Updates:

- New drug therapies for ITP (Rituxan, Eltrombopag, AMG 531)

Introduction

ITP is a common disorder with an incidence of 1.6 per 100,000 per year [1]. The incidence doubles over the age of 60, with loss of the female predominance seen in younger patients [2]. ITP is associated with a number of diseases including: HIV, Hepatitis C [3], CMV, EBV, Helicobacter pylori infection, ulcerative colitis [4, 5], diabetes insipidus [6], Grave’s disease [7, 8], Autoimmune Lymphoproliferative Syndrome (ALPS) [9-12], SLE, lupus anticoagulant, and anti-cardiolipin antibody [13]. The vast majority of patients tolerate platelet counts greater than 30 x 10^9/L without the need for treatment [14]. Patient factors that should be considered in the decision to commence treatment include: presence of bleeding, patient age, platelet count, risk of traumatic injury, other causes of platelet dysfunction (aspirin, uremia), and liver disease.

The management of HIV associated ITP, pregnancy-induced thrombocytopenia, and drug-induced thrombocytopenia have unique considerations, which are discussed below.

Prognosis

The risk of mortality and serious morbidity from ITP is low. In children, the rate of intracranial bleeding is 0.9% (in a series of 1693 children; 0.7% fatal ICH) [15]. In another series, 17% of children presented with bleeding (ICH, epistaxis requiring cautery, hematuria, or fall in hemoglobin) [16].

In a series of 1817 adults with chronic persistent ITP, 49 cases of fatal hemorrhage (2.7%; 0.02 cases per patient year) were reported. The 5-year mortality was considerable for chronic refractory patients over the age of 60, compared to those less than 60 (48% vs. 2%) [17]. A review of 5 series of patients with ITP estimated the risk of death from ITP at 4%, but higher for patients failing splenectomy (17%) [18]. Concern over treatment related deaths has been raised by one report of 7 ITP deaths, of which 6 were related to treatment (3 post-splenectomy and 3 infections from immunosuppressive therapy) [19].

Diagnosis

ITP is a diagnosis of exclusion. The following have been reported to mimic the findings of classic ITP:

- Drug-induced ITP (see abbreviated list in table on page 7) [20]
- MDS – note that oval macrocytes are usually recognized in most cases [21]
- Breast cancer metastatic to the spleen [22]
- Acute hepatitis B [23]

The differential diagnosis of thrombocytopenia is exhaustive and is not discussed in this treatment policy.
Baseline Testing

The following are mandatory:

- History: drug history (quinine/leg cramp history, antiplatelet drug therapy), HIV risk factor assessment, liver disease, constitutional symptoms, pregnancy history, symptoms of autoimmune diseases (including hyperthyroidism & hypothyroidism), contact sport exposure
- Physical exam: r/o lymphoproliferative disease, HIV, hyperthyroidism, hypothyroidism, autoimmune diseases, splenomegaly, liver disease
- Laboratory: complete blood count, blood film review, HIV serology.

In some situations the following may be appropriate:

- TSH – pre-splenectomy, or if patient has signs/symptoms of hyper/hypothyroidism
- Bone marrow biopsy – low yield in children [24] and adults less than 60 [25] presenting with no atypical features; may consider with atypical features and patients over age 60
- HIV serology – Recommended for all patients, may be omitted if patient felt to be low risk after detailed questioning
- Abdominal ultrasound – if splenomegaly is suggestive on physical exam or physical exam deemed unreliable due to obesity

Platelet associated IgG testing is not useful [26].

Front-line Treatment

A. Emergency Treatment

Patients with active bleeding or in need of emergency surgery require urgent and aggressive therapy. The following is recommended:

- Methylprednisolone 1 g/d for 3 days, then prednisone 1.5 mg/kg/day, and IVIG 1 g/kg/d x 2 days
- IVIG should not be used if there is no evidence of bleeding as it has not been shown in adults to prevent clinically significant bleeding or alter the natural history of the disease [27].
  - In addition, a single course of IVIG is approximately $10,000
- Tranexamic acid 1 gram IV q6h [28]
- Vaccination (pneumococcal, meningococcal, haemophilus influenza B) see section B below [29]
- For life-threatening bleeding platelet transfusions are appropriate (max. 1 pool q4-6h [30])
- Emergency splenectomy may be considered
- Management of intracranial bleeding should include: IV steroids, IVIG, platelets, emergency splenectomy, and then craniotomy; maintain plt >100 for at least 7 days post ICH where possible.

B. Non-Urgent Treatment

IVIG is not appropriate in non-bleeding patients

- Prednisone at a dose of 1 to 1.5 mg/kg/d is indicated if the platelet count is less than 20 x 10^9/L or the patient is experiencing significant bleeding symptoms and the platelet count is less than 50 x 10^9/L. High-dose dexamethasone (40 mg per day for 4 days) is an effective and well tolerated alternative [31].
  - Prednisone should be tapered once response is seen (plt >50 x 10^9/L) by 50% every 14 days.
  - Prednisone does not alter the natural history of the disease, but allows one to ‘buy time’ to determine who has acute ITP (13-22%) [32, 33], and who will become chronic, and thus need additional therapy. Two-thirds of patients respond to front-line corticosteroid therapy [34].
All patients should be vaccinated for pneumococcus, haemophilus, and meningococcus [29]

- PedvaxHIB HIB 0.5 mL IM (one time administration)
- Pneumovax 23 0.5 mL IM (q5 years)
- Meningococcal polysaccharide vaccine 0.5 mL SC (q5 years)

Counsel and monitor patients for the adverse effects of corticosteroids (diabetes, osteoporosis, avascular necrosis, infections, and cataracts).

- All patients should have a baseline bone mineral density performed and yearly thereafter if corticosteroids continued or osteopenia detected.

Patients should be given alendronate 70 mg weekly OR risedronate 35 mg weekly, calcium 1000 mg daily and vitamin D 1000 units daily during corticosteroid therapy as a reduction in the rate of new fractures on glucocorticoids (2.3% vs. 3.7%) and an improvement in bone density (+2.1% vs. -0.4%) compared to calcium and vitamin D alone has been reported [35].

The role of Helicobacter Pylori eradication in the management of ITP is controversial. Patients with chronic refractory ITP with platelet counts less than $30 \times 10^9/L$ appear not to benefit from HP eradication. Rates of response range from 22-71%. One guideline has suggested routine eradication for all patients with ITP and HP infection. Given the current state of the scientific literature on this topic, no formal recommendation is suggested until further information is available [36-39].

Second-line Treatment

For patients who either fail to respond to corticosteroids, relapse on tapering of steroids, or require greater than 10 mg of prednisone daily AND have a persistent severe thrombocytopenia ($< 20 \times 10^9/L$ or $20 \times 10^9/L$ to $50 \times 10^9/L$ with bleeding) should be considered candidates for laparoscopic splenectomy. Patients should be counseled regarding the following risks of splenectomy:

- Mortality 0.3% [40, 41]
- Morbidity 3-20% [40, 41]
- Lifetime risk of fulminant sepsis 1.5-1.8% [42]
- Fatal sepsis risk estimated at 1 in 1500 patient years (90% of cases of post-splenectomy sepsis are from streptococcus pneumoniae, of whom only 30% of patients had received an appropriate course of pneumococcal vaccination) [43]
- Response rate 60-90% [40, 41] (majority respond before day 10)
- The role of prophylactic antibiotics is unclear and not the current practice in Canada or the USA, but is recommended in one UK guideline (penicillin or erythromycin), although patient compliance was noted to be poor [44].

Responders to IVIG have a greater chance of success in 2 studies [40, 45], however, a test dose of IVIG is presently not recommended.
Post-Splenectomy Refractory ITP

Many drug therapies have been attempted, but no head to head trials are available for comparison of efficacy. The following treatments have been studied, but are not recommended for postsplenectomy failure due to too few patients treated, or no responses seen:

- Interferon [46-48] (18 patients)
- Ascorbic acid [49] (9 patients)
- Peripheral blood stem cell transplant [50, 51] (2 patients)
- Cyclosporin A [52-55] (11 patients)
- Staph A columns [56]
- Dapsone [57, 58]
- Splenic irradiation [59]
- Anti-D post-splenectomy [60, 61] (only of use pre-splenectomy in RH D positive individuals)
- Accessory splenectomy (variable response to accessory splenectomy [62], review of 28 cases showed CR in 13 patients (only 2 have platelets counts < 20 preoperatively [18])
- Helicobacter pylori eradication [36-39]

Efficacy of the common used agents are presented below:

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Dose</th>
<th># Studies</th>
<th>Total # of Patients</th>
<th>Plt &gt; 50 after Tx</th>
<th>Expected Time to Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexamethasone</td>
<td>40 mg x 4 days</td>
<td>4 [63-66]</td>
<td>48</td>
<td>42 %</td>
<td>3 months</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>1 g/m²*</td>
<td>2 [67, 68]</td>
<td>30</td>
<td>83 %</td>
<td>3 months</td>
</tr>
<tr>
<td>Imuran</td>
<td>2 mg/kg</td>
<td>3 [69-71]</td>
<td>68</td>
<td>54 %</td>
<td>6 months</td>
</tr>
<tr>
<td>IVIG</td>
<td>1 g/kg</td>
<td>2 [72, 73]</td>
<td>60</td>
<td>57 %</td>
<td>Days, but all relapse after 3-4 weeks</td>
</tr>
<tr>
<td>Vincristine</td>
<td>2 mg</td>
<td>4 [74-77]</td>
<td>50</td>
<td>58 %</td>
<td>1 month, but response transient</td>
</tr>
<tr>
<td>Danazol</td>
<td>200-400 mg</td>
<td>4 [78-81]</td>
<td>61</td>
<td>48 %</td>
<td>3 months</td>
</tr>
<tr>
<td>Rituximab</td>
<td>375 mg/m² qwk for 4 wks</td>
<td>19 [82-86]</td>
<td>313</td>
<td>63%</td>
<td>1 to 3 months</td>
</tr>
</tbody>
</table>

*Oral Cyclophosphamide is equivalent at a dose of 1-2 mg/kg/d x 3-6 months*

Novel drug therapies are being evaluated for patients with ITP. Two agents look particularly promising (AMG 531 and Eltrombopag) with response rates of 61% and 80% respectively in patients with chronic ITP refractory to at least one prior therapy [87, 88]. Patients should be encouraged to participate in clinical trials with these new agents, where available, given their effectiveness and minimal adverse effects.
CHRONIC ITP
Postsplenectomy
Platelet count <20 OR <50 & Bleeding

Wet purpura?
Platelets <10?
Active bleeding

YES
Tranexamic acid 500-1000 tid (for all)
BUT
IVIG 1 g/kg q4wk and platelet transfusion for severe bleeding

NO
Dexamethasone 40 mg x 4 days
q 28 days x 6 cycles

NO RESPONSE TO
Dexamethasone at 6 months

CONSIDER
1. Cyclophosphamide 1 g/m² q 28 days x 2 to 4 cycles or 1-2 mg/kg/d po x 3-6 months
2. Imuran 2 mg/kg x 4 months
3. Danazol 200 mg po bid x 4-month trial
4. IVIG 1 g/kg q 4 weeks
5. Rituximab 375 mg/m² qwk for 4 weeks
6. TPO agonists, where clinical trials available

Decision should be based on patient's risk of adverse side effects and disease severity
Pregnancy

ITP in pregnancy must be differentiated from the following:

- HELLP syndrome
- Gestational thrombocytopenia (note: these patients have no prior history of thrombocytopenia, thrombocytopenia is usually mild (>75 x 10^9/L), late gestation, not associated with fetal thrombocytopenia, resolves postpartum, very common with up to 5% of pregnancies affected)
- DIC

The management is controversial and is based primarily on expert opinion [15]. Patients should be managed in a centre that specializes in the care of high-risk maternity and neonatology. Therapy should be initiated if: platelet count of less than 20 x 10^9/L in any trimester, <50 x 10^9/L and bleeding in any trimester, or <30 x 10^9/L in the third trimester of pregnancy. First-line therapy should be prednisone in the lowest effective dose. IVIG is an acceptable alternative for women who do not tolerate prednisone (depression, weight gain, osteopenia, LGA fetus, gestational diabetes, etc.) or fail to respond to prednisone. The recommended dose is 1 g/kg IV q 4 weeks.

Incidence of thrombocytopenia (<150 x 10^9/L) in newborns of mothers with ITP is very variable study to study (range 7–56%), but severe thrombocytopenia <50 less common (7-25%), and fetal hemorrhage extremely rare [89-93]. Best estimate of severe thrombocytopenia (<50 x 10^9/L) is 9% [93]. Fetal thrombocytopenia less than 20 x 10^9/L is rare. Prenatal testing of the fetus (scalp sampling or PUBS) should NOT be performed unless there is evidence of fetal bleeding during the present pregnancy OR history of severe (<20 x 10^9/L) fetal thrombocytopenia, or fetal bleeding in a prior pregnancy.

HIV-Associated ITP

The pathogenic mechanism of HIV-related thrombocytopenia is multifactorial. Factors include: (1) immune mediated destruction, (2) drug induced marrow suppression, (3) reduced production of platelets. The incidence of HIV related thrombocytopenia is 11% [94]. The management of HIV-related thrombocytopenia is similar to management of non-HIV ITP, with the following exceptions:

- Prednisone should be used cautiously due to the concern of increasing the risk of opportunistic infections. Its use should be restricted to patients with platelet counts less than 20 x 10^9/L or <50 x 10^9/L and significant bleeding
- Splenectomy is at least as effective, if not more effective, than in non-HIV ITP. Response rate from 3 studies estimated at 84% (89 of 106) [94-96]. There is no evidence that more rapid progression of HIV results from splenectomy
- HAART is the most effective and appropriate therapy for HIV-ITP. In one recent series, 10 of 11 patients had a complete response to HAART [97].
- Dapsone has also been shown to improve platelet counts in patients with HIV-ITP at a dose of 50 to 125 mg/day [98].
The following management strategy is advocated:

- HAART as primary therapy
- Add prednisone at 0.5 to 1.0 mg/kg if platelet count is $<20 \times 10^9/L$ or $<50 \times 10^9/L$ and bleeding. Taper rapidly once HAART elevates the platelet count
- Splenectomy should be used as second line therapy as in non-HIV related ITP if platelet count $<20 \times 10^9/L$ or $<50 \times 10^9/L$ and bleeding
  - Patients refusing splenectomy should be treated with anti-D or dapsone
- Management of post-splenectomy failures has not been well studied. Possible therapeutic agents include: IVIG or dapsone.

### Drug Induced Thrombocytopenia

Drugs consistently indicated as causing drug-induced immune thrombocytopenia [20].

<table>
<thead>
<tr>
<th>Class of Drug</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac</td>
<td>Abciximab, Amiodarone, Digoxin, Eptifibatide, Hydrochlorothiazide, Methyldopa, Procainamide, Tirofiban, Quinidine</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>Rifampin, Sulfamethoxazole, Amphotericin B, Vancomycin, Ethambutol, Linezolid</td>
</tr>
<tr>
<td>Others</td>
<td>Carbamazepine, Gold salts, Heparins, Interferon-alpha, Phenytoin, Quinine, Valproic Acid, Fludarabine, Oxaliplatin</td>
</tr>
</tbody>
</table>

Consensus Statements:

- Acute Childhood ITP: AIEOP consensus guidelines for diagnosis and treatment (Review) [99]
- Guidelines for ITP [100]
- Laboratory Investigation of ITP [101]
References

Idiopathic Thrombocytopenia Purpura


Idiopathic Thrombocytopenia Purpura