Treatment pathway for adult patients with immune (idiopathic) thrombocytopenic purpura (ITP)

Immune thrombocytopenic purpura (ITP) is defined by a low platelet count and an increased risk of bleeding. Fatal bleeding is rare and occurs more frequent in elderly patients and in those with severe thrombocytopenia. Although treatment for ITP is strictly individualised, specific therapy for ITP may not be necessary unless the platelet count is < $10x10^9$/L or there is extensive bleeding. Another important consideration is that for some patients the morbidity from side effects of therapy may exceed any problems caused by the thrombocytopenia. Clinical management of this condition must therefore take into account the patient's age, the severity of the illness, and the anticipated natural history. Treatment for ITP is considered appropriate for symptomatic patients and for those at significant risk of bleeding.

International Working Group (IWG) Standardisation of Terminology, Definitions and Outcome Criteria

Terminology	Persistence of symptoms
Newly diagnosed ITP	Diagnosis to 3 months
Persistent ITP	3 – 12 months from diagnosis
Chronic ITP	Lasting for more than 12 months

Definition of response to treatment by ITP

Complete response	> 100 x 10^9/L and absence of bleeding	Measured on 2 occasions over 7 days apart
Adequate Response	> 30 x 10^9/L **And** greater than 2-fold increase in platelet count from baseline **and** absence of bleeding	Measured on 2 occasions over 7 days apart
No / Loss of response	< 30 x 10^9/L **or** less than 2-fold increase in platelet count from baseline **or** presence of bleeding	Measured on 2 occasions over 1 day apart
Loss of complete response	< 100 x 10^9/L **Or** less than 2-fold increase in platelet count from baseline **and / or** presence of bleeding	Measured on 2 occasions over 1 day apart

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Expected time to initial response:

Treatment type	Expected time to response	Peak response
IVIg	1-3 days	2 – 7 days
Prednisolone	4 – 14 days	7 – 28 days
Dexamethasone	1 – 9 days	7 – 28 days
Splenectomy	1 – 56 days	7 – 56 days
Azathioprine	30 – 90 days	30 – 180 days
Danazol	14 – 90 days	28 – 180 days
Mycophenolate		
Rituximab	7 – 56 days	14 – 180 days
Eltrombopag	7 – 28 days	14 – 90 days
Romiplostim	5 – 14 days	14 – 60 days

Acute Emergency Treatment (as below or follow local guidelines)

Management of severe or life-threatening bleeding – Acute Emergency Treatment Hospitalisation is required. General measures should be instigated to reduce the risk of bleeding, including avoidance of drugs that may exacerbate bleeding (such as anticoagulants, anti-platelets, NSAIDs), control of blood pressure and maintenance of urine output

Emergency Treatment

Platelet transfusions (e.g. two platelet units every 4-6 hours)

With / without

Intravenous Immunoglobulin (IVIg)* 1g/Kg

With / without

Intravenous methylprednisolone (1g per day for 3 days)

*It is recommended that a repeat dose of IVIg (1g/kg) should only be considered at day seven, if there is a failure to achieve a haemostatically adequate platelet count.

Approval from the local Immunoglobulin Assessment Panel IAP will be required if earlier use of a repeat dose is contemplated in cases of exceptional clinical circumstances such as active mucosal bleeding or the need for emergency surgery (see NHSE Circular SSC 1804 Oct 2017). Registration on National IVIg database required.

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General Management

1st line treatment - 'Rescue' treatment

Consider if patient is symptomatic, has a platelet count < $30x10^9$/L or requires a procedure that may induce blood loss

Oral prednisolone 1 to 2mg/kg per day, given as single or divided doses
OR
Oral dexamethasone 40mg daily for 4 days (dexamethasone significantly more expensive than prednisolone £30)
OR
IVIG 1g/kg per day for 1 day – RED INDICATION (if critical bleeding, unresponsive to corticosteroids, contraindication to corticosteroid)

2nd line treatment '**Active**' treatment for persistent ITP (symptoms lasting between 3 and 12 months) and chronic ITP (Symptoms lasting >12 months)

For patients unresponsive to first line treatment options or with persistent or chronic ITP consider second line pharmacological option and/or consider splenectomy

Rituximab (biosimilar) 100mg weekly* (more cost effective option) or 375mg/m^2 weekly for FOUR weeks
AND/OR
Splenectomy - Consider offering a splenectomy if severe thrombocytopenia (platelet count < 10-20x10^9/L), a high risk of bleeding for platelet counts < $30x10^9$/L, or patients who require continuous glucocorticoid therapy to maintain safe platelet counts

Splenectomy may not be appropriate due to medical co-morbidities. Remember the need for vaccinations and post-splenectomy antibiotic prophylaxis.

Rituximab is used off-label for treatment of persistent and chronic ITP. NICE ESUOM35* October 2014. Most of the evidence for the use of 'off label' rituximab for in adults with immune thrombocytopenic purpura comes from observational studies, with no comparator arm. However, as stated in NICE TA 221 Romiplostim for the treatment of chronic immune (idiopathic) thrombocytopenic purpura, clinicians increasingly prescribe rituximab as the first choice of active treatment in this setting and it is therefore considered as an option within the treatment pathway.

The following pharmacological agents **offer further alternative treatment** options for consideration **in unresponsive patients** (*none are licensed*). Responses to these agents are variable and for some of them may only be apparent after several weeks or months. The choice of one agent over another is based on the assessment of the side effect profile and the personal experience of the haematologist. International guidelines do not prioritise.

Mycophenolate mofetil (1000mg twice daily)
Danazol (200mg 2-4 times daily)
Dapsone (75-100mg daily)
Ciclosporin A (5mg/kg/day for 6 days then 2.5-3mg/kg/day)
Azathioprine (1-2mg/kg – max 150mg/day)

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3rd line treatment - Active treatment for chronic ITP (symptoms lasting > 12 months)

Third line options can be considered for patients with symptoms lasting for longer than 12 months in whom first AND second line treatment options have failed and there are ongoing complications from their thrombocytopenia.
OR
For patients in whom second line treatment options are contraindicated.
NB Eltrombopag and Romiplostim both licensed for non-splenectomised patients.

Thrombopoetin receptor agonists:

Eltrombopag – initial oral dose 50mg daily (for patients of East Asian ancestry start at a reduced dose of 25mg daily), titrate to desired response, max 75mg daily (see SPC and details)

OR (if patient is not suitable for eltrombopag)

Romiplostim – initial dose 1 microgram/kg SC once weekly, titrate to desired response (see SPC details)

Patients not suitable for Eltrombopag	Patients not suitable for Romiplostim
Patients with liver disease (Child Pugh ≥5) Patients with dietary restrictions/GIT pathology Patients who are unable to adhere to the dosing requirements of eltrombopag Patients who are intolerant of eltrombopag Patients who are known to be unresponsive to eltrombopag Patients at high risk of non-adherence	Patients with liver disease (Child Pugh ≥7) Patients who are intolerant of romiplostim Patients who are known to be unresponsive to romiplostim Patients at high risk of non-adherence or non-attendance to weekly clinic appointments Patients who have previously developed increased bone marrow reticulin during treatment with Romiplostim

- CCGs will fund Eltrombopag and Romiplostim according to NICE criteria TA 293 & TA221
- Blueteq forms are in place for Romiplostim, Eltrombopag and need to be completed prior to initiating treatment and at dose escalation .
- Eltrombopag is first line for patients who cannot self-administer romiplostim
- The CCG needs to be notified of dose increases over 500 micrograms (2 vials) of romiplostim by submitting a new Blueteq form
- Cost effective routes of dispensing (Home Care or Outsourced Pharmacy) are preferred options

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