***no patient handout*

Idiopathic thrombocytopenic purpura

Synopsis

Immune thrombocytopenic purpura (ITP), also known as idiopathic thrombocytopenic purpura, is an autoimmune disease in which platelet counts become decreased and manifests as a bleeding tendency. ITP patients have circulating antibodies that cause platelet destruction, the spleen being the primary site for destruction of circulating platelets. Platelet production may also be affected.

Severity of signs and symptoms varies according to the platelet levels. Patients with platelet counts of between 30 000 and 50 000 usually present with a complaint of easy bruising, whereas platelet levels of 10 000 to 20 000 lead to more significant petechiae, purpura, or ecchymoses.

Although usually idiopathic, ITP may be secondary to a number of conditions, and it is important to exclude these conditions before diagnosing ITP. Secondary thrombocytopenia may be drug induced, alcohol related, or caused by chronic liver disease. It may occur in connection with other autoimmune disorders such as systemic lupus erythematosus, antiphospholipid antibody syndrome, thyroid disease and autoimmune hemolytic anemia, lymphoproliferative disorders, and HIV infections.

ITP may be acute or chronic, and the 2 forms are differentiated by the duration of illness, the age groups affected, and the treatment approach. The acute form is more common in children, in whom it tends to be a self-limiting disease. In adults, the chronic form is the type more commonly seen, although acute ITP may also occur. The chronic form lasts longer than 6 months and usually requires treatment. In the chronic type, females show a 3:1 incidence compared with males, with onset usually between the ages of 20 and 40.

One hundred new cases per million each year develop, with half of them being children.

Signs and symptoms of ITP include purpura, epistaxis, easy bruising, bleeding gums, and menorrhagia. More severe or fatal bleeding, such as intracranial hemorrhage, hematuria, hemoptysis, and gastrointestinal bleeding, is rare.

The incidence and severity increases with age.

Codes

ICD10CM:
D69.3 – Immune thrombocytopenic purpura

SNOMEDCT:
32273002 – Idiopathic thrombocytopenic purpura

Look For

Look for signs of bleeding at the following areas:

- Mucous membranes
- Gingival epistaxis
- Conjunctiva

The lesions may take the form of the following:

- Petechiae
- Ecchymoses
- Purpura, which is nonpalpable

In addition, look for signs of the following:

- GI bleeding
- Hematuria
- Hematomas
- Hemarthrosis
- Neurological deficits

Diagnostic Pearls

The American Society of Hematology practice guidelines state that the diagnosis of ITP is one of exclusion and is based on the patient's history, physical exam, complete blood count, and peripheral smear.

Differential Diagnosis & Pitfalls

- Post-viral ITP (cytomegalovirus, Epstein-Barr virus, varicella-zoster virus)
- **Thrombotic thrombocytopenic purpura**
- **Disseminated intravascular coagulation**
- **Hemolytic uremic syndrome**
- **Lymphoma**

- Myelofibrosis
- Neuroblastomas
- **Rocky Mountain spotted fever**
- **Systemic lupus erythematosus**
- Pseudothrombocytopenia
- Drug- or radiation-induced aplastic anemia (drugs include heparin, quinine/quinidine, sulfonamides)
- Heparin-induced thrombocytopenia
- Thrombocytopenia in AIDS patients
- Liver disease
- **Leukemia**

Best Tests

Complete blood count:

- Platelet count
- Platelet size
- White blood count, morphology and size
- Red blood count, morphology and size

Electrolytes:

- Blood urea nitrogen
- Creatinine

HIV, HCV testing

Imaging studies – CT scan if intracranial hemorrhage is suspected.

Bone marrow biopsy should be considered in the case of:

- Adults older than 60 years

- Splenectomy may be required
- Atypical symptoms

Management Pearls

It is important that other causes of thrombocytopenia be excluded. A low platelet count may be the primary indicator of other disorders such as systemic lupus erythematosus or a hematologic disorder. It is, therefore, advised that a full workup of the patient be carried out.

According to the American Society of Hematology, consider treatment for patients with a platelet count of less than 30 x 10^9/L.

Therapy

According to the American Society of Hematology practice guidelines, the goal of treatment strategies is to achieve a platelet count that is associated with adequate hemostasis, rather than a normal platelet count.

The decision of whether and how to treat depends on stage and severity.

According to the American Society of Hematology, consider treatment for newly diagnosed patients with a platelet count of less than 30 x 10^9/L. Most patients with no bleeding or mild bleeding (defined by the guidelines as cutaneous manifestations only, ie, petechiae and ecchymoses), however, can be treated with observation alone, regardless of platelet count.

Oral corticosteroids are the first line of therapy. Intravenous immune globulin therapy (IVIG) is also considered a first-line treatment. Anti-D immune globulin (anti-D) can be considered under certain circumstances / in appropriate patients. If these prove to be ineffective, then intravenous steroids and splenectomy should be considered.

A hematologist is necessary for ongoing management.

Steroid Therapy

- Prednisone: 1 mg/kg p.o. every 24 hours for duration of 3-6 weeks. Tapering and discontinuation should be varied according to the patient response, or
- Methylprednisolone: 30 mg/kg IV over 30 minutes every 24 hours for 3 days, up to maximum of 1 g.

Immune Globulin Therapy

- Immune globulin: 1 g/kg IV every 24 hours for 2 days, or

- Rho (D) immune globulin: 75 µg/kg IV once.

IVIG may be used in conjunction with corticosteroids if a more rapid increase in platelet count is required.

In patients for whom corticosteroids are contraindicated, IVIG or anti-D are considered first-line treatment.

Because 20% of patients do not respond to these treatment measures, either due to relapse or an inability to tolerate the drugs, it is necessary to reassess the patient to ascertain if therapy can possibly be avoided; if not, then assess the possibility of other drug regimens. Splenectomy may also be considered in extremely ill patients who are not responding to treatment. Additional treatment options in adults at risk of bleeding who have failed one line of therapy such as corticosteroids, IVIG, or splenectomy or who relapse after splenectomy include thrombopoietin-receptor agonists (FDA approved in adults) and rituximab* (off-label use).

*An FDA boxed warning recommends that all patients be screened for hepatitis B virus (HBV) before starting rituximab treatment, due to a risk for reactivation of HBV in patients with prior infection. Screening should include both hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (anti-HBc). If screening indicates prior HBV infection, consult a hepatitis expert and closely monitor the patient during and several months after rituximab therapy.

Immunocompromised Patient Considerations:
Treatment of ITP in HIV-infected individuals is more complicated because the administration of glucocorticoids or carrying out a splenectomy may lead to opportunistic infections.

Drug Reaction Data

Below is a list of drugs with literature evidence indicating an adverse association with this diagnosis. The list is continually updated through ongoing research and new medication approvals. Click on Citations to sort by number of citations or click on Medication to sort the medications alphabetically.

Medication	Citations
ACE inhibitor	1
alemtuzumab	2
Anticoagulant	2

Medication	Citations
Antifungal	1
Antimalarials	1
Antimycobacterial	1
cobicistat	1
darunavir	1
efalizumab	1
fondaparinux	2
micafungin	1
minocycline	1
Monoclonal antibody	2
natalizumab	2
perindopril	1
protease inhibitors	1

Medication	Citations
quinine	1
rifampin	1
tetracycline antibiotic class	1

Thrombotic thrombocytopenic purpura

Synopsis

General ManifestationsThrombotic thrombocytopenic purpura (TTP) is a severe, life-threatening disease characterized by microangiopathic hemolytic anemia, thrombocytopenia, and organ dysfunction.

TTP is a subtype of the thrombotic microangiopathy (TMA) syndromes. Other subtypes of TMA include Shiga toxin-mediated TMA (Shiga toxin **hemolytic-uremic syndrome**), drug-mediated TMA, and complement-mediated TMA, among others. Accurate diagnosis of TTP and prompt initiation of treatment are essential to prevent morbidity and mortality.

The cause may be acquired or, in rare cases, hereditary (Upshaw-Schulman syndrome). In acquired TTP, autoantibodies form against ADAMTS13, which normally cleaves von Willebrand factor (vWF). As a result, vWF multimers accumulate, causing platelet aggregation and microvascular occlusion. Upshaw-Schulman syndrome results from genetic mutations in the *ADAMTS13* gene.

Classically, TTP was thought to be associated with a "pentad" of clinical and laboratory findings including microangiopathic hemolytic anemia, thrombocytopenia, neurologic abnormalities, fever, and renal dysfunction. However, the latter 3 findings are not reliably present in TTP, and consequently the presence of microangiopathic hemolytic anemia and thrombocytopenia are sufficient for a diagnosis of TTP.

Clinical features of TTP are varied and may include gastrointestinal symptoms (abdominal pain, nausea, vomiting), fatigue, malaise, neurologic abnormalities (altered mental status, confusion, headache), and purpuric rash.

TTP is more common in women and in Americans of African descent. Hereditary TTP usually

presents before age 5. Acquired TTP typically presents between the ages of 30 and 50.

Codes

ICD10CM:
M31.1 – Thrombotic microangiopathy

SNOMEDCT:
78129009 – Thrombotic thrombocytopenic purpura

Look For

- Thrombocytopenia
- Microangiopathic hemolytic anemia (anemia, schistocytes on peripheral blood smear)

Occasionally, the following features may be observed:

- Fever
- Neurologic abnormalities (confusion, headache)
- Renal dysfunction (less common)
- Jaundice (secondary to hemolysis)
- Nonpalpable purpuric macules or petechial hemorrhage

Diagnostic Pearls

Despite marked thrombocytopenia, overt evidence of bleeding is rarely seen.

Consider diagnosis of TTP in a patient with thrombocytopenia and microangiopathic hemolytic anemia without evidence of other causative factors (such as disseminated intravascular coagulation, among others – see the Differential Diagnosis section below).

Differential Diagnosis & Pitfalls

Thrombotic microangiopathy syndromes (microangiopathic hemolytic anemia, thrombocytopenia):

- Shiga toxin-mediated TMA (**hemolytic-uremic syndrome**) – diarrheal illness as prodrome; severe renal dysfunction
- Drug-mediated TMA (quinine, quetiapine, gemcitabine, and calcineurin inhibitors, among others)

- Complement-mediated TMA

The following conditions could also be considered in the differential of microangiopathic hemolytic anemia and thrombocytopenia:

- **Disseminated intravascular coagulation** (DIC)
- **Systemic lupus erythematosus**
- **Systemic sclerosis**
- **Antiphospholipid antibody syndrome**
- Systemic infection (eg, **cytomegalovirus**, **herpes simplex virus**, **meningococcus**)
- **Idiopathic thrombocytopenic purpura** (ITP)

During pregnancy:

- **HELLP syndrome** – hemolysis, elevated liver function tests, and low platelets
- **Preeclampsia**
- **Eclampsia**

Best Tests

- Complete blood count and peripheral smear: thrombocytopenia, anemia, and schistocytes
- ADAMTS13 assay

The following laboratory tests may also be useful:

- Serum lactate dehydrogenase, indirect bilirubin, reticulocyte count: increased
- Haptoglobin: decreased
- International normalized ratio (INR), partial thromboplastin time (PTT), fibrinogen: normal (important to exclude DIC)
- Blood urea nitrogen (BUN) and creatinine may be elevated or normal

Management Pearls

Criteria for initiating plasma exchange are microangiopathic hemolytic anemia and thrombocytopenia in the absence of clinical suspicion for other causes. Treatment for TTP should be initiated promptly, even if results from ADAMTS13 assay are unavailable.

Discontinue any inciting drugs such as oral contraceptives, penicillin, chemotherapeutic agents, clopidogrel, and ticlopidine.

Supportive care for end-organ damage may be needed (ie, hemodialysis).

Platelet transfusions are contraindicated except in severely thrombocytopenic patients who are bleeding.

Overall survival rates with therapy are above 80%, although relapse occurs in up to 40% of cases.

Therapy

Early plasma exchange is *critical*. Plasmapheresis with fresh frozen plasma or cryosupernatant replacement (1.0-1.5 times the predicted plasma volume) should be performed daily until hemolysis has stopped and the platelet count has normalized.

Systemic corticosteroids (prednisone 1-2 mg/kg every 24 hours) may be given with plasmapheresis or used alone in mild cases.

For TTP refractory to plasma exchange (no platelet response after 4-7 days of plasma exchange), rituximab is a first-line alternative treatment option. A rituximab dosage option is 375 mg/m^2 once weekly for 4 weeks.

TTP recalcitrant to plasma exchange and rituximab has been successfully treated with vincristine or cyclophosphamide. Newer agents that have shown promise include caplacizumab, bortezomib, and recombinant ADAMTS13. Splenectomy has been performed in severe recalcitrant cases.

Drug Reaction Data

Below is a list of drugs with literature evidence indicating an adverse association with this diagnosis. The list is continually updated through ongoing research and new medication approvals. Click on Citations to sort by number of citations or click on Medication to sort the medications alphabetically.

Medication	Citations
abacavir	1

Medication	Citations
abciximab	1
adalimumab	1
albendazole	1
Alkylating agent	4
Anthelmintic	1
Antibiotic	8
Antifungal	3
Antimalarials	6
Antimetabolite	8
Antimicrobial	2
Antimycobacterial	10
Antineoplastic antibiotic	4
Antineoplastic antimicrotubular	1

Medication	Citations
Antiparasitic	2
Antiretroviral	2
Antiviral	2
arsenic	1
Atypical antipsychotic	1
bevacizumab	1
bisphosphonate	2
bleomycin	1
bortezomib	2
bupropion	2
Calcineurin inhibitor	8
cefaclor	1
cefuroxime	1

Medication	Citations
cephalexin	1
cephalosporin	3
Chelating agents	2
ciprofloxacin	1
cisplatin	1
clarithromycin	1
clopidogrel	16
cocaine	1
cyclosporine	6
daunorubicin	1
docetaxel	1
doxycycline	1
efalizumab	1

Medication	Citations
estradiol	2
Estrogen	3
everolimus	1
famciclovir	1
fluoroquinolone	2
gemcitabine	6
ibuprofen	2
interferon	8
lamivudine	1
macrolide	1
mefloquine	1
metronidazole	1
micafungin	1

Medication	Citations
mifepristone	1
mitomycin	5
Monoclonal antibody	3
moxifloxacin	1
mTOR kinase inhibitor	2
non-NRTI antiretroviral	1
NRTI antiretroviral	2
NSAID	2
Opioid analgesic	1
Oral contraceptives	3
oxaliplatin	3
pemetrexed	1
penicillamine	5

Medication	Citations
penicillin antibiotic class	1
pentostatin	1
prasugrel	1
quetiapine	1
quinine	6
ribavirin	1
rifampin	5
simvastatin	3
sirolimus	1
statin	3
streptomycin	5
sulfadiazine	2
sulfamethoxazole + trimethoprim	2

Medication	Citations
sulfonamide	5
sunitinib	4
tacrolimus	5
tamoxifen	1
terbinafine	2
tetracycline antibiotic class	1
ticlopidine	11
tofacitinib	1
trastuzumab	1
Tyrosine kinase inhibitor	1
ustekinumab	1
zoledronic acid	2