Consensus Guidelines for the Management of

Adult Immune Thrombocytopenia (ITP)

in Australia and New Zealand

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THANZ
Thrombosis & Haemostasis society of Australia and New Zealand

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For more information about ITP Australia and New Zealand, visit our website:

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Consensus guidelines for the management of adult immune thrombocytopenia in Australia and New Zealand

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Abstract

Introduction: The absence of high quality evidence for basic clinical dilemmas in immune thrombocytopenic purpura (ITP) underlines the need for contemporary guidelines relevant to the local treatment context. ITP is diagnosed by exclusions, with a hallmark laboratory finding of isolated thrombocytopenia.

Main recommendations: Bleeding, family and medication histories and a review of historical investigations are required to gauge the bleeding risk and possible hereditary syndromes. Beyond the platelet count, the decision to treat is affected by individual bleeding risk, disease stage, side effects of treatment, concomitant medications, and patient preference. Treatment is aimed at achieving a platelet count > 20×10^9/L, and avoidance of severe bleeding. Steroids are the standard first line treatment, with either 6-week courses of tapering prednisone or repeated courses of high dose dexamethasone providing equivalent efficacy. Intravenous immunoglobulin can be used periprocedurally or as first line therapy in combination with steroids.

Changes in management as a result of this statement: There is no consensus on choice of second line treatments. Options with the most robust evidence include splenectomy, rituximab and thrombopoietin receptor agonists. Other therapies include azathioprine, mycophenolate mofetil, dapsone and vinca alkaloids. Given that up to one-third of patients achieve a satisfactory haemostatic response, splenectomy should be delayed for at least 12 months if possible. In life-threatening bleeding, we recommend platelet transfusions to achieve haemostasis, along with intravenous immunoglobulin and high dose steroids.

Local guidelines are needed to assist clinicians treating immune thrombocytopenic purpura (ITP) in Australia and New Zealand. Although many excellent summaries have recently been published for audiences elsewhere, we present our accumulated consensus perspectives on the diagnosis and management of ITP, specifically addressing clinically relevant areas where there are limitations to the available evidence[1-3] (the guideline development process is described in the online Supporting Information, box). We are members of the Thrombosis and Haemostasis Society of Australia and New Zealand (THANZ). This consensus statement has been endorsed by the THANZ Council and ITP Australia. ITP Australia provided patient perspective feedback on our recommendations.

We have used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to evaluate this evidence and provide recommendations.[4] Recommendations have been graded dichotomously as either strong (1) or weak (2), and appended based on the levels of available evidence, rated according to their quality (Box 1).

We followed the internationally accepted guidelines on determining response defined as: "response" if platelet count is ≥ 30×10^9/L and there is at least a twofold increase of the baseline platelet count and absence of bleeding; "complete response" if platelet count is ≥ 100×10^9/L and absence of bleeding.[6]

Initial investigations

The diagnosis of ITP is one of exclusion, and the extent to which other potential diagnoses need to be excluded varies depending on age, sex and response to treatment. A definitive diagnosis cannot always be made before starting treatment. A response to first line therapy with steroids supports the diagnosis of ITP, whereas absence of response does not exclude ITP but raises the likelihood of alternative causes of thrombocytopenia. Detection of autoantibodies in immune thrombocytopenia is neither sensitive nor specific enough for diagnostic utility.[7]

The most common alternative diagnoses are myelodysplastic syndrome, familial thrombocytopenia syndromes, hypersplenism, liver disease, and pseudothrombocytopenia.[8]

Bleeding, family and medication histories and review of historical investigation results are required to gauge bleeding risk and possible hereditary syndromes. A large number of medications and substances can cause thrombocytopenia, such as tonic water (quinine), antibiotics (sulphonamides, chloramphenicol), and alcohol; therefore, a thorough clinical history is critical and reference to comprehensive online resources may be helpful.[9,10]

Physical examination should focus on assessing for bleeding manifestations as well as splenomegaly and lymphadenopathy. Dysmorphic features are associated with some familial thrombocytopenia syndromes.[11]

The hallmark laboratory finding of ITP is an isolated thrombocytopenia, and a raised immature platelet fraction can be helpful.[12] Microcytic anaemia may be coexistent if thrombocytopenia has contributed to chronic blood loss and subsequent iron deficiency.

Blood film examination is critical in excluding alternative diagnoses, particularly those requiring urgent therapy, such as thrombotic thrombocytopenic purpura (TTP) (Supporting Information, table S1).

Renal and liver function tests should be normal in ITP. New renal dysfunction may raise the possibility of diseases such as a complement-mediated thrombotic microangiopathy, or TTP. Congenital thrombocytopenia may be suspected if there is a relevant family history, concomitant clinical features, no prior

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1 Grading system employed to append recommendations*

Strength of recommendation	
1	Strong
2	Weak
Levels of Evidence	
A	High quality meta-analysis
B	Robust phase 3 studies
C	Well designed phase 2 studies, or good quality case series
D	Expert panel consensus

*Strength of recommendation and grading of evidence as reviewed by the expert panel from 1 January 1996 to 1 February 2021.[4,5] Statements graded (1A) are strong consensus recommendations supported by high quality meta-analyses, while statements graded (2D) are weak opinions unsupported by any evidence but agreed upon by all authors. ◆

normal platelet count, or lack of response to first line therapy. Consider genetic testing in such patients.

Hepatitis C virus and human immunodeficiency virus (HIV) infections are recognised secondary causes of ITP and without treatment of the underlying virus, the response to therapy can be suboptimal.[13]

Women of childbearing potential should be investigated for pregnancy. Unlike most autoimmune diseases, ITP tends to flare during pregnancy, and the management of ITP in pregnancy is more constrained due to potential fetal toxicities.[14] It is vital that new onset thrombocytopenia occurring later in pregnancy is evaluated expeditiously to exclude pre-eclampsia and other potentially life-threatening diseases of pregnancy. Differentiation between ITP and gestational thrombocytopenia can be difficult. An approach to thrombocytopenia in pregnancy has been recently published.[15]

Detection and eradication of *Helicobacter pylori* with subsequent remission of ITP has been reported, with highest rates of success in Asian populations.[16] In our experience, this has not been successful in most areas of Australia and New Zealand, but may be considered in patients of ethnic backgrounds where supportive data exist (Asia, Middle East, Mediterranean, Latin America), and particularly in those with mild to moderate thrombocytopenia (GRADE 2A).[17,18] As eradication is inexpensive and treatment reasonably well tolerated, we also consider testing for *H. pylori* before performing an irreversible procedure such as splenectomy (GRADE 2C).[19]

Bone marrow biopsy is not generally required as part of the initial work-up, unless myelodysplasia needs to be excluded in older patients (aged > 60 years), or in the presence of laboratory abnormalities such as macrocytosis, blood film dysplasia, or after an atypical presentation with slowly deteriorating platelet counts over many years without fluctuation.[20] Cytogenetic analysis is recommended (GRADE 1D). We would usually consider performing a bone marrow biopsy before splenectomy (GRADE 2D).

Initial treatment

When to treat

The decision to treat should factor in not only the platelet count but also individual bleeding risk (based on personal history and comorbidities), disease stage (newly diagnosed *v* persistent or chronic), side effects of treatment, age, concomitant medications, and patient preference.[3] We recommend treatment for newly diagnosed ITP when platelet counts are consistently < 20×10^9/L, even in the absence of bleeding (GRADE 1C).[21,22] If the patient has no or only mild bleeding and platelets > 20×10^9/L, then a watch-and-wait strategy is usually appropriate (GRADE 2C).[23]

First line treatment

Steroids. Steroids are the standard first line treatment, usually prednisone or dexamethasone. Several regimens are used, but if choosing prednisone, we recommend a starting dose of 1 mg/kg/day for the first 2 weeks, followed by a tapering regimen over 6 weeks (GRADE 1C).[24] Consider initially capping the dose to 75–80 mg once daily, even for patients weighing > 80kg (GRADE 2D).[1]

An alternative regimen is dexamethasone 40 mg or 0.6 mg/kg orally once daily for 4 days, every 14–28 days for one to six cycles (GRADE 1C).[3,25] Some investigators report higher remission rates with pulsed dexamethasone as opposed to standard-dose prednisone, with fewer adverse effects.[26,27] The dexamethasone dose can be attenuated to 20 mg for older patients (GRADE 2D).

Patients requiring longer term steroid therapy (steroid-dependent after more than 8–10 weeks) or repeated courses of steroid therapy should be referred to a tertiary centre with experience in ITP (GRADE 2D).

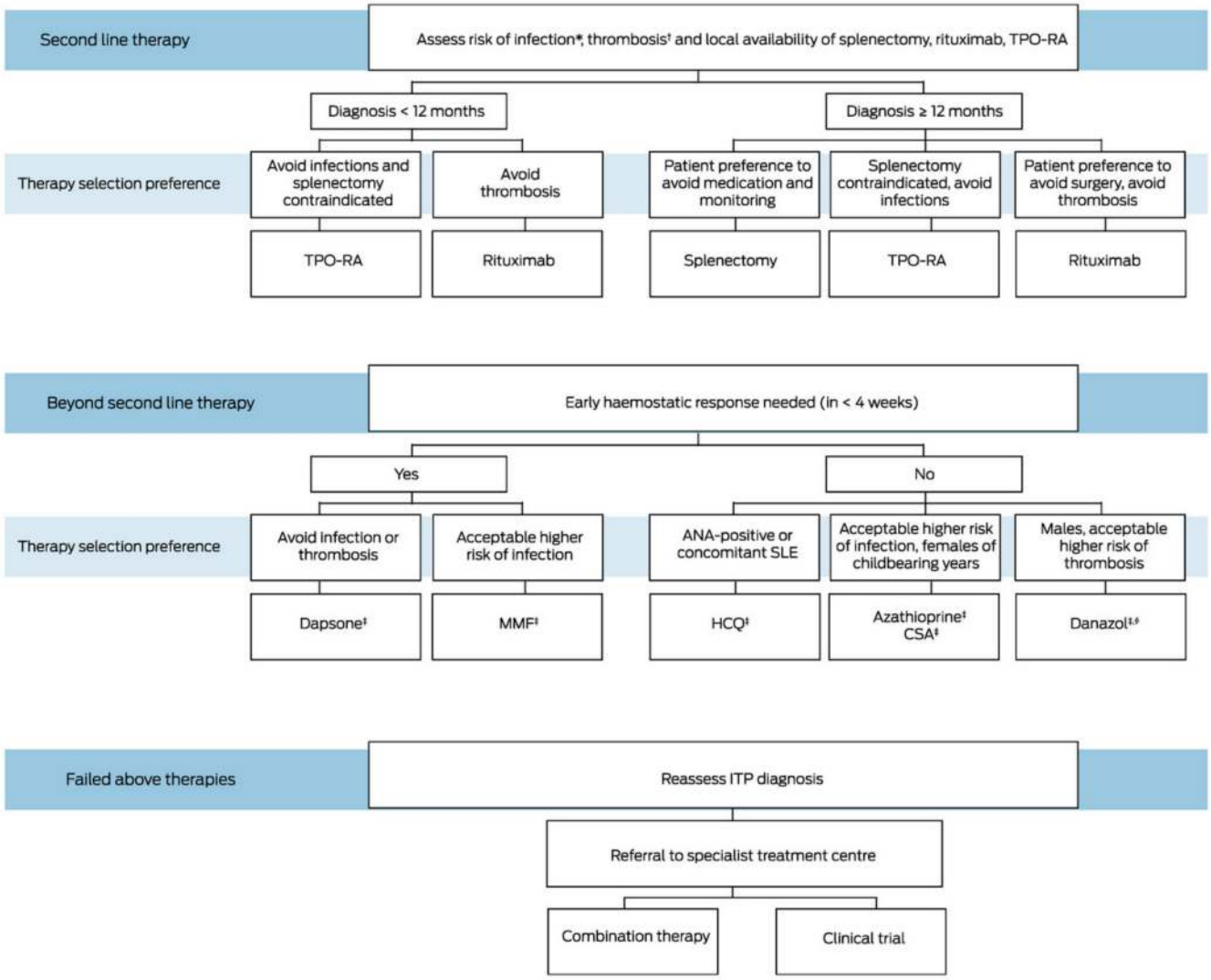
Our panel agrees there is clinical equipoise between prednisone versus dexamethasone, with prednisone favoured in older patients less likely to tolerate the neuropsychiatric side effects of dexamethasone, and dexamethasone favoured in those seeking a more rapid response with shorter overall duration of steroid exposure.

Intravenous immunoglobulin (IVIg). IVIg can be used periprocedurally as on-demand or as first line therapy in combination with steroids. The 5% and 10% formulations appear to have similar efficacy (response rates about 75%).[28] Dosing options include 0.4 g/kg daily for 3–5 days or 1 g/kg for 1–2 days, with the latter option being associated with a faster response.[1,29] Therapy with prednisone or dexamethasone can be combined with IVIg, or intravenous methylprednisolone can be substituted for the oral steroid, if there is a need for a more rapid response (GRADE 1C).[30] In Australia, IVIg availability is facilitated through the BloodSTAR program and in New Zealand via New Zealand Blood Service. Criteria permitting access to IVIg generally require thrombocytopenia < 30×10^9/L, the presence or perceived risk of bleeding, poor response to other therapies (steroids in newly diagnosed ITP or splenectomy in chronic ITP), and special clinical circumstances (pregnancy, periprocedural).[31] In New Zealand, IVIg is available as first line therapy at the discretion of the haematologist. Subcutaneous immunoglobulin and anti-D are not available in Australia and New Zealand for ITP.

Second line treatments

There is no consensus on which second line treatment for ITP should be attempted first. There is also no reliable predictor of response to second line treatments. Patients should switch to a second line treatment when the first line treatment has not obtained a haemostatic response. The risk of bleeding and mortality increases with platelet counts < 20×10^9/L; hence, treatment is often aimed at achieving a platelet count > 20×10^9/L and avoidance of severe bleeding.[24,32]

2 Management of immune thrombocytopenic purpura with second line therapies and beyond



CSA = ciclosporin; HCQ = hydroxychloroquine; MMF = mycophenolate mofetil; SLE = systemic lupus erythematosus; TPO-RA = thrombopoietin receptor agonists. * Patient with acute or chronic infections or a past history of life threatening infection. † Patient with a past history of thrombosis. ‡ Steroids are often administered concurrently with these medications while awaiting response. § Access issues as described in text above. ◆

Inadequate haemostatic response with > 5 mg/day of prednisone, three to four cycles of high dose dexamethasone, or with one or more courses of IVIg represent failure of first line treatment.[1,3]

Patient preferences, age, lifestyle, comorbidities, and drug availability are important when considering when to start a second line treatment and which treatment modality to adopt (GRADE 1D).

Splenectomy, rituximab and thrombopoietin receptor agonists (TPO-RAs) have the most robust evidence in terms of efficacy and safety and hence it is recommended that these three options be discussed with patients as suitable second line treatments (GRADE 1C)[33] (Box 2). Some patients are reluctant to undergo splenectomy if there is a non-surgical alternative.[34,35] Public reimbursement for TPO-RAs in Australia and New Zealand is limited to later lines of therapy unless there are medical contraindications to splenectomy.

Given that up to one-third of patients achieve a satisfactory haemostatic response (either spontaneously or with treatment), we agree with most other international guidelines on ITP that splenectomy be delayed for at least 12 months (GRADE 1C).[1,36] Therefore, for patients with ITP with a disease duration of less than 12 months, TPO-RAs and rituximab should be pursued as first choice second line treatment. If TPO-RAs and rituximab are not accessible or have failed, other options need to be explored, as described below.

Splenectomy

Efficacy. Splenectomy is associated with the greatest likelihood of durable remission, with a long term response rate of 60–70%.[37,38] Splenic patterns of uptake on indium-labelled autologous platelet scanning have been reported to be predictive of splenectomy response, but this radioisotope is difficult to obtain in Australasia.[39-41] Higher relapse rates to splenectomy have been reported in older patients (aged > 65 years).[42]

Adverse events. Infections and thromboembolism are the main complications associated with splenectomy, both acutely and longer term.[37,42] Patients aged over 65 years are more susceptible to these complications.[42,43] Laparoscopic splenectomy is associated with shorter hospitalisation stay and reduced perioperative bleeding and patient discomfort compared with laparotomy.[44,45]

Vaccinations against encapsulated bacteria *Neisseria meningitidis*, *Streptococcus pneumoniae* and *Haemophilus influenzae* should be administered before splenectomy and rituximab when possible (GRADE 1C).[46] Postoperative thromboprophylaxis and antibiotic prophylaxis should be administered as per local and national guidelines for splenectomy, but patients with ITP are at a higher risk of thrombosis. For patients living in Victoria, Queensland and Tasmania, patient registration with Spleen Australia (http://spleen.org.au) can assist in optimising follow-up and surveillance.

Patient selection. Splenectomy should be considered in patients aged less than 65 years, with disease duration greater than 12 months, and for whom this option impacts least on their lifestyle (GRADE 2D).[1,42] Patients without a history of thrombosis or infections are favourable candidates for splenectomy (GRADE 2D).

Rituximab

Efficacy. Rituximab is an antibody directed against CD20, leading to B lymphocyte depletion. Early (1–2 weeks) and late (8–12 weeks) responses have been observed with rituximab.[47] While 50–70% of patients achieve an initial response to rituximab monotherapy, the long term response rate of 20–25% is less and lower than splenectomy.[48] Response rates are reported to be higher in females, in patients with shorter disease duration (< 1–2 years), in younger patients (aged < 40 years), and when combined with dexamethasone.[49,50]

Administration and dosing. Rituximab dosing regimens administered in ITP include 375 mg/m^2/week for 4 weeks, 1 g rituximab on day 1 and day 15, and 100 mg/week for 4 weeks.[51,52] Time to response has been reported to be slower in lower dose strategies, but there is no advantage in response rate with standard or higher dose regimens.[53] While in Australia rituximab is not reimbursed for ITP by the Pharmaceutical Benefits Scheme (PBS), the advent of rituximab biosimilars has reduced the cost of rituximab, and we anticipate this will improve access through local institutions. In New Zealand, rituximab is available on the Pharmaceutical Management Agency (PHARMAC) before splenectomy or in refractory cases. Readministration of rituximab can be considered in patients who have obtained an initial response of more than 12 months (GRADE 2C).[54]

Adverse events. Rituximab is generally well tolerated. Infusion reactions are more likely to occur with standard dose or 1 g rituximab infusions, and successful B-cell depletion is associated with an increased risk of infections. A serious but very rare complication of rituximab is progressive multifocal leukoencephalopathy. Hepatitis B carrier status should be reviewed before treatment commencement due to the risk of reactivation (GRADE 1C).[55] Vaccine responses can be suppressed by rituximab for up to 6 months; therefore, potential candidates for subsequent splenectomy in rituximab failure should be offered vaccinations before commencing rituximab therapy (GRADE 1D).[56]

Patient selection. Rituximab should be considered in patients who have expressed a strong preference to avoid surgery. We recommend administering rituximab with high dose dexamethasone (up to three cycles) (GRADE 1C).[49] Rituximab is favoured for patients without a concomitant immunodeficiency and for those at risk of thrombosis (GRADE 1D). Rituximab should be considered in younger, female patients with short disease duration (< 1–2 years) (GRADE 2C).[49]

TPO-RAs: eltrombopag and romiplostim

Efficacy. Eltrombopag and romiplostim have been validated in randomised placebo-controlled trials in patients with persistent and chronic ITP, showing response rates of 60–90% as early as 2–3 weeks.[57,58] However, durable responses with persisting robust platelet counts is lower and in the order of 40–60%.[59,60] Nevertheless, TPO-RAs significantly reduce the incidence of severe bleeding and the need for rescue therapy, and improve health-related quality of life measures.[61,62]

Administration and dosing. Eltrombopag is given once daily orally while romiplostim is dosed as a weekly subcutaneous injection. Eltrombopag dosing starts at 50 mg daily (25 mg daily in East Asian people) and can be increased up to a maximum of 75 mg daily.[63] Eltrombopag must be given on an empty stomach; in particular, it should be taken 4 hours after or 2 hours before products or food containing cations (calcium, dairy products, iron supplements).

Romiplostim dosing starts at 1 µg/kg/week, and can be increased up to a maximum of 10 µg/kg/week until a response is achieved. In cases where a rapid response is needed, we recommend starting with the contents of one small vial (250–375 µg), which is often approximately 3–4 µg/kg (GRADE 1D).

Approval for continuing PBS reimbursement after 24 weeks for TPO-RAs requires demonstration of a platelet-count response. In Australia, this response is defined as four separate platelet counts i) ≥ 50 × 10^9/L or ii) > 30 × 10^9/L and double baseline platelet count; in New Zealand, response is defined as platelet counts ≥ 50 × 10^9/L.

Unfortunately, these response definitions fail to recognise a clinically observed response where platelet counts improve, patients experience less bleeding, but the platelet counts may not meet strict response criteria. It is helpful to document the lowest baseline platelet count before TPO-RAs commencement to meet these criteria subsequently (GRADE 2D). In addition, we recommend repeat platelet count testing frequently to establish the required evidence of response for PBS reimbursement rather than abandoning therapy, as platelet counts can fluctuate in some cases (GRADE 2D). Without resorting to rescue therapies, adjunctive strategies may also be helpful to support platelet counts to help meet PBS criteria for reimbursement (Box 3) (GRADE 2D).

Treatment-free response and discontinuation. About 10–30% of patients taking TPO-RAs are able to discontinue and maintain a treatment-free response.[72] Predictors for treatment-free response are not established; however, TPO-RAs discontinuation may be considered in patients maintaining platelet responses > 50 × 10^9/L for more than 6–12 months, absence of previous major bleeding, and/or requiring only low doses of TPO-RAs (GRADE 2D). Given the risk of rebound thrombocytopenia, TPO-RAs discontinuation should not occur abruptly, but it should be done with a slow taper. We recommend that discontinuation be delayed if there is a history of significant platelet count fluctuation, variable adherence to therapy, past major bleeding, or sudden relapse (GRADE 1D). Tapering to cessation can be commenced sooner if platelet counts are persistently above 200 × 10^9/L (GRADE 2D). In contrast, about 30% of patients discontinue TPO-RAs because of a lack of response.[73] Switching from one TPO-RA to another has been shown to be effective for some patients and is permissible for PBS reimbursement with written application.[61]

3 Other long term therapy options for adult patients with immune thrombocytopenic purpura

Medication	Funding	Patient selection	Recommended dose and treatment strategy	Response rate	Time to response	Toxicities
Azathioprine[64]	• General schedule on the PBS • PHARMAC-funded	• No access to TPO-RAs or rituximab, and patients who have expressed a preference to avoid surgery • Acceptable safety profile in pregnancy[14,65]	• 1–3 mg/kg per day (50–200 mg daily) • Concomitant steroids are usually required when starting treatment	40–60%	3–4 months	• Perform TPMT assay to confirm normal enzyme clearance • Interaction with allopurinol • Nausea, infection and neutropenia
Mycophenolate mofetil[66]	• General schedule on the PBS • PHARMAC-funded	• No access to TPO-RAs or rituximab, and patients who have expressed a preference to avoid surgery	• Start at 250 mg twice a day, double the dose every 2 weeks until response or as tolerated • May start higher or increase sooner if less concerned about gastrointestinal side effects • Maximum dose 3000 mg per day	50–60%	50% of patients respond by 4 weeks	• Monitor FBC carefully for cytopenias • Diarrhoea is common • Other toxicities: neutropenia, anaemia and viral infections • Small increased risk of malignancy and progressive multifocal leukoencephalopathy with prolonged use
Hydroxychloroquine[67]	• Streamlined authority; PBS reimbursement as "autoimmune disease" • PHARMAC-funded	• ANA-positive and unable to access TPO-RAs or rituximab • Use with caution in patients with pre-existing heart disease or risk of retinopathy	• 200 mg twice a day • Concomitant steroids are usually required when starting	60%	2–3 months	• Most common adverse effects include gastrointestinal symptoms and/or rash • Rare, but significant adverse effects, include arrhythmias, cardiomyopathy and retinopathy • Long term users should have annual ophthalmology review
Danazol[68]	• No reimbursement from PBS • In Australia, it needs SAS application to import from international supply • No longer generally available in New Zealand	• Consider in men with no history of prostate cancer, who do not have a history of thromboembolic disease, who have previously responded to corticosteroids, and who are unable to access rituximab or TPO-RAs	• 200 mg given two to four times a day. Dose can be tapered once response is obtained	40–50%	3–6 months	• Increased risk of thrombosis and liver toxicity • Androgenic side effects • PSA should be checked in men before use
Dapsone[69]	• General schedule on the PBS • PHARMAC-funded	• No access to rituximab or TPO-RAs • Comorbidities such as thromboembolic disease may make use of TPO-RAs less desirable • Additional benefit as *Pneumocystis jiroveci* pneumonia prophylaxis for patients who may be at increased risk from immunosuppression	• 100 mg/day	50%	3 weeks	• G6PD assay before commencement • Monitor haemolysis markers (haptoglobin, reticulocyte count and LDH) to guide effectiveness and toxicity. Ideally, target a small amount of subclinical haemolysis • Severe oxidative haemolysis especially in patients with G6PD deficiency • Other side effects include abdominal distension, anorexia, and methaemoglobinaemia, which manifests as cyanosis and breathlessness
Ciclosporin[70]	• General schedule on the PBS • PHARMAC-funded	• No access to TPO-RAs or rituximab, and patients who have expressed a preference to avoid surgery • Acceptable safety profile in pregnancy[71]	• 3–5 mg/kg per day in two divided doses (75–300 mg twice a day) • Concomitant steroids are usually required when starting	40–60%	1–3 months	• Common side effects include hypertension, renal impairment, headaches and infections • Trough levels can be monitored but consult with local reference ranges to minimise toxicity

ANA = antinuclear antibodies; FBC = full blood count; G6PD = glucose-6-phosphate dehydrogenase; LDH = lactate dehydrogenase; PBS = Pharmaceutical Benefits Scheme (Australia); PHARMAC = Pharmaceutical Management Agency (New Zealand); PSA = prostate-specific antigen; SAS = Special Access Scheme; TPMT = thiopurine methyltransferase; TPO-RAs = thrombopoietin receptor agonists. ◆

Adverse events. Reports of increased bone marrow fibrosis by TPO-RAs have raised concerns of myelofibrosis risk, but clinically significant myelofibrosis is rare.[61] An increased risk of venous and arterial thrombosis has been observed in patients with ITP treated with TPO-RAs compared with patients with ITP without TPO-RAs exposure. These observations are largely based on registry and retrospective studies, and patients with a history of thrombosis should be informed of this risk (GRADE 2C).[59,74] Adverse events more commonly observed with eltrombopag include transaminitis, and liver function monitoring is recommended (GRADE 1B).[61]

Patient selection. In Australia, TPO-RAs are approved for treatment of chronic ITP following splenectomy and inadequate response to IVIg, or in patients for whom splenectomy is contraindicated. In New Zealand, TPO-RAs are approved as fourth line therapy after splenectomy or as third line therapy if splenectomy is contraindicated.

We recommend romiplostim in patients with gastrointestinal diseases, abnormal liver function, or who are unable to adhere to prescribed dietary restrictions (GRADE 1D). We recommend eltrombopag in patients who have a needle phobia and in those who prefer the simplicity of once daily dosing (GRADE 1D). Paradoxically, as eltrombopag can be difficult to administer effectively in an aged care environment due to the uncertainty of dose timing in relation to meal service, we recommend romiplostim in this setting (GRADE 2D).

Other therapies

For patients for whom rituximab, TPO-RAs or splenectomy are not accessible or have an unfavourable risk–benefit profile, there are a number of alternative medications that can be considered (Box 3).

Mycophenolate mofetil and dapsone are preferred in this setting, with a quicker onset of action compared with the other medications (GRADE 1C).[75,76] While these drugs are generally more accessible and affordable, evidence regarding efficacy is less robust. Their onset of action can be more prolonged than that of rituximab, splenectomy or TPO-RAs. In view of this, steroids are often administered concurrently with these medications while awaiting response, resulting in additional toxicity. Prolonged treatment may also be required, and alternative strategies should be quickly considered if toxicity is encountered.

While there is currently no Australian or New Zealand supplier of danazol, in Australia the drug can be accessed by the Special Access Scheme, which is approved by the Therapeutic Goods Administration.

For further discussion on less commonly used alternatives, the reader may refer to Cuker and Neunert.[68]

Beyond second line therapies

Clinical trial enrolment of eligible patients with ITP who have not responded to currently available therapies is strongly recommended where available in limited sites around Australia and New Zealand (GRADE 1D).

Imaging could be performed in patients who initially achieved a response after splenectomy but subsequently relapsed to exclude the development of an accessory spleen.[77]

Non-rescue low dose steroids, such as prednisolone ≤ 5 mg/day or 10 mg once a week, can be considered to improve the response to many second line therapies, including TPO-RAs (GRADE 2D). Combination therapy can also have a synergistic effect (eg, TPO-RAs plus an immunosuppressant such as mycophenolate mofetil or azathioprine) (GRADE 2D).[78]

Supportive care in ITP

The supportive care of patients with ITP includes management of acute bleeding, avoidance of long term side effects of therapies (particularly steroids), and identification of fatigue. Adjunctive therapies that may be helpful in acute bleeding include tranexamic acid (avoid if haematuria) and proton pump inhibitors in major gastrointestinal bleeding.[1]

Avoidance of long term high dose steroid use in patients with ITP is imperative (GRADE 1B).[79] Patients taking steroids should be monitored for known side effects, including hyperglycaemia, mood or sleep disturbance, osteopenia, and infection. Patients taking an equivalent of prednisolone 20 mg daily for more than 2 weeks are at increased risk of infection, and the Therapeutic Guidelines provide further recommendations for such patients.[80]

Bone mineral density assessments should be considered for patients who have received prolonged steroids and are at risk of osteopenia, such as post-menopausal women, and they should be proactively managed with calcium and vitamin D supplements. Currently, PBS reimbursement exists for intravenous zoledronic acid 5 mg annually with corticosteroid-induced osteopenia (GRADE 2D).

Fatigue appears common in patients with ITP, but its optimal management has not been ascertained.[81] Referral to counselling and ITP-specific patient support networks may be helpful.

Splenectomised patients should be reviewed for their risk of infection and thrombosis, adherence to local guidelines on long term antibiotic use, immunisation status, and modifiable vascular risk factors (GRADE 1D).

Special situations

Treatment of emergency bleeding in ITP

Life-threatening bleeding, such as intracranial haemorrhage, has been reported in 0.1–0.4% of children and 1.4% of adults.[82] Severe bleeding is reported in 9.5% of adults.[82,83] When considering the treatments and outcomes for patients with acute life-threatening bleeding in ITP, the wide range of options underpins the lack of evidence.[84] We therefore recommend a number of measures introduced simultaneously rather than sequentially (GRADE 1D).[85-87]

In life-threatening bleeding, we recommend platelet transfusions to achieve haemostasis, along with IVIg (1–2 g/kg), and steroids (methylprednisolone up to 1000 mg intravenous daily for 1–5 days or high dose dexamethasone 40 mg daily intravenous or orally for 4 days) (Grade 1D).[22,88,89]

Vinka alkaloids can be considered for rare cases of refractory or multiply relapsed disease and life-threatening bleeding (GRADE 2D). Some authors have experience with using vincristine 1–2 mg intravenously (over 4–6 hours) weekly for two to four doses, and treatment effect can be seen in less than 48 hours.[90]

Supportive red cell transfusions, antifibrinolytic therapy with tranexamic acid (up to 1000 mg intravenous three times a day) and other blood products may be useful.[3,22] Local measures such as endoscopic cautery need to be considered in gastrointestinal bleeding and epistaxis (GRADE 1D).

Splenectomy for emergency bleeding is difficult given the dangers of unplanned surgery.[91]

Platelet thresholds for planned interventions in ITP

Stable patients with ITP may require a rapid increment in their platelet counts for scenarios such as emergency or elective surgery or imminent childbirth. Although there is little direct evidence in ITP, we support a risk–benefit approach to platelet targets dependent on the intervention proposed (Supporting Information, table S2).

Therapeutic interventions to raise platelet counts before surgery or procedures

For emergency procedures (within hours), IVIg (1 g/kg) with intravenous methylprednisolone (500–1000 mg) should be given immediately (GRADE 1B),[86,87] and platelet transfusion (at induction of anaesthesia, and subsequently intra- and/or postoperatively depending on bleeding) should be given as close to the time of the procedure as possible or on induction of anaesthesia, with expected platelet survival of 1–4 hours (GRADE 1C).[92] Do not delay any procedure to confirm a platelet increment, as very little would be expected (GRADE 1D). Repeat doses of IVIg may be needed if postoperative bleeding risk remains high.

For elective procedures (days to one week), options include IVIg (GRADE 1B),[93] steroids (GRADE 1B),[87] or TPO-RA (romiplostim 500 µg subcutaneous weekly for two doses; commencing 10 days before surgery) (GRADE 1D).

Pregnancy

In the first and second trimesters, the indication for treatment is a platelet count < 20×10^9/L. For vaginal or Caesarean delivery, a platelet count ≥ 50×10^9/L is generally adequate.[94]

For women with platelet counts < 20×10^9/L, prednisone 50 mg daily could be considered (GRADE 2D). If IVIg is used before delivery or for life-threatening haemorrhage, the recommended dose is 1–2 g/kg as a single or divided dose (GRADE 1D). Patients may respond to the combination of steroids and IVIg if they do not respond to monotherapy. It is sometimes useful to rehearse ITP treatment several weeks before term, in order to plan for a neuraxial anaesthesia, where a platelet target ≥ 70×10^9/L is reasonable (GRADE 2D).

We suggest referring to the Haematology in Obstetrics and Women's Health (HOW Collaborative) guidelines on managing thrombocytopenia in pregnancy for assistance on pregnant patients who fail first line therapies.[95]

Arterial disease and severe thrombocytopenia in ITP

Older patients are being increasingly recognised and diagnosed with ITP.[96] The increased prevalence of vascular disease in older patients becomes difficult to manage in more severe thrombocytopenia with ITP.[97]

Second line immunosuppressive therapies may be more attractive, as splenectomy would be less likely to be safe in patients with vascular comorbidities, in addition to the inherent increased risk of thrombosis following splenectomy.[97] After balancing the risk of vascular disease against the risk of bleeding, the clinician is advised to target the greater problem; if they are both unacceptable, we advise increasing ITP therapy to mitigate the risk of bleeding from treating the vascular disease (GRADE 2D).[2]

It is generally safe to administer antiplatelet therapy if platelet counts are ≥ 30×10^9/L, and dual antiplatelet therapy if platelet counts are ≥ 50×10^9/L (GRADE 1D). Bare metal stents may reduce the duration of antiplatelet therapy required and may be preferred in patients with unstable or refractory thrombocytopenia (GRADE 2D). Anticoagulation for atrial fibrillation can be considered when the likely benefits outweigh the risk of bleeding, and it is usually safe with platelet counts ≥ 50×10^9/L, but may be individualised in patients without a history of thrombocytopenic bleeding down to 30×10^9/L (GRADE 1D).

Platelet transfusions have no role in routinely supporting platelet counts for antiplatelet therapies or anticoagulation in patients with ITP (GRADE 1D).

Venous thromboembolic disease and severe thrombocytopenia in ITP

The diagnosis and treatment of venous thromboembolic disease (VTE) can be complicated by ITP. Severe thrombocytopenia can be misunderstood as a negative risk factor for thrombosis, delaying the time to diagnosis. Paradoxically, both ITP and its treatments may increase the risk for VTE.[98-100]

It is much easier to administer prophylaxis against deep vein thrombosis than to treat established thrombosis in severe thrombocytopenia. Prophylactic doses of low molecular weight heparin are generally safe to administer with platelet counts ≥ 30×10^9/L (GRADE 1D).

Therapeutic anticoagulation is generally safe to administer for VTE management with platelet counts ≥ 30×10^9/L, and reduced intensity (half dose) anticoagulation is probably safe for platelet counts 20–30 × 10^9/L (GRADE 1D).[101-103] The duration of anticoagulation and selection of anticoagulant are mostly unaffected by ITP, although patients with unstable platelet counts or a history of recent bleeding may be safer on anticoagulants with reversibility such as vitamin K antagonists (warfarin) and dabigatran, which is not reimbursed by the PBS in Australia, but it is funded by PHARMAC in New Zealand for VTE (GRADE 2D). There is increasing familiarity with direct oral anticoagulants, but these should be used with caution in patients with labile platelet counts.

ITP therapy can be titrated to raise the platelet count for safer anticoagulation, but this should be balanced against the risk of provoking VTE (GRADE 2D). Prothrombotic ITP therapies (eg, TPO-RA) can usually be continued while remaining on indefinite anticoagulation (GRADE 2D). After excluding other causes of VTE (eg, antiphospholipid syndrome), strong consideration should be given to changing ITP therapies if the thromboembolic event was life-threatening (GRADE 1D).

Conclusions

Most recommendations are made with low Levels of Evidence (Supporting Information, table S4). Paradoxically, this is not a weakness of these guidelines, but instead the quintessential *raison d'être* for these guidelines targeted at the Australasian audience. The absence of high quality evidence for basic clinical dilemmas in ITP underlines the need for updated guidelines relevant to the local treatment context, as well as ongoing collaborative scientific and clinical research in ITP (Supporting Information, table S3).

We stand on the precipice of a new age in the treatment of ITP, with novel therapeutics targeting Fc neonatal receptors, Bruton tyrosine kinase (BTK) and spleen tyrosine kinase (SYK) signalling,

and complement inhibition at varying stages of promising research maturity.[104-107] Anticipating the best way to incorporate these new modalities into our already crowded but flawed treatment armamentarium remains a challenge for us in the future.

Updates of these guidelines are anticipated as major milestone advances in therapy become available in the Australasian market in the coming years.

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Supporting Information

Additional Supporting Information is included with the online version of this article.

RACP Specialists. Together

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EDITORIAL

Updated treatment options for immune thrombocytopenia

We would like to update readers on the treatment landscape for severe chronic immune thrombocytopenia (ITP) in the wake of recent welcome changes to the Pharmaceutical Benefits Scheme (PBS) reimbursement criteria in Australia and since the publication of our consensus treatment guidelines.[1]

First, splenectomy is no longer required to access thrombopoietin receptor agonists (TPO-RAs) such as romplostim and eltrombopag. This change aligns with management guidelines and clinical data showing no difference in outcome between patients with splenectomy versus those without splenectomy receiving TPO-RAs and permits ITP treatment selection best tailored towards patient preferences and clinical factors.[1–4]

Second, a new TPO-RA avatrombopag is now PBS listed as an alternative to romiplostim and eltrombopag. There are no head-to-head data to suggest superiority of one TPO-RA over another, but differing administration routes, dose schedules, interactions and side effect pro- files may assist clinician–patient decision-making with treatment selection. Table 1 highlights the main differences between the available TPO-RA agents.

Third, switching between TPO-RAs for any reason including tolerance or failure is now permissible at any time. Previously, switching was not allowed after 24 weeks of therapy, even after the development of an unanticipated adverse event or eventual loss of response. Although one may anticipate an equivalent TPO-RA class effect with these agents, retrospective data demonstrate switching between these drugs for inadequate responses can be successful with improved platelet counts and reductions in concomitant medications.[5,6] Thus, with the relaxation of switching rules and the PBS listing of avatrombopag, we now have an additional line of therapy rather than just another oral alternative to romiplostim or eltrombopag.

Fourth, a clinical response as determined by the treating physician is sufficient to warrant ongoing PBS reimbursement in lieu of absolute platelet targets that were insensitive to clinically apparent improvements in bleeding and quality of life (QoL). Previously, the threshold for some patients to meet platelet response criteria devised for clinical trial environments was extremely difficult to achieve for PBS reimbursement purposes, even though there was clear benefit for patients in terms of reduced bleeding, improved platelet counts and lower concomitant ITP therapies. Along with penalising patients who needed intermittent rescue therapies, these measures had seemed to restrict TPO-RA access for the patients with the most severe disease. This has now been rectified as the threshold for ongoing use is clinically determined by the treating physician most cognisant of their patients' medical priorities.

Finally, rituximab (intravenous B-cell depleting anti-CD20 monoclonal antibody) is now unrestricted on the PBS. Previously, off-label rituximab use was either self-funded or compassionately supported with a bias towards lower dosing schedules that were more cost- effective.[7] Any new enthusiasm for PBS-reimbursed rituximab is probably balanced by recent coronavirus disease 2019 (COVID-19) pandemic concerns and tem- pered by previous analyses demonstrating only a modest long-term success rate, particularly when administered in monotherapy.[8,9]

There are still many uncertainties ahead for optimal ITP management such as targeting the natural history of ITP before it becomes chronic, exploring the role of TPO- RAs in earlier stages of ITP, predicting and targeting patients at the highest risk of bleeding and rationally drafting the optimal sequence or combination of novel and existing therapies for severely refractory patients.

Data from the iWISh survey suggest that patients pre- fer to halt the progression or worsening of their ITP above QoL and bleeding, in contradistinction to their physicians.[10] The ultimate goal for most patients is to optimise initial therapy of newly diagnosed ITP to prevent progression to the chronic phase. The recent FLIGHT (Newly Diagnosed Immune Thrombocytopenia Testing the Standard Steroid Treatment Against Com- bined Steroid & Mycophenolate) study, which explored the addition of mycophenolate mofetil to corticosteroids in first-line therapy, demonstrated an improved response and a halving of the progression rate to chronic ITP. This was at the expense of worsened patient-reported QoL measures at the end of the study[11]; however, it seems reasonable to expect that the longer-term impact on cumulative disease and treatment burden by preventing the development of chronic ITP will eventually lead to better QoL.

Treatment strategies addressing the pervasive but insidious symptom of fatigue in ITP are also lacking. Patients with newly diagnosed ITP remain vulnerable to the uncertainties of their diagnosis, anxious about their

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Table 1 PBS-listed TPO-RA available for use in chronic ITP

	Description	Mode of delivery	Dose schedule	Metabolism	Interactions	Toxicities
Romiplostim	Fc-peptide fusion protein	Subcutaneous injection	Weekly, 1-10 mcg/kg†	$t_{1/2}$ = 3.5 days	Other Fc receptor–binding therapies	Bone marrow reticulin Thrombosis Rebound thrombocytopenia Risk of progression of myeloid malignancies
Eltrombopag	Nonpeptide small molecule	Oral tablet	Daily, 25–75 mg‡	$t_{1/2}$ = 26–35 h, CYP1A2 and CYP2C8	Chelates polyvalent cations (such as calcium and iron) OATP1B1 and BCRP substrates caution (e.g. ciclosporin) Reduce statin dose	Hepatotoxicity Cataracts Thrombosis Rebound thrombocytopenia Bone marrow reticulin Risk of progression of myeloid malignancies
Avatrombopag	Nonpeptide small molecule	Oral tablet	Daily, 20–40 mg‡	$t_{1/2}$ = 19 h, CYP2C9 and CYP3A4	CYP2C9 and CYP3A4 inhibitors may increase avatrombopag levels (e.g. fluconazole) CYP2C9 and CYP3A4 inducers may reduce avatrombopag levels (e.g. rifampicin)	Bone marrow reticulin Thrombosis Rebound thrombocytopenia Risk of progression of myeloid malignancies

†Some authors prefer to start at 200 to 250 mcg sc weekly and titrate by 50- to 100-mcg increments.
‡Although on-label dosing for new patients begins daily, careful titration is possible with alternate day dosing (e.g. increase avatrombopag from 20 mg daily to 20 mg/40 mg alternate days) and tapering off may be achieved by increasing dosage intervals up to once weekly before trialling cessation.
BCRP, human breast cancer resistance protein; CYP1A2, cytochrome P450 family 1 subfamily A member 2; CYP2C8, cytochrome P450 family 2 subfamily C member 8; CYP2C9, cytochrome P450 family 2 subfamily C member 9; CYP3A4, cytochrome P450 family 3 subfamily A member 4; ITP, immune thrombocytopenia; OATP1B1, organic anion transport proteins 1b1; PBS, Pharmaceutical Benefits Scheme; TPO-RA, thrombopoietin receptor agonist.

prognosis, and still have limited treatment options available to them.

Despite these therapeutic challenges, we welcome these updates to the PBS listings for the TPO-RAs. We look forward to the promise of these and other novel agents in the modern treatment landscape ahead. Amongst newer therapies, fostamatinib (spleen associ- ated tyrosine kinase inhibitor) was listed by the Food and Drug Administration for chronic ITP in 2018 but remains unavailable in Australia. Clinical trials in ITP have recently been completed for rilzabrutinib (Bruton's tyrosine kinase [BTK] inhibitor) and efgartigimod (neonatal Fc receptor [FcRn] inhibitor).[12,13] As new clinical trials are opening across Australia now with B-cell activating factor [BAFF] and a proliferation-inducing ligand [APRIL] inhibitors, the prospect of better targeting the immune lesion in ITP beckons.

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