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# Guidelines for

# Immune Thrombocytopenic Purpura in Adults

**Presented by: Dr Maryam Khan**

**Armed Forces Bone Marrow Transplant Center Rawalpindi**

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# GUIDELINES FOR IMMUNE THROMBOCYTOPENIC PURPURA IN ADULTS

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## Indications of Treatment

1. **Newly diagnosed adults** with platelet count less than or equal to $30x10^9$/l with or without mucocutaneous bleeding should be offered treatment[1]
2. Newly diagnosed adults with platelet count more than or equal to $30x10^9$/l and no mucocutaneous bleeding can be managed with observation alone (treatment can be considered in special circumstances like age>60 years (ASH 2020), pregnancy, ischemic heart disease or equivalent requiring antiplatelet therapy, need for anticoagulation, invasive procedure planned, trauma risk high).
3. **For soldiers** at high risk of trauma including those deployed at ops area, platelet threshold of $50x10^9$/l should be considered as indication of treatment.
4. **First line treatment options** include
    A. Prednisolone at 1mg/kg/day (max 80mg/day).
    B. Dexamethasone 40mg IV od for 4 days
    C. IVIG 1g/kg single dose (can be repeated) only in special circumstances where rapid increase in platelet count is desired e.g. peripartum phase, life threatening hemorrhage, emergency surgery
    D. Anti D-(should be offered in special circumstances including uncontrolled diabetes, steroid intolerance, those requiring rapid increment in platelet count but IVIG contraindicated e.g. renal failure etc).
5. **Supportive treatment** should be offered to all adults on corticosteroids
    A. PPI/H2 Blocker
    B. Bone protection( anticipated dose and duration of GC>2.5mg/day for > 3months)[2]
        i. Daily Calcium1000mg/day and 600-800 IU Vit D supplementation is recommended.
        ii. All adults should undergo initial fracture risk assessment at outset.
        iii. All adults> 40years should undergo BMD testing within 6 months and fracture risk assessment using FRAX score with steroid dose adjustment.
        iv. All adults at moderate or high risk of fracture, should receive oral bisphosphonate, IV bisphosphonate, Teriparatide or Denosumab in order of priority.
    C. Advice on glycemic control, blood pressure monitoring,
    D. Psychological support /behavioral therapy for mood alterations associated with steroid use.
6. **Response to 1st line** agent will be assessed at 2-3 weeks
    A. If there is increase in platelet count to more than or equal to $30x10^9$/l and at least doubling of platelet count from baseline, steroids should be tapered over next 4 weeks. (If platelet count is more than $100x10^9$/l steroids can be tapered without addition of steroid sparing drug, otherwise slow taper with addition of Azathioprine)
    B. Steroids should not be continued if there is no response (PLT <$30x10^9$/l) at 4 weeks
    C. Steroids should preferably not be continued for more than 6 weeks, but duration can be extended based on patient response and physician discretion. For few selected patients, continuation of low dose steroids may be considered at physician discretion keeping in view

risk benefit ratio. For these patients, preferably dose of steroids should not exceed 10mg every other day (EOD).

D. Azathioprine could be added as steroid sparing agent in steroid dependent ITP.
**Steroid dependence**: Daily steroid requirement >5mg/day OR multiple frequent courses of prednisolone required to maintain above defined parameters.

7. Adults not responding to 1st line treatment should be offered 2nd line treatment unless contraindicated.
8. **Second line options include**
   A. Splenectomy (open or laparoscopic) should not be offered before 3 months from diagnosis.
   B. TPO agonists (eltrombopag, romiplostin) can be administered at 4 weeks for those who have platelet count less than $30x10^9$/l and muco-cutaneous bleeding (clinically significant).
   C. IV Rituximab ($375x10^9$/l IV weekly for 4 doses or 100mg/$m^2$ at weekly interval for 4 weeks)
   **EVIDENCE suggests that both high and low doses have same efficacy[3]**
   **TPO Agonists**: Eltromobopag to be administered at 50mg/day (25mg/day for South Asian), if platelet count less than $30x10^9$/l after 2 weeks, increase dose to 75mg/day. If platelet count between 30-$100x10^9$/l maintain dose, if >100-$400x10^9$/l reduce dose to 25mg every fortnightly, if more than $400x10^9$/l stop, restart after 2 weeks at lowest dose to maintain platelet count more than $30x10^9$/l manually verified). Tapering can be attempted after discussion in departmental meeting.
   **NB: All patients requiring 2nd and later lines to be discussed in departmental meeting. If bone marrow not done at outset, should be done before 2nd line.**
9. Choice of 2nd line depends upon
   A. Socioeconomic status of patient.
   B. Willingness for surgical procedure
   C. Weightage placed by physician/patient on durable response against risk associated with splenectomy/cost of TPO agonists.
10. Refractory ITP (defined as patient failing 2 or more lines of treatment). Extended workup required to exclude other causes
11. Options beyond second line
    a. Splenectomy, rituximab or TPO agonists[1] if not offered before
    b. TPO+CsA[2] (Cui et al)
    c. Pred (10-20mg/d) +CSA(6mg/kg/d) [3]
    d. Rapamycin(6mg-2mg/d) + CSA[4]
    e. Dexa40mg-4 d, Ritux-100mg/m2-4 dose, CSA 2.5-3mg/kg/d-28 days[5]
    f. TPO+ Ritux(100mg/m2-4 doses[6]

**POST SPLENECTOMY** options include

1. With no prior Rituximab exposure, Rituximab can be given.
2. TPO analogs preferred if no financial constraints.
3. Other third line options as described above.

**SPECIAL CONSIDERATIONS**

**1.PREGNANCY[4]**

a. Women with no bleeding a platelet >$30x10^9$/l do not require treatment in first 2 trimesters unless invasive procedure planned.
b. If needed a lower dose of 10-30mg/day is used, but higher doses have been used too (3.4 fold risk of cleft palate by use in 1st trimester).
c. **If no response to 1st line treatment, should be discussed in departmental meeting**.
d. Other options include combining IVIG with steroids (limited to late trimester in preparation of delivery), Splenectomy (second trimester).
e. Mode of delivery as per obstetric indication, avoid instrumentation.
f. Platelet count for delivery >$50x10^9$/l
g. Platelet count for neuraxial anesthesia > $80x10^9$/l.
h. Fetal platelet count monitoring not recommended.
i. No nrrat evidence for TPO agonists use as they are secreted in breast milk
j. Neonatal cord blood platelet count should be tested at birth and 24 hours later, if neonate is found to be thrombocytopenic, platelet count should be monitored by venipuncture daily for next 5-7 days. IVIG should be given if platelet count<$30x10^9$/l after discussion with neonatologist[6].

2**. Elderly, Frail Patients [7]**

Increased risk of bleeding

a. Threshold of $50x10^9$/l appropriate in those with falls risk, on antiplatelet, anti-coagulants, severe co morbidities like renal failure, severe gastritis, very elderly (>75 years)
b. Options include short course of steroids (4 weeks), IVIG alone or in combination can be given in severe risk of bleeding only as increased risk of thrombosis, fever, inflammatory response, renal failure and fluid overload
c. TPO analogs can be used alone or in combination (off label) except LPD associated ITP as concern for increased mortality.

**3. Life threatening bleeding[8]**

a. High dose steroids (high dose Dexamethasone or Methylprednisolone) +IVIG (1g/kg) + platelet transfusion (multiple doses or continuous transfusions)
b. Platelet transfusions once or twice daily or multiple transfusions/continuous transfusions to achieve recommended platelet target for the particular type and site of bleeding.
c. Consideration for emergency splenectomy

4. **HCV associated ITP**

a. Anti -viral therapy to be started if no contra indications,
b. Platelet count closely monitored if interferon used.
c. If thrombocytopenia unresponsive to HCV treatment and bleeding diathesis and thrombocytopenia attributed to ITP rather than HCV associated CLD, then ITP treatment with IVIG/TPO analogs.[9]

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**EVALUATION OF RESPONSE**

**Early response**: Platelet >30x$10^9$/l, at least doubling and no bleeding by 1 week.

**Initial Response**: Platelet>30x$10^9$/l, at least doubling and no bleeding by 1 month.

**Durable Response**: Platelet >30x$10^9$/l, at least doubling and no bleeding sustained by 6 months.

**Steroid dependence**: Daily steroid requirement >5mg/day OR multiple frequent courses of prednisolone required to maintain above defined parameters.

**Remission**: Platelet count >100x$10^9$/l at 12 months.

**Major Bleeding**: WHO grade 3 or 4 bleeding (severe or debilitating blood loss)

## TPO Analog Taper Recommendations

### Requirements to initiate TPO taper [10]

1. Patients with platelets >100x$10^9$/l, no history of major bleeding, no treatment intensification required in past 3 months.
2. A subset of patients with platelet >50-100x$10^9$/l, but no major bleeding and did not require treatment intensification in last 3-6 months.
3. Tapering of Eltrombopag can be done by first reducing to lowest dose and then increasing dosing frequency or first increasing dosing interval and then dose.For Romiplostin,increasing dosing interval appropriately is recommended rather than dosing interval.
4. Platelet count should be monitored weekly or fortnightly or earlier if indicated.
5. If at any point, platelets drop more than 30x$10^9$/l treatment should be restarted at the same dose at which taper was started.
6. About 15-25% patients can achieve treatment free remission.

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