We advise IVIg as a second-line therapy for children with NDITP unless corticosteroids are contraindicated (e.g. hypertension, obesity, hyperglycaemia, presence of severe infection) (GRADE 2C).

Second-line/alternate therapies

Platelet transfusions used in isolation are ineffective in ITP and should be limited to severe or life-threatening bleeding in combination with alternative treatments.[9,11,14]

The role for splenectomy in paediatric NDITP is limited, although may be warranted if disease is refractory the patient continues to demonstrate frequent or severe bleeding or those with impaired quality of life (GRADE 1B).[9]

Thrombopoietin receptor agonists are similarly effective in treating children ITP providing a sustained and durable platelet count in many children. Thrombopoietin receptor agonists are not routinely used in NDITP (used rather in persistent or chronic ITP) as they have limited impact on acute bleeding given the time to platelet incrementation is typically weeks.[33,34]

Medication avoidance

International and local guidelines for NDITP suggest avoidance of anti-platelet or anticoagulant medications with platelet counts <30 109/L despite minimal evidence.[9]

Local guidance

We advise avoidance of anti-platelet or anticoagulation medication if possible although not an absolute contraindication (GRADE 2D).

Hospitalisation indications

Rates of international hospitalisation have significantly reduced following recent publications of paediatric NDITP guidelines.[9] Aligning with the ICG guidelines, we suggest hospitalisation for children with high risk moderate bleeding (3B or above), overt mucosal bleeding, younger age or problematic circumstances (non-compliance, behavioural issues or rural/remote location) (GRADE 2C).[9]

Although a rural paediatric patient with typical NDITP with no or mild bleeding may be able to be managed locally, hospitalisation or transfer to a tertiary service should be considered in those who demonstrate atypical signs or symptoms, given the potential limitations in primary or rural settings in ANZ.

Discussion

In the last decade, international guidelines have suggested a more conservative approach in the treatment of NDITP in children. There has been no single consistent ANZ ITP guideline available for the investigation, bleeding assessment and management of paediatric NDITP, leaving inconsistencies between differing states, territories and islands. These inconsistencies are most likely due to the lack of robust evidence available in the paediatric population.

These guidelines aim to provide consensus recommendations provided by ANZ experts for the use of physicians and families. The absence of high-quality evidence-based data remains and additional large paediatric studies are required. This paediatric collaborative group aims to collect ANZ national data, review international literature and new therapies and use this information to further update and review these guidelines as new evidence becomes available. This guideline has been endorsed by ANZCHOG.

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Pretty girl in rain by Sofia Edelbi (aged 5) from "A Pop of Colour" art competition, Youth Arts, Children's Hospital at Westmead

Notes

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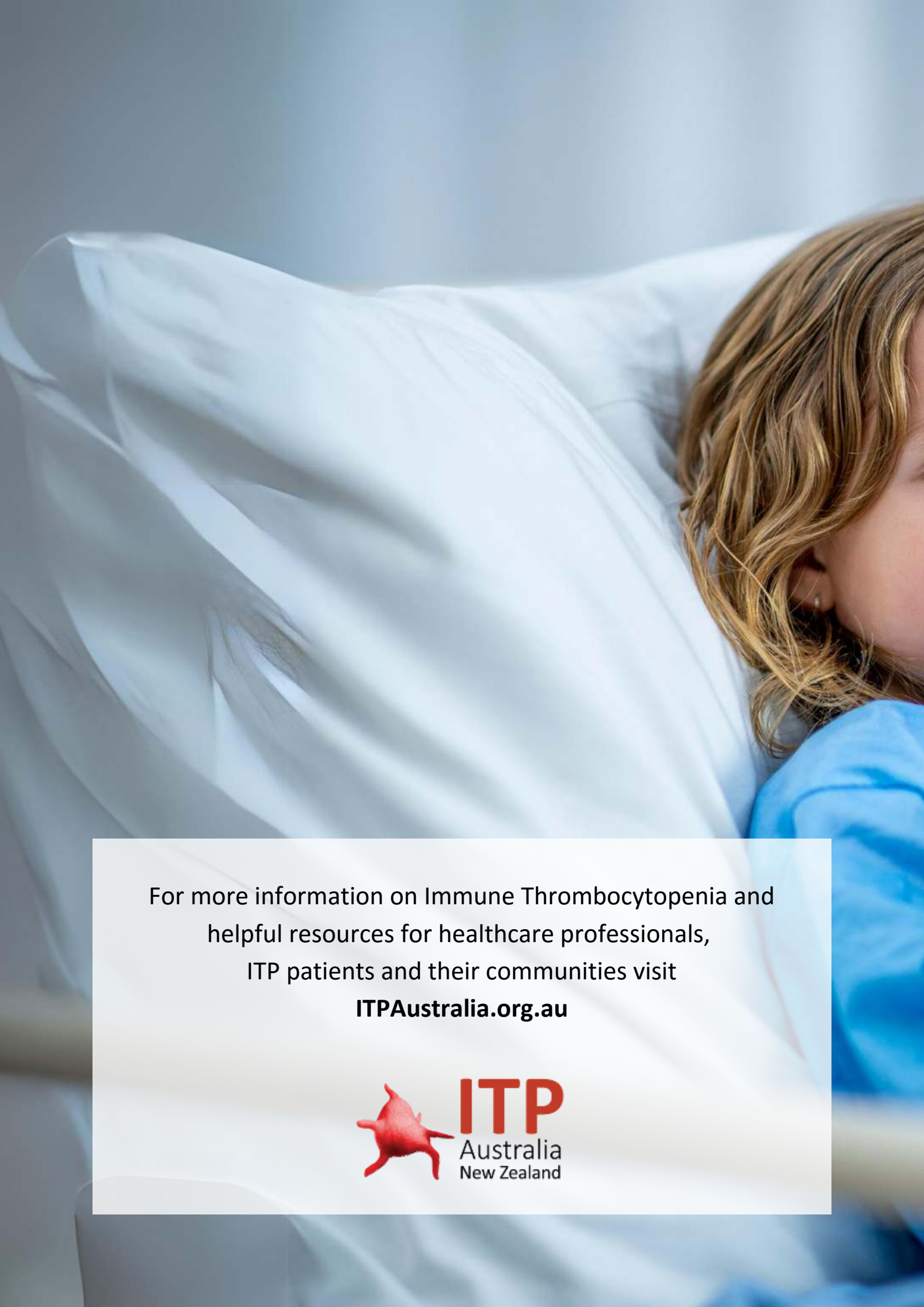

For more information on Immune Thrombocytopenia and helpful resources for healthcare professionals, ITP patients and their communities visit **ITPAustralia.org.au**

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