Specialist Working Group for Haematology

Proposed changes to the *Criteria for the clinical use of intravenous immunoglobulin in Australia, Second Edition*

ITEM	CRITERIA FOR THE CLINICAL USE OF INTRAVENOUS IMMUNOGLOBULIN IN AUSTRALIA, SECOND EDITION (CRITERIA)	PROPOSED REVISIONS TO THE CRITERIA	SWG RATIONALE FOR PROPOSED CHANGE (A) Administrative) (B) Progressive (C) Programmed
Condition Name	**Idiopathic (autoimmune) thrombocytopenic purpura (ITP) — in children 15 years and younger**	**Immune thrombocytopenic purpura (ITP) — in children 15 years and younger**	Condition name amended.
Specialty	Haematology	Haematology	
Chapter	6	6	
Specific Conditions		Newly Diagnosed ITP Persistent ITP Chronic ITP Evans syndrome	Revised terminology introduced for phase of disease as defined by the International Working Party on ITP. The use of specific conditions will support data analysis by phase of disease. SWG recommends tracking of Evan's Syndrome within AIHA, ITP –child and ITP-Adult, rather than a stand alone condition.
Level of Evidence	Clear evidence of benefit (Category 1).	Clear evidence of benefit (Category 1).	Unchanged
Description and Diagnostic Criteria	ITP is a reduction in platelet count (thrombocytopenia) resulting from shortened platelet survival due to anti-platelet antibodies. When counts are very low (<30x10^9/L) bleeding into the skin (purpura) and mucous membranes can occur. Bone marrow morphology is normal. In some cases, there is additional impairment of platelet function related to antibody binding to glycoproteins on the platelet surface. ITP is	ITP is a reduction in platelet count (thrombocytopenia) resulting from shortened platelet survival due to anti-platelet antibodies. When counts are very low (<30 x 10^9/L), bleeding into the skin (purpura) and mucous membranes can occur. Bone marrow morphology is normal. In some cases, there is additional impairment of platelet function related to antibody binding to glycoproteins on	

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	divided into chronic and acute forms. In children, the acute form is the most common. The disease tends to present abruptly with dramatic evidence of bleeding into the skin (petechiae and purpura) and mucous membranes (gum bleeding, nose bleeds, blood blisters). **Occurrence** Girls and boys are affected equally. In 75% of patients, the episode follows vaccination or a viral infection such as varicella or infectious mononucleosis. **Prognosis** At least 80–90% of children will have spontaneous remission of their disease within 6–12 months. In 5–10% of cases, the disease may become chronic (lasting >6 months). Morbidity and mortality from acute ITP is very low.	the platelet surface. ITP is divided into three phases of disease : newly diagnosed (less than 3 months since diagnosis), persistent (greater than 3 months but less than 12 months) and chronic (greater than 12 months).. In children, the newly diagnosed and persistent forms are the most common. The disease tends to present abruptly with dramatic evidence of bleeding into the skin (petechiae and purpura) and mucous membranes (gum bleeding, nose bleeds, blood blisters). **Occurrence** Girls and boys are affected equally. In 75% of patients, the episode follows vaccination or a viral infection such as varicella or infectious mononucleosis. **Prognosis** At least 80–90% of children will have spontaneous remission of their disease within 6–12 months. In 5–10% of cases, the disease may become chronic (lasting >12 months). Morbidity and mortality from newly diagnosed	Revised terminology is described and includes definitions of phases of disease. ITP IWP definition of Chronic ITP is >12 months.

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		or persistent ITP is very low.	
Justification for Evidence Category	Category 1 classification in the Biotext (2004) review was based on four low–moderate quality RCTs. The Frommer and Madronio (2006) review identified a good-quality systematic review/meta-analysis of RCTs to support the Category 1 classification.	Category 1 classification in the Biotext (2004) review was based on four low–moderate quality randomised controlled trials (RCTs). The Frommer and Madronio (2006) review identified a good-quality systematic review/meta-analysis of RCTs to support the Category 1 classification. A 2005 review on the management of Evans syndrome, based on Massachusetts Hospital data and a literature review, showed a transient response in all patients unless IVIg was given every three weeks (Norton and Roberts 2006). The review concluded that the data supported a role for IVIg in first-line therapy. It was not clear whether it was important for steroids to be given at the same time, although this is common practice. A total dose of 2 g/kg in divided doses appeared to be sufficient. The review also stated that there might be a role for IVIg in preference to steroids in the acute setting in very young children. A recent meta-analysis of 13 small RCTs comparing high dose (2g/kg) to lower dose (1g/kg) IVIg in newly diagnosed /persistent ITP demonstrated equivalent efficacy for all endpoints including platelet responses and	Unchanged

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		control of bleeding (Qin YH et al 2010).	
Diagnosis is required		No / Which Speciality	
Diagnosis must be verified		No / Which Specialty	
Exclusion Criteria	1. Platelet count >30x10^9/L. 2. Absence of significant bleeding.	Platelet count >30 x 10^9/L. Absence of significant bleeding.	
Indication for use	**ITP with platelet count <30 x10 ^{9}/L with significant bleeding**	**Newly diagnosed or persistent ITP with life-threatening bleeding.** **Newly diagnosed or persistent ITP with platelet count <30 x 10^9/L with significant bleeding.** **Chronic ITP with life-threatening bleeding.** **Chronic ITP in responsive patients with platelet count <30 x 10^9/L with moderate to severe bleeding symptoms where other therapeutic options have failed or are contraindicated.** **Chronic ITP in responsive patients prior to surgery to elevate platelet count to haemostatically safe levels.**	Original indication has been split into 5 indications to support the differing qualifying criteria and evidence items required for each. Amendments have been made to terminology for phase of disease.
Qualifying Criteria	**Note:** While the effectiveness of IVIg is not disputed, clinical experts advise that most children with ITP do not require IVIg therapy;	**Newly diagnosed or persistent ITP with life-threatening bleeding.** • Patients qualify for initial intravenous	Script has been deleted as it is incorrect. The indications have been tightly controlled however, where indicated, Ig is an important treatment option in children. Ongoing therapy however is

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	indeed, no treatment at all is required for many children. Corticosteroids are the alternative therapy to IVIg. **Acute ITP** 1. Life-threatening bleeding due to thrombocytopenia; OR 2. Thrombocytopenia with platelet count <30x10^9/L and moderate to severe mucosal and/or cutaneous bleeding. **Chronic ITP** 1. Life-threatening bleeding due to thrombocytopenia; OR 2. In responsive patients for treatment of thrombocytopenia (<30x10^9/L) with moderate to severe bleeding symptoms where other therapeutic options have failed or are contraindicated;	immunoglobulin (IVIg) therapy with life-threatening bleeding AND • Thrombocytopoenia <50 x 10^9/L. **Newly diagnosed or persistent ITP with platelet count <30 x 10^9/L with significant bleeding.** • Patients qualify for initial IVIg therapy when current platelet count is <30 x 10^9/L. AND • Moderate to severe mucosal and/or cutaneous bleeding. A repeat dose at 24–48 hours may be given if response is inadequate and recurrent symptomatic thrombocytopenia occurs. The duration of response to the initial dose is typically two to four weeks. **Chronic ITP with life-threatening bleeding.** • Patients qualify for initial IVIg therapy when ITP has been diagnosed for longer than 12 months AND • Patient has life-threatening bleeding due to thrombocytopenia <50 x 10^9/L.	not indicated. (A) SWG noted that above 50, life threatening bleeding is unlikely to be due to the low platelets and vessel injury must be sought. (A) Terminology for phase of disease has been amended.

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	OR 3. In responsive patients given before surgery to elevate the platelet count to haemostatically safe levels.	**Chronic ITP in responsive patients with platelet count <30 x 10^9/L with moderate to severe bleeding symptoms where other therapeutic options have failed or are contraindicated.** • Thrombocytopenia <30 x 10^9/L in a patient with chronic ITP with previously demonstrated response to Ig therapy AND • Moderate to severe bleeding symptoms AND • Other therapeutic options have failed or other treatment options are contraindicated. **Chronic ITP in responsive patients prior to surgery to elevate platelet count to haemostatically safe levels.** • IVIg responsive patient with chronic ITP and previous documented response to Ig therapy. AND • Pending surgery requiring haemostatically safe platelet count for relevant procedure: o minor dental work (>30 x 10^9/L) o major dental (>80 x 10^9/L)	

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		o minor surgery (>50 x 10^9/L) o major surgery (>80 x 10^9/L) o major neurosurgery (>100 x 10^9/L).	
Review Criteria	• Platelet count at 48 hours. • Control or resolution of bleeding. • Duration of effect. • Progression to chronic ITP.	**Newly diagnosed or persistent ITP with life-threatening bleeding.** Review Is not mandated for this indication however the following may be useful in assessing the effectiveness of Ig therapy. **Outcome data to be measured** o Resolution of active bleeding o A reduction in evidence of bleeding correlating with a doubling of platelet count or in platelet count > 10^9/L within 7 days o In patients without active bleeding a doubling of baseline platelet count and a rise in platelet count > 30 x 10^9/L was demonstrated within 7 days of previous Ig therapy **Newly diagnosed or persistent ITP with platelet count <30 x 10^9/L with significant bleeding.** Review Is not mandated for this indication however the following may be useful in assessing the effectiveness of Ig therapy.	SWG advised that ongoing treatment is inappropriate in children and maintenance dosing is not required. Each dose should be requested as required (when the patient is bleeding) and eligibility criteria than are to be fulfilled on each occasion. SWG observed that the treatment of life threatening bleeding is IVIg, steroids and platelets given as quickly as possible so difficult to know what is the most important element in each case. Outcome measures have been amended in response to feedback and aligned with outcome measures in Adult ITP. The revised measures recognise that a demonstration of response to Ig therapy may take up to 7 days.

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		One repeat dose at 24–48 hours may be given if response is inadequate and recurrent symptomatic thrombocytopenia occurs. The duration of response to the initial dose is typically two to four weeks. **Outcome data to be measured** o Resolution of active bleeding o A reduction in evidence of bleeding correlating with a doubling of platelet count or in platelet count > 10^9/L within 7 days o In patients without active bleeding a doubling of baseline platelet count and a rise in platelet count > 30 x 10^9/L was demonstrated within 7 days of previous Ig therapy **Chronic ITP with life-threatening bleeding.** Review Is not mandated for this indication however the following may be useful in assessing the effectiveness of Ig therapy. **Outcome data to be measured** o Resolution of active bleeding o A reduction in evidence of bleeding correlating with a doubling of platelet count or in platelet count >	

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		10 ^{9}/L within 7 days o In patients without active bleeding a doubling of baseline platelet count and a rise in platelet count > 30 x 10 ^{9}/L was demonstrated within 7 days of previous Ig therapy **Chronic ITP in responsive patients with platelet count <30 x 10^{9}/L with moderate to severe bleeding symptoms where other therapeutic options have failed or are contraindicated.** Review Is not mandated for this indication however the following may be useful in assessing the effectiveness of Ig therapy. **Outcome data to be measured** o Resolution of active bleeding o A reduction in evidence of bleeding correlating with a doubling of platelet count or in platelet count > 10 ^{9}/L within 7 days o In patients without active bleeding a doubling of baseline platelet count and a rise in platelet count > 30 x 10 ^{9}/L was demonstrated within 7 days of previous Ig therapy **Chronic ITP in responsive patients prior to surgery to elevate platelet count to haemostatically safe levels.**	

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		Review Is not mandated for this indication however the following may be useful in assessing the effectiveness of Ig therapy. **Outcome data to be measured** o Resolution of active bleeding o A reduction in evidence of bleeding correlating with a doubling of platelet count or in platelet count > 10^9/L within 7 days o In patients without active bleeding a doubling of baseline platelet count and a rise in platelet count > 30 x 10^9/L was demonstrated within 7 days of previous Ig therapy	
Dose	**Acute ITP** Life-threatening bleeding: up to 2 g/kg total dose, generally given as 2 doses of 1 g/kg. Other indications: 0.5 g/kg given as a single dose,	**Newly diagnosed or persistent ITP with life-threatening bleeding.** **Induction Dose:** 0.8 given as a single dose. One repeat dose at 24–48 hours may be given if response is inadequate and recurrent	

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	repeated at 24–48 hours if the response is inadequate. A higher total dose of 2 g/kg may be required in 5–10% of cases. Duration of response to initial dose is typically two to four weeks. A repeat dose may be considered if recurrent symptomatic thrombocytopenia occurs. **Chronic ITP** Life-threatening bleeding: up to 2 g/kg total dose, generally given as 2 doses of 1 g/kg. **Other indications:** 0.5 to 1 g/kg at intervals generally > three weekly. **Dosing above 1 g/kg per day is contraindicated for some IVIg products.** **Refer to the current product information sheet for further information.** **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.**	symptomatic thrombocytopenia occurs. The duration of response to the initial dose is typically two to four weeks. The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient. Dosing above 1 g/kg per day is contraindicated for some IVIg products. **Refer to the current product information sheet for further information.** **Newly diagnosed or persistent ITP with platelet count <30 x 10^9/L with significant bleeding.** **Initial therapy:** 0.8 g/kg given as a single dose. One repeat dose at 24–48 hours if the response is inadequate and symptomatic thrombocytopenia occurs. The duration of response to the initial dose is typically two to four weeks. The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient. Dosing above 1 g/kg per day is contraindicated	Dosing scripts have been revised.

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		for some IVIg products. **Refer to the current product information sheet for further information.** **Chronic ITP with life-threatening bleeding.** **Initial therapy:** 0.8 g/kg given as a single dose. One repeat dose at 24–48 hours if the response is inadequate and symptomatic thrombocytopenia occurs. The duration of response to the initial dose is typically two to four weeks. The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient. Dosing above 1 g/kg per day is contraindicated for some IVIg products**.** **Refer to the current product information sheet for further information.** **Chronic ITP in responsive patients with platelet count <30 x 10^9/L with moderate to severe bleeding symptoms where other therapeutic options have failed or are contraindicated.** **Initial therapy:** 0.8 g/kg given as a single dose.	Maintenance treatment has not been supported for chronic ITP or any other indications.

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		The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient. Dosing above 1 g/kg per day is contraindicated for some IVIg products. **Refer to the current product information sheet for further information.** **Chronic ITP in responsive patients prior to surgery to elevate platelet count to haemostatically safe levels.** **Initial therapy:** 0.8 g/kg given as a single dose. The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient. Dosing above 1 g/kg per day is contraindicated for some IVIg products. **Refer to the current product information sheet for further information.**	

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