South East London guideline for the investigation and management of Immune Thrombocytopenia (ITP) in adult patients over 18 years old

Summary

This guideline outlines the recommended initial investigations and management of patients with newly diagnosed immune thrombocytopenia or relapse and those with persistent immune thrombocytopenia and chronic thrombocytopenia that require treatment. It also outlines the management of ITP in pregnancy. This document incorporates the updated international consensus report on the investigation and management of primary immune thrombocytopenia. D Provan et al. Blood-2019.

Patients with ITP are kept under close and ongoing haematology review and monitoring, therefore this guideline is aimed for use by haematology specialists, and the content is not intended for use in primary care. All of the medicines referred to in this document are RED listed (hospital only prescribing and supply), and are not for prescribing in the primary care setting.

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Table of Contents

Management of Acute Emergency treatment 3
Management algorithm for patients with symptomatic acute immune thrombocytopenia 4
Introduction 5
Recommended initial investigations: 5
Further investigations to be considered based on history/blood tests: 5
Investigations recommended in patients with atypical disease: 6
Treatment Triggers 6
Classification of immune thrombocytopenia 7
Acute Emergency Treatment (for severe or life-threatening bleeding) 7
1st line treatment - Management of patients with symptomatic acute immune thrombocytopenia, bleeding and/or platelets <10-20 x 10^9/L (non-life threatening bleed), or requires a procedure that may induce blood loss 8
2nd line treatment: 'Active' treatment for a) Persistent ITP (symptoms lasting between 3 and 12 months) and b) Chronic ITP (symptoms lasting > 12 months) 9
3rd line treatment - Management of patients with persistent/chronic immune thrombocytopenia requiring treatment 11
Ongoing management of immune thrombocytopenia 12
ITP in pregnancy 12
Resources 12
Contact list 13
References 13

Management of Acute Emergency treatment

Acute Emergency Treatment

Management of severe or life-threatening bleeding

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

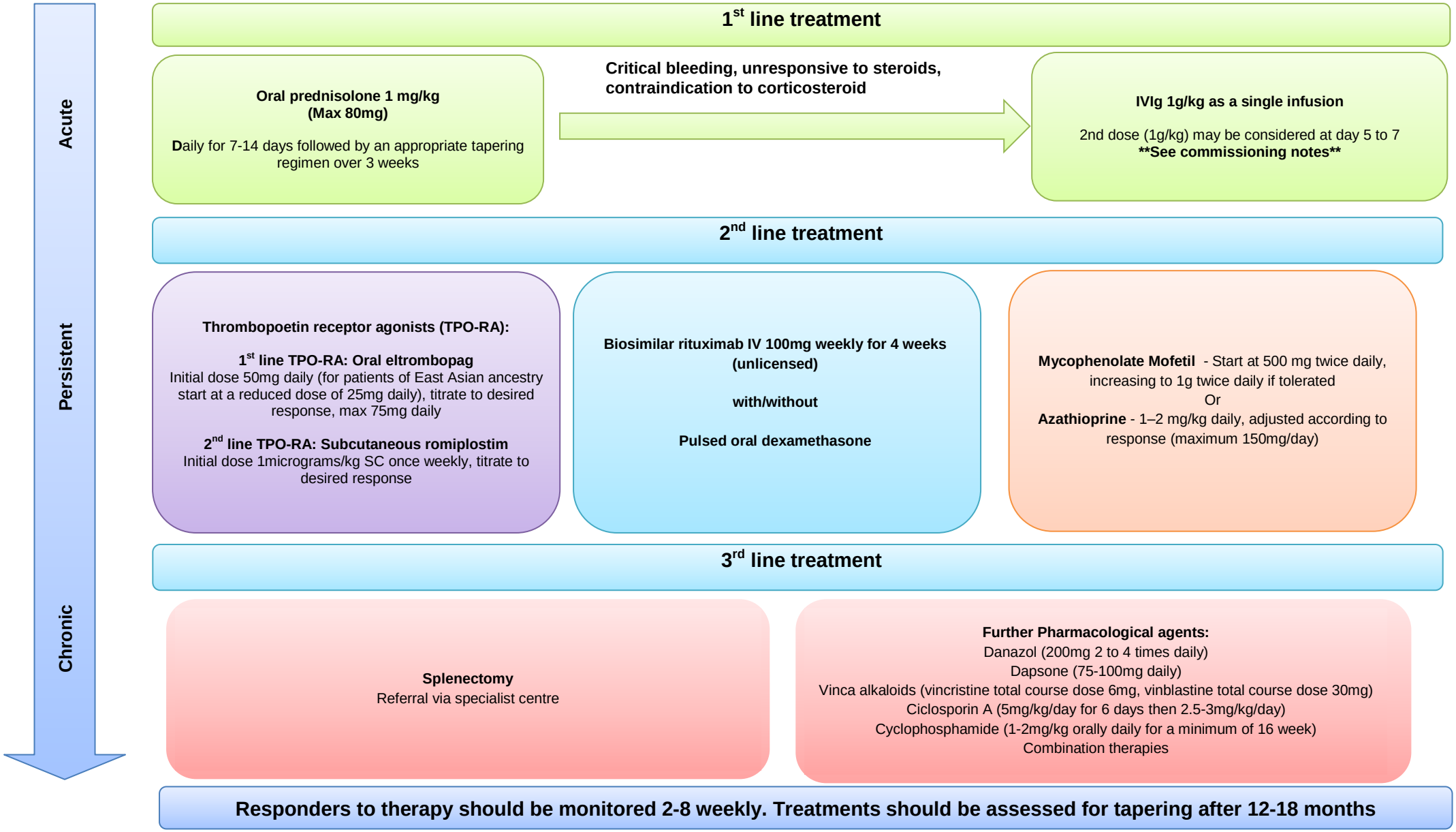
With / without

Intravenous Immunoglobulin (IVIg) (1g/kg, repeated the following day if clinically appropriate)

with / without

Pulsed steroids as per clinician decision (e.g. IV methylprednisolone or IV/PO dexamethasone)

Management algorithm for patients with symptomatic acute immune thrombocytopenia



South East London Area Prescribing Committee. A partnership between NHS organisations in South East London: South East London Clinical Commissioning Group (covering the boroughs of Bexley, Bromley, Greenwich, Lambeth, Lewisham and Southwark) and GSTFT/KCH /SLAM/ & Oxleas NHS Foundation Trusts/Lewisham & Greenwich NHS Trust

Introduction

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

ITP is a diagnosis of exclusion. If a patient with suspected ITP is admitted to hospital please contact the general haematology registrar, or if out of hours contact the haematology registrar on call. Contact details for haematology teams at individual trusts are listed on page 13 of this document.

All patients with suspected ITP need a thorough history and examination (including lymphadenopathy, hepatosplenomegaly) as well as documentation of extent of bleeding symptoms.

Patients should not be discharged from hospital without a documented blood film review. ITP typically present with isolated thrombocytopenia and if there are other abnormalities in the full blood count alternative diagnoses should be considered.

Recommended investigations from the consensus document (Provan et al. 2019) and the American Society of Haematology (ASH) guidelines (Neunert et al, 2011) are outlined below:

Recommended initial investigations:

Full blood count
Blood film
Liver profile
Renal profile
Coagulation screen
Hepatitis B
Hepatitis C
Human Immunodeficiency Virus (HIV)
Autoimmune screen-ANA, ds DNA, ENA

Further investigations to be considered based on history/blood tests:

Immunoglobulins
Thyroid function tests
Antiphospholipid antibodies
Abdominal ultrasound scan
Serum protein electrophoresis
Helicobacter pylori antigen test
Reticulocyte count and DAT – if anaemic
Haematinics
Viral PCR for EBV, CMV, and parvovirus

Investigations recommended in patients with atypical disease:

Bone marrow examination
Consider alternative diagnosis including work up for hereditary thrombocytopenia

Consider bone marrow examination in those:

Refractory to treatment or atypical features
Prior to starting Thrombopoietin Receptor Agonists (TPO-RA)
In patients who develop any changes in blood film or blood parameters whilst on TPO-RA

Treatment Triggers

Generally, adults with a persistent platelet count above 30 $x10^9$/L are not at risk of serious bleeding. Unless they have another reason to require a higher platelet count, patients can be managed with observation alone.

Treatment is recommended in adults with platelet counts persistently less than $20x10^9$/L.

Decision to treat adults with platelet counts between $20x10^9$/L and $30x10^9$/L depends on other factors: age, activity, fatigue, bleeding and bruising symptoms, and anaemia suggestive of significant bleeding.

Treatment triggers	Potential treatment triggers
Blood blisters in mouth and epistaxis	Persistent severe symptomatic thrombocytopenia
Organ bleeding (Intracranial haemorrhage, gastrointestinal)	Significant bruises and petechiae
Haematuria	Stage of life related to considered risk
Anaemia and microcytosis caused by bleeding	Inability to review case regularly or to access emergency treatment (e.g. off shore working)
Menorrhagia	Risk activity (e.g. Skiing)
Loss of work activities	
Planned interventional procedure/surgery for which higher platelet count required	

Figure 1. Treatment Triggers (Cooper N et al. State of the art- how I manage immune thrombocytopenia. BJH 2017, 177, 39-54)

Classification of immune thrombocytopenia

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 from diagnosis

Figure 2: International Working Group (IWG) Standardisation of Terminology, Definitions and Outcome Criteria

Established data states 30% of newly diagnosed patients will go into remission after a short period of thrombocytopenia with or without treatment within the first 12 months. Fewer patients will go into remission after 12 months (Rodeghiero et al, 2009).

Patients with newly diagnosed ITP may need urgent treatment to increase the platelet count. Irreversible treatment such as splenectomy should be avoided at this stage. Steroid sparing agents are preferred for treatment of persistent disease. In chronic disease, long-term safety aspects are most important. Patients with severe disease may require more than one modality of treatment at a time.

Acute Emergency Treatment (for severe or life-threatening bleeding)

Emergency Treatment

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

with/without

- Intravenous immunoglobulin (IVIg) (1g/kg*), repeated after 24-48 hours if severe or life-threatening bleed persists**

with/without

- Pulsed steroids as per local clinician decision (e.g. IV methylprednisolone / IV dexamethasone or PO dexamethasone)

with/without

- Tranexamic acid

* IVIg - Refer to local policy for IVIg prescribing and NHSE IVIg commissioning guidelines
**A second dose of IVIg may be required after 24 – 48 hours, if severe or life-threatening bleeding: e.g. Intracranial bleed or gastrointestinal/pulmonary haemorrhage. Otherwise, if a haemostatically adequate platelet count is not achieved a second dose (1g/kg) may be considered at day 5 to 7 (*Immunoglobulin Commissioning GuidelinesV1.4 November 2019*)

In acute bleeding, supportive agents including tranexamic acid (1g three times a day) and platelets may be required (caution using tranexamic acid in pregnancy / haematuria). In life threatening bleeding, use of thrombopoietin receptor agonists (TPO-RA) may be required

1st line treatment - Management of patients with symptomatic acute immune thrombocytopenia, bleeding and/or platelets <10-20 x 10^9/L (non-life threatening bleed), or requires a procedure that may induce blood loss

- Prednisolone 1 mg/kg daily* (maximum of 80mg) for 7-14 days followed by an appropriate tapering regimen**

OR (if critical bleeding, unresponsive to steroids, contraindication to corticosteroid)

- IVIg 1g/kg as a single infusion***

* Alternative: Dexamethasone 40 mg once daily IV or orally for 4 days repeated every 2-4 weeks for up to four cycles
** If response seen (Platelets >50 x 10^9/l), taper with aim to stop by 6 weeks (maximum 8 weeks) even if platelets fall during taper. If no response to initial dose within 2 weeks, rapid taper and stop over 1 week.
*** IVIg repeat dosing: if a haemostatically adequate platelet count is not achieved a 2nd dose (1g/kg) may be considered at day 5 to 7. Usage should be discussed with the designated panel lead.

If the platelet count falls on tapering steroids, consider second line agents (see below). A steroid card is issued by pharmacy when they are dispensed. Patient on steroids need consideration of screening for steroid-induced diabetes and bone protections (as per local policy).

In patients who have a contraindication to steroids, or in patients where the diagnosis is not yet clear (and where the use of steroids may mask other underlying diseases) IVIg can be considered as per NHS England guidelines.

2nd line treatment: 'Active' treatment for a) Persistent ITP (symptoms lasting between 3 and 12 months) and b) Chronic ITP (symptoms lasting > 12 months)

For patients unresponsive to first line treatment options or with persistent or chronic ITP consider either TPO-RA therapy, rituximab, or alternative immunosuppressive agents

Choice of primary 2nd line agent is clinician lead depending on patient presentation, performance status and potential contraindications. If sub therapeutic response or treatment failure to therapy is observed clinicians can proceed with utilise all possible 2nd line agents sequentially to achieve response at their clinical discretion.

Thrombopoietin receptor agonists (TPO-RA)

Thrombopoetin receptor agonists (TPO-RA)*:

- Eltrombopag (NICE TA293) – initial dose 50mg orally daily (for patients of East Asian ancestry start at a reduced dose of 25mg daily), titrate to desired response, max 75mg daily (see 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 (NICE TA221) – initial dose 1microgram/kg subcutaneous once weekly, titrate to desired response (see SPC for full details)

* Caution in patients with risk factors for venous/arterial thromboembolism'

Oral therapy with eltrombopag is considered 1st line TPO-RA in this guideline, with romiplostim to be considered for those with reduced oral intake or intolerances to either eltrombopag or any excipients included in the formulation.

Eltrombopag must be administered at least 2 hours before or 4 hours after polyvalent cation-containing antacids, dairy products (or any foods, drinks, or medicines containing ≥50 mg calcium) and other products containing polyvalent cations, such as mineral supplements.

Eltrombopag and romiplostim have shown good efficacy in both splenectomised and non-splenectomised patients. They are both licensed for use in adults with refractory ITP and supported by NICE guidance

TPO-RA are contraindicated in pregnancy.

Biosimilar rituximab (unlicensed)

- Biosimilar rituximab* IV 100mg weekly for 4 weeks**

  With/without

- Pulsed oral dexamethasone

* Rituximab should be avoided in patients with Hepatitis B positivity
** Best competitive contract brand biosimilar rituximab to be utilised

Recent updated international consensus guidance has shown non-inferior outcomes and 100mg rituximab weekly for 4 weeks appears to be as effective as 375mg/m^2 weekly for 4 weeks in improving platelet count and achieving partial response. Data shows that both doses are equally as effective in reducing bleeds with no difference in the median time to next treatment. This would suggest, that for patients with primary ITP, 100mg rituximab weekly for 4 weeks may be a more cost-effective option than the standard dosing regimen (375mg/m^2 weekly for 4 weeks) (Li et al. 2019; Gracie et al 2018)

Rituximab use in ITP is an unlicensed indication. Its use in this guideline at 100mg weekly for 4 weeks is suggested following the release of the updated international consensus document.

Individualised combinations of treatment may be required. If a complete response is achieved, treatment is reduced slowly to the lowest possible treatment dose.

Immunosuppressive agents (Unlicensed)

- **Mycophenolate Mofetil (MMF)** - Start at 500 mg twice daily, increasing to 1g twice daily if tolerated

Or

- **Azathioprine** - 1–2 mg/kg daily, adjusted according to response (maximum 150mg/day)

Consider withdrawal if no improvement within 3 months.

Immunosuppressive agents (including mycophenolate mofetil [MMF] and azathioprine) may be used in patients failing other therapies.

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.

MMF is teratogenic – women of childbearing age should be counselled on strict use of contraceptives whilst on the medication or alternatives considered (e.g. azathioprine).

3rd line treatment - Management of patients with persistent/chronic immune thrombocytopenia requiring treatment

Third line options can be considered for:

i. 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

ii. For patients in whom second line treatment options are contraindicated.

Splenectomy

Offer if severe thrombocytopenia (platelet count < 10 – 20 x 10^9/L), a high risk of bleeding for platelet counts < 30 x 10^9/L, or patients who require continuous glucocorticoid therapy to maintain safe platelet counts

Splenectomy is an option for response in a high percentage of patients if they have failed pharmacological interventions. 80% of patients respond and 66% achieve prolonged response for approximately 5-10 years.

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 Indium (111In) labelled platelets.

Referrals for patients who are appropriate for Splenectomy should be referred to a local specialist centre via the correct pathway.

Further pharmacological therapeutic agents:

Responses to these agents are variable and for some of them may only be apparent after several weeks or months. The International guidelines list these as having less robust evidence, and choice of one agent over another is based on the assessment of the side effect profile and the personal experience of the haematologist.

Danazol - 200mg 2-4 times daily (unlicensed indication)
Dapsone - 75-100mg daily (unlicensed indication)
Vinca alkaloids - Vincristine total course dose 6mg, vinblastine total course dose 30mg (unlicensed indication)
Ciclosporin A - 5mg/kg/day for 6 days then 2.5-3mg/kg/day
Cyclophosphamide - 1-2mg/kg orally daily for a minimum of 16 weeks (unlicensed indication)

Combination therapies

H.pylori eradication therapy (see local guidance)

H. pylori-associated ITP is a subset of ITP in which H. pylori infection is actively involved in the pathogenic process. In patients with H. pylori-associated ITP, H. pylori eradication increases the platelet count in parallel with a suppression of anti-platelet autoantibody production, and results in the remission or even cure of the disease in many patients.

Since eradicating H. pylori does not increase the platelet count in non-ITP subjects, the platelet recovery after successful H. pylori eradication is specific to ITP patients, and is likely to be mediated through the inhibition of an ongoing autoimmune response to platelets.

Clinical Trials
For adults failing adults failing multiple therapies and where clinically appropriate, consideration should also be given to enrollment in a clinical trial.

Ongoing management of immune thrombocytopenia

Long term toxicities of various treatments needs to be considered for patients with chronic ITP requiring treatment.

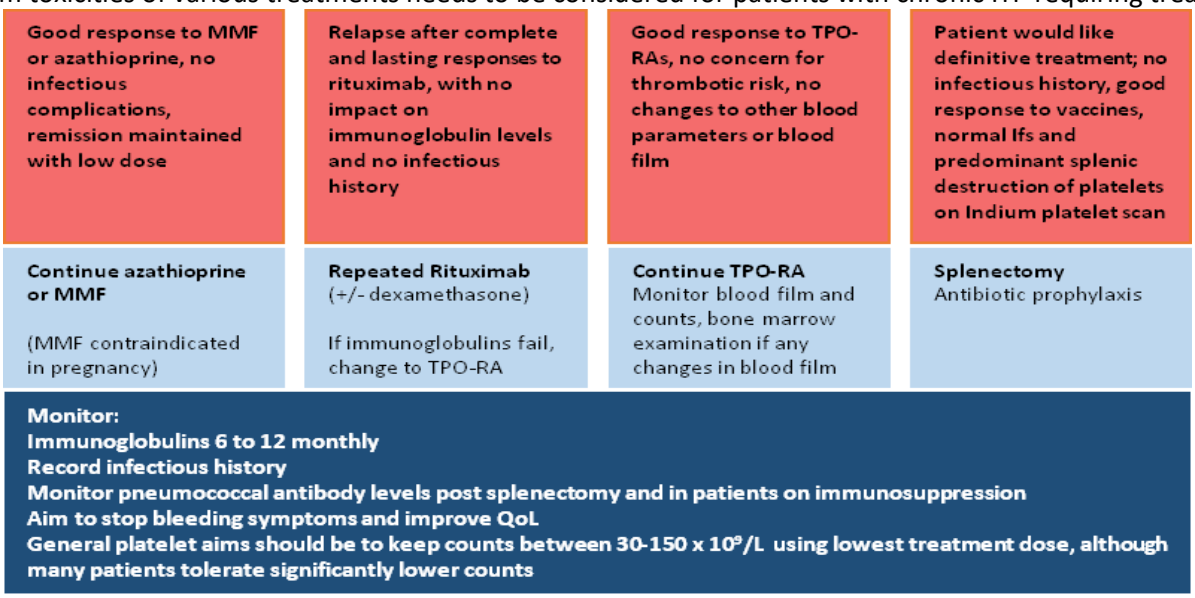


Figure 3. Treatment Algorithm for patients with chronic immune thrombocytopenia requiring treatment (Adapted from Cooper N et al. State of the art- how I manage immune thrombocytopenia. BJH 2017, 177, 39-54).

ITP in pregnancy

Pregnant patients with ITP should be referred to specialist haematology obstetric clinic. Prior to delivery a bespoke birth plan will be provided.

Treatment options:

- Prednisolone (starting at 20 mg daily)
- IVIg (in accordance with Department of Health guidelines)
- Further therapeutic options should be made within the bespoke plan provided by the specialist haematology obstetric clinic
- Splenectomy is not commonly performed in pregnancy but can induce a remission and be associated with few complications when performed in the second trimester

Resources

UK ITP support group - www.itpsupport.org.uk

Contact list

Guy's and St Thomas' NHS Foundation Trust
Thrombosis haematology registrar (Mon to Fri 0900 – 1730) – Available via switchboard on 020 7188 7188
On-call haematology registrar (Mon to Friday after 1730; Weekends all day) – Available via switchboard
Clinical Nurse Specialist (Mon to Fri 0900 – 1730) – Bleep 3288 via switchboard
Haematology specialist pharmacist (Mon to Fri 0900 – 1730) – Bleep 3138 via switchboard

Medicines Information at Guy's and St Thomas' NHS Foundation trust
Patient Helpline: 020 7188 8748 (Mon to Fri 0900 - 1700)
Email: medicinesinformation@gstt.nhs.uk

Kings College Hospital NHS Foundation Trust
Coagulation registrar (Mon to Fri 0900 – 1700) available via switchboard (020 3299 9000)
Out of hours: Haematology Registrar on call via switchboard
Coagulation Specialist Pharmacist (Mon to Fri 0900 – 1730) via switchboard (020 3299 1549)

Lewisham and Greenwich NHS Trust
Medicines Information at Lewisham and Greenwich Trust
Patient helpline: 020 8836 4900 (Mon to Fri 9:00 – 17:00)
Email: LG.QE-MedInfo@nhs.net

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