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**

<table>
<thead>
<tr>
<th>Terminology</th>
<th>Persistence of symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newly diagnosed ITP</td>
<td>Diagnosis to 3 months</td>
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<tr>
<td>Persistent ITP</td>
<td>3 – 12 months from diagnosis</td>
</tr>
<tr>
<td>Chronic ITP</td>
<td>lasting for more than 12 months</td>
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</tbody>
</table>

**Definition of response to treatment by ITP**

<table>
<thead>
<tr>
<th>Response Type</th>
<th>Criteria</th>
<th>Measured on occasions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>≥ 100 x 10^9/L and absence of bleeding</td>
<td>2 occasions over 7 days apart</td>
</tr>
<tr>
<td>Response</td>
<td>≥ 30 x 10^9/L and greater than 2-fold increase in platelet count from baseline and absence of bleeding</td>
<td>2 occasions over 7 days apart</td>
</tr>
<tr>
<td>No response</td>
<td>&lt; 30 x 10^9/L or less than 2-fold increase in platelet count from baseline or presence of bleeding</td>
<td>2 occasions over 1 day apart</td>
</tr>
<tr>
<td>Loss of complete response</td>
<td>&lt; 100 x 10^9/L or less than 2-fold increase in platelet count from baseline and/or presence of bleeding</td>
<td>2 occasions over 1 day apart</td>
</tr>
<tr>
<td>Loss of response</td>
<td>&lt; 30 x 10^9/L or less than 2-fold increase in platelet count from baseline or presence of bleeding</td>
<td>2 occasions over 1 day apart</td>
</tr>
</tbody>
</table>

**Expected time to initial response:**

<table>
<thead>
<tr>
<th>Treatment type</th>
<th>Expected time to response</th>
<th>Peak response</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVlg</td>
<td>1-3 days</td>
<td>2 – 7 days</td>
</tr>
<tr>
<td>Prednisone</td>
<td>4 – 14 days</td>
<td>7 – 28 days</td>
</tr>
<tr>
<td>Splenectomy</td>
<td>1 – 56 days</td>
<td>7 – 56 days</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>30 – 90 days</td>
<td>30 – 180 days</td>
</tr>
<tr>
<td>Danazol</td>
<td>14 – 90 days</td>
<td>28 – 180 days</td>
</tr>
<tr>
<td>Vincristine/Vinblastine</td>
<td>7 – 14 days</td>
<td>7 – 42 days</td>
</tr>
<tr>
<td>Rituximab</td>
<td>7 – 56 days</td>
<td>14 – 180 days</td>
</tr>
<tr>
<td>Eltrombopag</td>
<td>7 – 28 days</td>
<td>14 – 90 days</td>
</tr>
<tr>
<td>Romiplostim</td>
<td>5 – 14 days</td>
<td>14 – 60 days</td>
</tr>
</tbody>
</table>
Acute Emergency Treatment

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, repeated the following day if the platelet count remains < 2nd line - RED INDICATION as per DH)
  - with/without
    - Intravenous methylprednisolone (1g per day for 3 days)

* IVIg - Refer to local policy for IVIg prescribing
  - RED indication as per DH Clinical Guidelines for Immunoglobulin Use 2nd edition, 2011
  - Registration on National IVIg database required

**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 (if critical bleeding, unresponsive to corticosteroids, contraindication to corticosteroid)
    - IVIG* 1g/kg per day for 2 days – RED INDICATION*

**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 splenectomy.

- Rituximab 375mg/m² weekly for 4 weeks
  - AND/OR
    - Splenectomy - offer 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. It is not recommended in elderly patients or those who have hepatic or mixed hepatic/splenic sequestration of 111In-labelled platelets.
- Rituximab is used off-label for treatment of persistent and chronic ITP. 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 and it is therefore considered as an option within the treatment pathway.

- Rituximab is excluded from Tariff and currently not routinely commissioned in SWL. Treatment with Rituximab therefore requires prior approval from the CCG/CSU. See ‘Funding application for 2nd line treatment of Persistent or Chronic immune (idiopathic) thrombocytopenic purpura – Rituximab’ for submission to SECSU.HCD@nhs.net.

The following pharmacological agents offer further alternative treatment options for consideration in unresponsive patients:

- Mycophenolate mofetil (1000mg twice daily)
- Danazol (200mg 2-4 times daily)
- Dapsone (75-100mg daily)
- Vinca alkaloids (vincristine total course dose 6mg, vinblastine total course dose 30mg)
- Ciclosporin A (5mg/kg/day for 6 days then 2.5-3mg/kg/day)
- Azathioprine (1-2mg/kg – max 150mg/day)
- Cyclophosphamide (1-2mg/kg orally daily for a minimum of 16 weeks)

- 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.

### 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.

**Thrombopoietin receptor agonists:**
- **Eltrombopag** – initial 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 local Eltrombopag prescribing policy and/or Summary of Product Characteristics (SPC) for full details)

OR (if patient is not suitable for eltrombopag (see below for contraindications and other reasons such as intolerance or treatment failure)

- **Romiplostim** – initial dose 1mcg/kg SC once weekly, titrate to desired response (see local Romiplostim prescribing policy and/or SPC for full details)
### Patients not suitable for Eltrombopag
- 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 not suitable for Romiplostim
- Patients with liver disease (Child Pugh ≥7)
- Patients who are unable to adhere to the dosing or administration (SC injection) requirements of romiplostim
- 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

- Funding for Eltrombopag and Romiplostim is subject to NICE TA 293/221. See ‘Funding application for 3rd line treatment of Chronic immune (idiopathic) thrombocytopenic purpura – Eltrombopag/Romiplostim’ for submission to SECSU.HCD@nhs.net.

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### References
4. NICE technology appraisal guidance 221. Romiplostim for treating chronic immune (idiopathic) thrombocytopenic purpura. May 2014