Consultative hematology:

Common inpatient hematology consultations:

THROMBOCYTOPENIA I

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The role of the hematology consultant

AGENDA:

Thrombocytopenia:

I. **Inpatient consultation.**
II. **Outpatient consultation**

II. Inpatient consultation for thrombocytopenia

1. Inpatient consultation for thrombocytopenia

Thrombocytopenia in hospitalized patient:

- Defined as a platelet count $<150 \times 10^9/L$
- One of the most common reasons for hematology consultation in the hospitalized patient e.g.:
  - Acute coronary syndromes: 6.8% at baseline and 13% developed it during their hospital stay.
  - Medical patients receiving heparin for at least 4 days: 36% developed thrombocytopenia.
  - ICU: 8%-68% on admission, and 13%-44% during ICU stay.
- The main challenges are to identify the underlying cause and to recognize when urgent intervention is required.

1. Inpatient consultation for thrombocytopenia

Traditional classification of thrombocytopenia:

1. Conditions of decreased platelet production
2. Conditions of increased platelet destruction (sequestration).

Many disorders have >1 mechanism of thrombocytopenia e.g.:

ITP may be caused by both platelet destruction and platelet underproduction.

1. Inpatient consultation for thrombocytopenia

Practical approach to the patient with thrombocytopenia:

1. Exclude thrombocytopenic emergencies
2. Examine the blood film
3. Consider the clinical context
4. Assess the degree of thrombocytopenia
5. Establish the timing of thrombocytopenia
6. Assess the patient for signs of bleeding

Practical approach to the patient with thrombocytopenia:

1. Exclude thrombocytopenic emergencies:

- **Severe thrombocytopenia with serious bleeding:**

  e.g. intracranial hemorrhage in a patient with severe ITP

- **Some thrombocytopenic disorders are emergencies in themselves** because of their associated risk of significant morbidity and mortality if not promptly recognized and managed:
  - Drug-induced immune thrombocytopenia (DITP),
  - Heparin-induced thrombocytopenia (HIT).
  - Thrombotic thrombocytopenic purpura (TTP)
  - Sepsis and DIC
  - Catastrophic antiphospholipid antibody syndrome (CAPS)
  - Post-transfusion purpura (PTP).
  - Acute leukemia: also red and white cells are abnormal.

1. Thrombocytopenic emergencies

Drug-induced immune thrombocytopenia (DITP):

Idiosyncratic reaction caused by drug-dependent platelet- reactive antibodies → rapid platelet clearance.

Category	Common examples
Antimicrobials	• Trimethoprim/sulfamethoxazole, • Vancomycin, • Ceftriaxone, Cephamandole. • Penicillin , Ampicillin, Piperacillin, • Ciprofloxacin, • Rifampin, Ethambutol, Quinine
NSAID	• Ibuprofen, Acetaminophen, Naproxen, Gold.
CNS drugs	• Lorazepam, Diazepam, Phenytoin, Carbamazepine, Haloperidol
CVS and heart	• Quinidine, Amiodarone, • Amlodipine, Furosemide
Anticoagulant	• Heparin
Chemotherapy	• Oxaliplatin
GIT	• Rantidine

Practical approach to the patient with thrombocytopenia:

1. Thrombocytopenic emergencies (cont.)

Heparin-induced thrombocytopenia (HIT):

- A distinct clinical syndrome associated with thrombosis rather than bleeding.
- Without proper treatment, up to 55% of patients develop thrombosis and approximately 5%-10% of patients will die as a result of thrombotic complications.

ASH (2009) Clinical Practice Guideline on Evaluation and Management of HIT:

Features of the history and physical examination that support diagnosis:

Feature	Comments
Fall in platelet count ≥ 50%	From highest platelet count after heparin exposure; platelet count fall is 30-50% in 10% of cases
Fall in platelet count begins 5-14 days after heparin exposure	
Fall in platelet count begins 48 hours after heparin exposure	In patients with previous heparin exposure within last 100 days
Nadir platelet count ≥ 20 x 10^9/L	May be < 20 x 10^9/L in cases associated with thrombosis and DIC
Venous or arterial thrombosis	Occurring ≥ 5 days after heparin exposure and up to 30 days after heparin cessation
Skin necrosis	At subcutaneous heparin injection sites
Anaphylactoid reaction	Within 30 minutes after intravenous heparin bolus
Absence of alternative causes of thrombocytopenia	Such as infection, other medications known to cause thrombocytopenia, cardiopulmonary bypass within previous 96 hours, etc.
Absence of petechiae and other significant bleeding	

Practical approach to the patient with thrombocytopenia:

ASH (2009) Clinical Practice Guideline on Evaluation and Management of HIT:

The 4Ts: A clinical probability scoring model :

4T's	2 Points	1 Point	0 Points
Thrombocytopenia	Platelet count fall > 50% and platelet nadir ≥ 20 x 10^9/L	Platelet count fall 30-50% or platelet nadir 10-19 x 10^9/L	Platelet count fall < 30% or platelet nadir < 10 x 10^9/L
Timing of platelet count fall	Clear onset between days 5-14 or platelet fall ≤ 1 day (prior heparin exposure within 30 days)	Consistent with days 5-14 fall, but not clear (e.g. missing platelet counts) or onset after day 14 or fall ≤ 1 day (prior heparin exposure 30-100 days ago)	Platelet count fall ≤ 4 days without recent exposure
Thrombosis or other sequelae	New thrombosis (confirmed); skin necrosis at heparin injection sites; anaphylactoid reaction after IV heparin bolus	Progressive or recurrent thrombosis; Non-necrotizing (erythematous) skin lesions; Suspected thrombosis (not confirmed)	None
oTher causes of thrombocytopenia	None apparent	Possible	Definite

Probability	Points
High	6-8
Intermediate	4-5
Low	≤3

ASH (2009) Clinical Practice Guideline on Evaluation and Management of HIT:

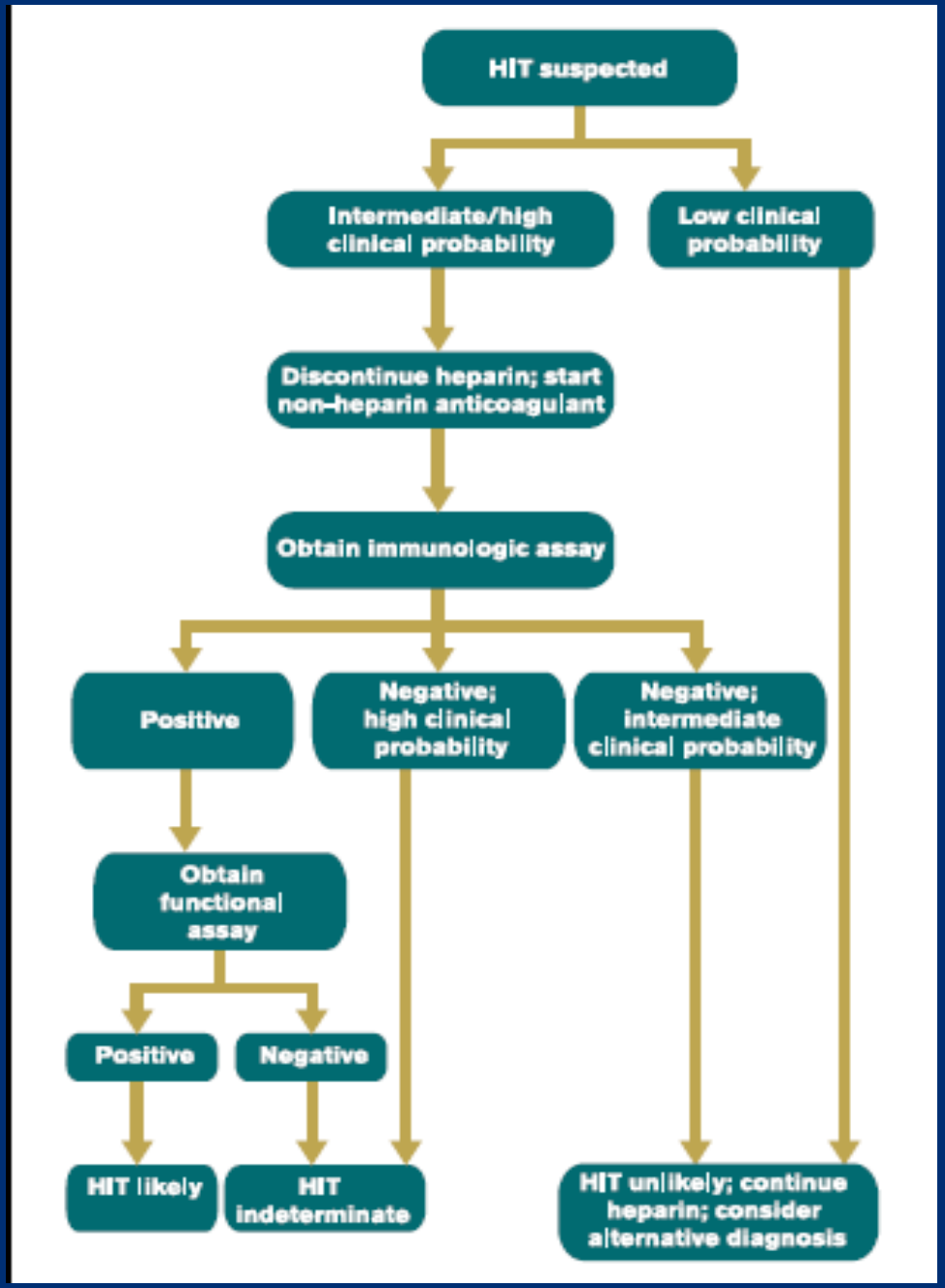
Laboratory Diagnosis:

Assay category	Mechanism	Examples	Sensitivity	Specificity	Comments
Immunologic	Detects antibodies against PF4/ heparin, regardless of their capacity to activate platelets	1. Polyspecific ELISA 2. IgG-specific ELISA 3. PGIA	>95%	50-89%	OD of ELISA result correlates with clinical probability of HIT
Functional	Detects antibodies that induce heparin-dependent platelet activation	1. SRA 2. HIPA 3. PAT	>90%	>90%	Not available at many centers; may require referral to a reference laboratory

PF4: Platelet factor 4;
OD: Optical density;
PGIA: Particle gel immunoassay;
SRA: Serotonin release assay;
HIPA: Heparin-induced platelet activation assay;
PAT: Platelet aggregation test.

ASH (2009) Guideline of HIT:

Diagnostic and Initial Treatment Algorithm:



ASH (2009) Clinical Practice Guideline on Evaluation and Management of HIT:

Treatment:

A. Non-heparin anticoagulants:

Agent	Recomm.	Dose	Monitoring
Danaparoid (Orgaran)	1B	**Bolus:** • Weight <60 kg: 1500 U • Weight 60-75 kg: 2250 U • Weight 75-90 kg: 3000 U • Weight >90 kg: 3750 U **Accelerated initial infusion:** 400 U/hr x 4 hrs, then 300 U/hr x 4 hrs **Maintenance infusion:** • Normal renal function: 200 U/hr • Renal insufficiency: 150 U/hr	Adjust dose to anti-Xa level of 0.5-0.8 U/ml
Lepirudin (Refludan)	1C	**Bolus:** • 0.2 mg/kg • only if life- or limb-threatening thrombosis is present) **Continuous infusion:** • Cr <1.0 mg/dl: 0.10 mg/kg/hr • Cr 1.0-1.6 mg/dl: 0.05 mg/kg/hr • Cr 1.6-4.5 mg/dl: 0.01 mg/kg/hr • Cr >4.5 mg/dl: 0.005 mg/kg/hr	• Adjust dose to aPTT of 1.5-2.0 times patient baseline. • Monitor aPTT every 4 hrs during dose titration.

ASH (2009) Clinical Practice Guideline on Evaluation and Management of HIT:

Treatment:

A. Non-heparin anticoagulants *(cont.)*:

Agent	Recomm.	Dose	Monitoring
Argatroban (Argatroban)	1C	**Bolus:** None **Continuous infusion:** • Normal organ function: 2 mcg/kg/min • Liver dysfunction (total bilirubin >1.5 mg/dl), HF, post-cardiac surgery, anasarca: 0.5-1.2 mcg/kg/min	• Adjust dose to aPTT • of 1.5-3.0 times patient baseline. • Monitor aPTT every 4 hrs during dose titration.
Bivalirudin (Angiomax or Angiox)	2C	**Bolus:** None **Continuous infusion:** • Normal organ function: 0.15 mg/kg/hr • Renal or hepatic insufficiency: dose reduction may be necessary	Adjust dose to aPTT of 1.5-2.5 times patient baseline..
Fondaparinux (Arixtra)	2C	No specific recommendations given minimal data supporting efficacy and appropriate dosing in HIT	

ASH (2009) Clinical Practice Guideline on Evaluation and Management of HIT:

Treatment:

B. Transitioning to warfarin

- HIT patients are at risk of venous limb gangrene during initiation of warfarin.
- Warfarin should not be initiated until platelet count is ≥ 150.
- Initial warfarin dose should be ≤ 5 mg/day (larger loading doses should be avoided).
- A parenteral non-heparin anticoagulant should be overlapped with warfarin for ≥ 5 days and until INR has reached intended target.

ASH (2009) Clinical Practice Guideline on Evaluation and Management of HIT:

Treatment:

B. Transitioning to warfarin (cont.):

Because argatroban raises the INR, the following steps should be taken when transitioning a patient from argatroban to warfarin:

If argatroban dose is	
≤2 mcg/kg/min	>2 mcg/kg/min
1. Stop argatroban when INR on combined argatroban and warfarin is >4 2. Repeat INR in 4-6 hours 3. If INR is <2, restart argatroban 4. Repeat procedure daily until INR ≥2 is achieved	1. Reduce argatroban dose to 2 mcg/kg/min 2. Repeat INR in 4-6 hours 3. Stop argatroban when INR on combined argatroban and warfarin is >4 4. Repeat INR in 4-6 hours 5. If INR is <2, restart argatroban 6. Repeat procedure daily until INR ≥2 is achieved

ASH (2009) Clinical Practice Guideline on Evaluation and Management of HIT:

Treatment:

Duration of anticoagulation:

- For patients with HIT-associated thrombosis (i.e. HITT):
  - Anticoagulate for 3-6 months as with other provoked thromboses.
- For patients with HIT without thrombosis (i.e. isolated HIT):
  - Because there is an elevated risk of thrombosis extending at least 30 days after the diagnosis of HIT, anticoagulation for at least one month should be considered.

ASH (2009) Clinical Practice Guideline on Evaluation and Management of HIT:

Treatment:

C. Bilateral lower extremity compression ultrasonography:

Should be performed in all patients with HIT, whether or not there is clinical evidence of lower-limb DVT, because the finding of DVT may influence the recommended duration of anticoagulation.

D. Platelet transfusion

- Should not be given to patients with confirmed or strongly suspected HIT (PLT transfusion may precipitate thrombosis)
- May be appropriate in situations of diagnostic uncertainty, high bleeding risk, or clinically significant bleeding.

Heparin Re-Exposure in Patients with a History of HIT (ASH 2009):

Clinical Picture	HIT Laboratory Profile		Recommended intraoperative anticoagulation	
	Immunologic assay	Functional assay	Cardiac and vascular surgery*	Cardiac catheterization and percutaneous coronary intervention
Remote HIT	Negative	Negative	1. Use UFH (1B)	1. Use a non-heparin anticoagulants** 2. If a non-heparin anticoagulant is not available, use UFH
Sub-acute HIT	Positive	Negative	1. Delay surgery, if possible, until immunologic assay becomes negative (1B) 2. If surgery cannot be delayed, use UFH (2C)	1. Use a non-heparin anticoagulants**
Acute HIT	Positive	Positive	1. Delay surgery, if possible, until functional and immunologic assays become negative (1B) 2. If surgery cannot be delayed, use bivalirudin (1B)	1. Use a non-heparin anticoagulants**

* If pre- or post-operative anticoagulation is indicated, a non-heparin anticoagulant should be used.

** Non-heparin anticoagulants: bivalirudin (1B), or argatroban, lepirudin, danaparoid (1C).

Practical approach to the patient with thrombocytopenia:

1. Thrombocytopenic emergencies (cont.)

Thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS):

- TTP and HUS are thrombotic microangiopathies characterized by microangiopathic hemolytic anemia and thrombocytopenia.
- The clinical manifestations of these disorders overlap, however:
  - Patients with TTP often have neurological complications
  - Renal impairment predominates in HUS

Practical approach to the patient with thrombocytopenia:

Thrombotic thrombocytopenic purpura (TTP):

- With proper treatment, survival of TTP patients is 85%.
- Management requires early institution of daily plasma exchange with 1.0-1.5 plasma volumes; without it, survival drops to 10%.
- Corticosteroids and rituximab have been used successfully to treat patients with relapsed or refractory TTP
- Splenectomy has been shown to reduce the rate of relapse in some high-risk patients.

Practical approach to the patient with thrombocytopenia:

Hemolytic uremic syndrome (HUS):

1. **Typical HUS (diarrhea-positive HUS):**

- The most common form of HUS
- Accounts for up to 95% of all HUS in children, often occurs in epidemics, and generally is self limited.
- Associated with bloody diarrhea
- Caused by enteric infection with strains of Escherichia coli that produce Shiga-like toxins
- Patients with HUS often do not require plasma exchange

Practical approach to the patient with thrombocytopenia:

Hemolytic uremic syndrome (HUS):

2. Atypical HUS (diarrhea-negative HUS):

- Occurs without a diarrheal prodroma
- Associated with a higher incidence of end-stage kidney disease and mortality.
- More commonly in adults
- Often caused by a dysregulation of the complement system.
- Mutations in genes encoding complement proteins, including factor H, membrane cofactor protein (CD46), factor I, and factor B and C3.
- Complement inhibition with the monoclonal antibody eculizumab that targets C5 may be beneficial for some patients with atypical HUS.

1. Thrombocytopenic emergencies (cont.)

Disseminated intravascular coagulation (DIC):

- Occurs in critically ill patients with a serious underlying disease:
  - Sepsis
  - Classical meningococcemia
  - Trauma
  - Malignancy
  - Pregnancy catastrophes: placental abruption and amniotic fluid embolism.
  - Poisoning,
  - Major hemolytic transfusion reactions
  - Severe HIT.
- DIC is caused by unimpeded thrombin generation as a result of an imbalance in the normal procoagulant and anticoagulant pathways.
- As a result, many patients develop significant thrombotic complications, including peripheral ischemia and skin gangrene.

Practical approach to the patient with thrombocytopenia:

Disseminated intravascular coagulation (DIC):

Numerous tests of hemostasis become abnormal :

- Thrombocytopenia
- FDPs
- Elevated D-dimers
- Prolongation of the PT and aPTT
- Decreased fibrinogen concentration
- Decreased protein C concentration.
- A significant reduction in the level of fibrinogen may indicate DIC even if it does not result in hypofibrinogenemia.
- Fragmentation of RBCs may be seen on the peripheral blood film.

DIC is a dynamic process requiring repeated measurements of hemostasis and careful clinical monitoring.

Practical approach to the patient with thrombocytopenia:

Disseminated intravascular coagulation (DIC):

Guidelines for the management of DIC:

- Treating the underlying condition.
- Platelet transfusion:
  - Should be reserved for patients with a platelet count <50 X 10^9/L who have or who are at high risk of bleeding.
  - Prophylactic platelet transfusions may be reasonable in the context of worsening thrombocytopenia.
- Plasma transfusions: reserved for patients with an increased PT and bleeding
- Cryoprecipitate or fibrinogen concentrates are indicated for patients with severe hypofibrinogenemia (fibrinogen <100 mg/dL).

Practical approach to the patient with thrombocytopenia:

Disseminated intravascular coagulation (DIC):

Guidelines for the management of DIC:

- UFH or LMWH:`
  - Prophylactic doses: is recommended for prevention of VTE.
  - Therapeutic doses : should be considered for patients with thrombotic complications, such as venous or arterial thrombosis, severe purpura fulminans, or vascular skin infarctions.

Practical approach to the patient with thrombocytopenia:

Disseminated intravascular coagulation (DIC):

Guidelines for the management of DIC:

- Several coagulation factor concentrates have been investigated:
  - Neither recombinant antithrombin concentrate nor recombinant tissue factor pathway inhibitor have demonstrated a benefit.
  - Activated protein C:
    - Initial clinical trials were promising
    - Follow-up studies showed no benefit and raised concerns about bleeding risk.
    - As a result, it has been withdrawn from the market

1. Thrombocytopenic emergencies (cont.)

Catastrophic antiphospholipid antibody syndrome (CAPS):

- Occurs in <1% of patients with the antiphospholipid antibody syndrome.
- It is a life-threatening condition that requires prompt recognition and management.
- Diagnostic criteria:
  - (i) Involvement of three or more organs, systems or tissues;
  - (ii) Development of symptoms simultaneously or in <1 week;
  - (iii) Confirmation by histopathology of small vessel occlusion in at least one organ or tissue; and
  - (iv) Laboratory confirmation of the presence of antiphospholipid antibodies (lupus anticoagulant; or anticardiolipin or anti-B-2-glycoprotein I antibodies).

Practical approach to the patient with thrombocytopenia:

Catastrophic antiphospholipid antibody syndrome (CAPS):

Precipitating Factors:

- Infection is the most commonly identified precipitant
- Trauma
- Withdrawal of anticoagulation
- Neoplasia.
- 40% of patients have no obvious underlying cause

Practical approach to the patient with thrombocytopenia:

Catastrophic antiphospholipid antibody syndrome (CAPS):

Management:

- Mortality can be up to 50%.
- Anticoagulation is the mainstay of therapy with or without high-dose corticosteroids.
- The highest rates of response have been achieved with the combination of anticoagulation, corticosteroids, and plasma exchange.
- IV Ig, cyclophosphamide, and rituximab have been used with some success.

Practical approach to the patient with thrombocytopenia:

1. Thrombocytopenic emergencies (cont.)

Posttransfusion purpura (PTP):

- A syndrome characterized by severe thrombocytopenia and bleeding
- Develops 7-10 days after the transfusion of RBCs or platelet concentrates.
- It typically affects women who have had a previous pregnancy or blood transfusion
- Incidence of PTP is estimated at 1-2 per 10,0000 transfusions,
- Appears to be less common with leukodepleted blood products.

Practical approach to the patient with thrombocytopenia:

Posttransfusion purpura (PTP):

- Most commonly is due to antibodies against human platelet antigen (HPA)-1a.
- The pathophysiology remains uncertain, but may involve:
  1. Formation of immune complexes
  2. Adsorption of soluble platelet antigens onto autologous platelets
  3. Induction of platelet autoantibodies.

Practical approach to the patient with thrombocytopenia:

2. Examine the blood film:

Examination of the blood film is necessary for all patients:

Platelet clumps:

- Suggestive of pseudothrombocytopenia
- A laboratory artifact caused by naturally occurring antibodies directed against the anticoagulant EDTA.
- A repeat sample collected in citrate or at 37°C usually resolves the platelet clumping.

Large platelets: inherited thrombocytopenia

Small platelets: Wiskott-Aldrich syndrome

Practical approach to the patient with thrombocytopenia:

Examine the blood film:

Morphological assessment of erythrocytes and leukocytes:

- Fragmented RBCs (schistocytes): TTP or DIC;
- Poikilocytes or nucleated RBCs: myelophthisic process;
- Abnormal leukocytes: hematologic malignancy or MDS;
- Toxic granulation of neutrophils: in sepsis;
- Neutrophilic inclusions (Döhle bodies): hereditary forms of thrombocytopenia, such as the May-Hegglin anomaly.

Practical approach to the patient with thrombocytopenia:

3. Consider the Clinical Context:

The clinical context in which the thrombocytopenia developed is an important clue to the underlying diagnosis:

- Postoperative patients:
  - Dilutional (due to massive transfusion of 15-20 units of RBCs)
  - HIT
- ICU: sepsis, drugs, DIC, etc.
- Cancer patients: DIC, TTP
- Age: in neonates, consider neonatal alloimmune thrombocytopenia, HIT is uncommon
- liver disease: chronic thrombocytopenia may be exacerbated by acute illness.
- HIV or hepatitis C: secondary ITP

Practical approach to the patient with thrombocytopenia:

Clinical Context:

Thrombocytopenia in patients admitted to the ICU:

- 40% of critically ill patients will have thrombocytopenia
  - On admission to ICU: 8.8%-67.6%
  - During the course of the ICU stay: 13.1%-44.1%.
- Independent risk factor for mortality.
- The association between thrombocytopenia and bleeding remains uncertain in this population.

Practical approach to the patient with thrombocytopenia:

Clinical Context:

HIT in the ICU:

- Frequency: 0.3%-0.5% (1 in 100 patients with thrombocytopenia in this setting
- After major surgery:
  - A rapid decline in platelet count occurring by days 1-3 is expected due to consumption and dilution
  - **Suspect HIT if:**
    1. Delayed platelet count recovery beyond day 7
    2. Worsening thrombocytopenia between days 5 and 14
    3. Development of new thrombosis in an already thrombocytopenic patient may indicate HIT.

Practical approach to the patient with thrombocytopenia:

Clinical Context:

HIT in the ICU:

- Testing for anti-PF4-heparin antibodies lacks specificity and may lead to false-positive results in critically ill patients
- Thus, functional platelet-activation tests such as the serotonin release assay should be used to confirm the diagnosis.
- Treatment of HIT requires anticoagulation with a non-heparin alternative.

Practical approach to the patient with thrombocytopenia:

Clinical Context:

Thrombocytopenia in patients on anticoagulation:

- Although thrombocytopenia can increase the risk of bleeding, it does not protect against thrombosis.
- Anticoagulation in thrombocytopenic patients with cancer is likely to be safe for most patients with platelet counts above 30 X 10^9/L;
- The need for anticoagulation in patients with thrombocytopenia is most compelling in antiphospholipid antibody syndrome, HIT, and DIC when thrombosis predominates.

Practical approach to the patient with thrombocytopenia:

Clinical Context:

Thrombocytopenia in patients on anticoagulation:

- The need for anticoagulation may be an indication to treat the underlying thrombocytopenia when possible.
- Lowering the intensity of warfarin anticoagulation to reduce bleeding risk is inadequate for secondary prevention of thrombotic events.

Practical approach to the patient with thrombocytopenia:

4. Consider the severity of thrombocytopenia:

- <20 X 10^9/L: Primary or secondary ITP (including DITP)
- 20-100 X 10^9/L: HIT (typical nadir is 70 x 109/L)
- 100 X 10^9/L: splenomegaly/ hypersplenism
- In sepsis, platelet counts are variable but thrombocytopenia tends to be mild or moderate.

Practical approach to the patient with thrombocytopenia:

5. Determine the timing of thrombocytopenia exposures:

- **Within 5-10 days:**
  - Drugs: Classic HIT, DITP;
  - Blood transfusions (PTP)
- **Within hours:**
  - Rapid-onset HIT: when platelet-reactive antibodies are already present,
  - Other drugs: tirofiban, eptifibatide, abciximab,
- **Several weeks after heparin exposure:** delayed-onset HIT (thrombocytopenia and thrombosis).

Practical approach to the patient with thrombocytopenia:

6. Assess for signs of bleeding:

Presents as petechiae or bruising; oral petechiae or purpura; and GIT, genitourinary, or intracerebral hemorrhage.

- **Bleeding signs present:** DITP, PTP, severe primary ITP, NAIT
- **Bleeding signs absent:** HIT, TTP, APS (predominantly prothrombotic disorders).

Inpatient consultation for thrombocytopenia

Thrombocytopenia:

Clinical Case:

- A 57-year-old man is in the ICU following complications from abdominal surgery seven days ago.
- He is intubated and mechanically ventilated.
- He is requiring vasopressor medications to maintain his blood pressure and is receiving broad spectrum antibiotics.
- You are consulted because his platelet count is 30×10^9/L.
- His left leg and several toes are a dusky color and one patch of skin around his left ankle is gangrenous.

Inpatient consultation for thrombocytopenia

Thrombocytopenia:

Clinical Case:

- The PT and aPTT are prolonged and both correct to within the normal range when the test is repeated using mixed normal plasma.
- The D-dimer and fibrinogen degradation products are elevated.
- The fibrinogen concentration is 0.8 g/L.
- You suspect he has DIC with thrombotic complications and recommend full-dose UFH with careful monitoring.