

Approach to Thrombocytopenia in Critical Care

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Introduction

Thrombocytopenia is one of the most frequently encountered haematological abnormalities in critically ill patients, with reported incidence ranging from 13–65% [1]. It is defined as a platelet count <150,000/ μ L or a decline of >50% from baseline. The condition may develop due to multiple, often overlapping mechanisms, and its presence in ICU patients correlates with increased morbidity, mortality, and prolonged ICU stay.

Mechanisms of Thrombocytopenia

The causes can be broadly categorized into

- **Decreased Production** (e.g., chemotherapy, sepsis, alcohol, viral infections).
- **Increased Destruction** (immune and non-immune mechanisms, e.g., HIT, ITP, sepsis, DIC).
- **Increased Consumption** (DIC, TTP/HUS, trauma, HELLP syndrome).
- **Increased Sequestration** (splenomegaly, CHF, hypothermia).
- **Haemodilution** (massive transfusion, fluid resuscitation).
- **Pseudo Thrombocytopenia** (EDTA-dependent clumping, satellitism) [2,3].

Common Clinical Scenarios in ICU

In ICU patients, the absolute platelet count alone is often insufficient to accurately characterize thrombocytopenia. Instead, the time course and trend of platelet changes provide critical clinical insights. For example, a drop of more than 50% in platelet count is typically considered a normal physiological response following cardiac surgery; however, the same degree of decline occurring later, such as during the second week of ICU stay, is abnormal and may signal an underlying complication. Similarly, patients who fail to show any increase in platelet count within five days of ICU admission may be at higher risk of poor outcomes, possibly due to ongoing infection, bone marrow suppression, or disseminated intravascular coagulation. Therefore, a comprehensive assessment of thrombocytopenia in the ICU must take into account both the absolute platelet count and its dynamic changes over time to guide diagnosis and management effectively. Various common clinical scenarios where thrombocytopenia is encountered in critical care setting are as follows.

Sepsis

Sepsis is one of the most important and frequent causes of thrombocytopenia in the intensive care unit (ICU). It not only contributes to platelet consumption but also alters their production

and function, making it a multifactorial process. The major mechanisms include:

Endothelial Injury and Sepsis-Associated Coagulopathy

- Sepsis triggers systemic inflammation with widespread endothelial activation and damage.
- This leads to exposure of subendothelial collagen and tissue factor, promoting thrombin generation and fibrin deposition.
- The end result is **Sepsis-associated coagulopathy** (ranging from mild clotting abnormalities to overt disseminated intravascular coagulation, DIC), where platelets are consumed in microvascular thrombi.
- The microthrombi not only cause platelet depletion but also contribute to organ dysfunction.
- **Impaired Thrombopoiesis**
- Inflammatory cytokines such as TNF- α and IL-6 suppress bone marrow activity.
- Sepsis reduces the hepatic synthesis of **thrombopoietin (TPO)**, a critical regulator of platelet production.
- Bone marrow studies in severe sepsis have demonstrated ineffective megakaryopoiesis, leading to decreased platelet output.

Immune-Mediated Platelet Destruction

- Sepsis can induce the production of autoantibodies against platelet glycoproteins.
- Activated macrophages and neutrophils promote **immune-mediated clearance of platelets**.
- In severe cases, **haem phagocytosis** may occur, where activated macrophages engulf platelets and other blood elements.

Platelet Dysfunction

- Beyond reduced counts, sepsis causes **qualitative platelet defects**:
- Impaired aggregation and adhesion responses.
- Reduced ability to interact with leukocytes and endothelium.
- Altered release of granule contents affecting haemostasis and immunity.

Dysfunctional platelets further compromise host defence, since platelets are increasingly recognized as immune cells that interact with pathogens and modulate inflammatory responses.

Direct Effects of Pathogens and Endotoxins

- Certain bacteria release toxins that can activate platelets,

leading to accelerated clearance.

- Viral and fungal sepsis may directly impair bone marrow progenitors.

Clinical Implications

- **Severity Marker:** Thrombocytopenia in sepsis often correlates with illness severity and predicts higher mortality.
- **Bleeding vs. Clotting Risk:** While low platelet counts increase bleeding risk, consumption in microthrombi can paradoxically predispose to thrombotic organ damage.
- **Management Considerations:** Addressing the underlying infection, supporting coagulation balance, and judicious use of platelet transfusion are essential, but no targeted therapy for sepsis-induced thrombocytopenia exists yet.

Trauma and Massive Transfusion

Trauma and massive transfusion represent important non-septic causes of thrombocytopenia in the intensive care unit, arising from a complex interplay of dilutional, consumptive, and functional mechanisms. Severe trauma is accompanied by extensive tissue injury, systemic inflammatory activation, and endothelial disruption, all of which trigger coagulation cascades and platelet activation. Platelets are consumed at bleeding sites as well as within microvascular thrombi, particularly in patients who develop trauma-induced coagulopathy. In parallel, massive transfusion commonly defined as replacement of an entire blood volume within 24 hours or transfusion of more than 10 units of packed red blood cells exerts additional effects on platelet counts. The infusion of large volumes of red blood cells, plasma, and crystalloids that lack functional platelets results in dilutional thrombocytopenia, while transfused platelets themselves may be dysfunctional due to storage lesions and reduced post-transfusion survival. Moreover, the metabolic and physiological derangements that accompany massive transfusion such as hypothermia, acidosis, hypocalcaemia, and haemodilution further impair platelet aggregation and interaction with coagulation factors, thereby compounding the haemostatic deficit. Importantly, platelet dysfunction in trauma is not merely quantitative; trauma-related platelet hypo reactivity has been demonstrated even when platelet counts appear preserved, reflecting impaired signalling, granule secretion, and adhesion. Taken together, trauma and massive transfusion contribute to both reduced platelet numbers and impaired platelet quality, significantly heightening the risk of bleeding, complicating resuscitation, and influencing outcomes in critically ill patients **DIC** systemic activation of coagulation with consumption of platelets [4].

TTP/HUS

Thrombotic Microangiopathies (TMAs), most notably Thrombotic Thrombocytopenic Purpura (TTP) and Haemolytic Uremic Syndrome (HUS), represent uncommon but life-threatening causes of Thrombocytopenia in the ICU. Both conditions are characterized by widespread microvascular platelet aggregation leading to consumptive thrombocytopenia, Microangiopathic Haemolytic Anaemia (MAHA), and end-organ dysfunction. In TTP, the central defect is a severe deficiency of the metalloprotease ADAMTS13, most often acquired due to autoantibodies, which results in the accumulation of ultra-large von Willebrand factor (vWF) multimers and uncontrolled platelet aggregation in the microcirculation. Clinically, TTP classically presents with the pentad of thrombocytopenia, MAHA, neurological dysfunction, renal impairment, and fever, though many patients may not exhibit all features. By contrast, HUS is typically associated with endothelial injury, either in the context of Shiga toxin-producing *Escherichia coli* infection (typical HUS)

or complement dysregulation (atypical HUS). In both forms, endothelial damage triggers platelet activation and microthrombi formation, predominantly affecting the renal vasculature and leading to acute kidney injury alongside thrombocytopenia and haemolysis. Importantly, in the ICU, these syndromes may be difficult to distinguish from sepsis-associated coagulopathy or disseminated intravascular coagulation (DIC), yet early recognition is crucial as management differs significantly. TTP requires urgent plasma exchange and immunosuppressive therapy, while HUS may respond to supportive care, plasma therapy, or complement inhibition (eculizumab) in atypical forms. Thus, although relatively rare, TTP and HUS are critical considerations in the differential diagnosis of ICU-acquired thrombocytopenia, as timely identification and intervention can be lifesaving.

Drug-Induced Thrombocytopenia

Drug-induced Thrombocytopenia (DITP) is an important but often underrecognized contributor to thrombocytopenia in the ICU, given the extensive polypharmacy to which critically ill patients are exposed. The mechanisms are heterogeneous and include immune-mediated platelet destruction, direct bone marrow suppression, and impaired platelet function. Immune-mediated DITP typically results from drug-dependent antibodies that bind to platelet glycoproteins (such as GPIIb/IIIa or GPIb/IX) only in the presence of the offending drug, leading to rapid clearance of antibody-coated platelets. This can cause an abrupt fall in platelet counts, sometimes within hours of drug re-exposure, and may be associated with bleeding complications. Classic agents implicated include quinine, sulphonamides, β -lactam antibiotics, vancomycin, and linezolid. A distinct and clinically significant form is **Heparin-Induced Thrombocytopenia (HIT)**, a prothrombotic disorder caused by antibodies against platelet factor 4–heparin complexes, which not only reduces platelet counts but also paradoxically predisposes to thrombosis. In addition to immune-mediated mechanisms, chemotherapeutic agents, antivirals, and some antibiotics (e.g., linezolid) may exert direct marrow toxicity, leading to impaired megakaryopoiesis and gradual thrombocytopenia. The diagnostic challenge in the ICU lies in distinguishing DITP from thrombocytopenia caused by sepsis, transfusion, or coagulopathy, since temporal association with drug exposure may be obscured in critically ill patients on multiple therapies. Management primarily involves prompt identification and withdrawal of the offending drug, with supportive care and platelet transfusions as needed. In HIT, anticoagulation with non-heparin agents is essential to mitigate thrombosis risk. Therefore, drug-induced mechanisms remain a critical consideration in the differential diagnosis of ICU thrombocytopenia, particularly when platelet decline is abrupt, severe, or temporally linked to a specific medication.

Heparin-Induced Thrombocytopenia (HIT)

Heparin-Induced Thrombocytopenia (HIT) is a distinct and clinically significant cause of thrombocytopenia in the ICU, notable for its paradoxical association with thrombosis rather than bleeding. It is an immune-mediated disorder in which antibodies develop against platelet factor 4 (PF4)–heparin complexes, leading to Fc receptor-mediated platelet activation, release of procoagulant microparticles, and excessive thrombin generation. Unlike other forms of drug-induced thrombocytopenia, HIT typically presents with a **moderate fall in platelet counts (30–50% of baseline, rarely $<20 \times 10^9/L$)** occurring 5–10 days after heparin exposure, or sooner in previously sensitized patients. Clinically, HIT is strongly associated with new or progressive thromboembolic complications, both venous (deep vein thrombosis, pulmonary embolism) and arterial (limb ischemia, stroke, myocardial infarction). In ICU patients, diagnosis can

be challenging as thrombocytopenia is multifactorial; however, suspicion is raised when platelet decline coincides with heparin therapy. The **4Ts scoring system** (thrombocytopenia degree, timing, thrombosis, and other causes) is often used as a clinical screening tool, supported by laboratory testing for HIT antibodies (ELISA for PF4-heparin complexes) and functional assays such as the serotonin release assay. Prompt recognition is critical, as continuation of heparin markedly increases thrombotic risk. Management requires **immediate discontinuation of all forms of heparin (including flushes and coated catheters)** and initiation of alternative non-heparin anticoagulation such as argatroban, bivalirudin, or fondaparinux. Platelet transfusion is generally avoided unless bleeding is life-threatening, due to the risk of fuelling thrombosis. In the ICU, where patients are often critically ill and exposed to heparin for prophylaxis or extracorporeal circuits, HIT remains a high-risk and time-sensitive diagnosis with significant morbidity and mortality if not recognized and treated promptly.

Differential Diagnosis of Thrombocytopenia in ICU

The following table summarises the various differentials for thrombocytopenia in ICU settings –

Differential Diagnosis	Findings
Sepsis	Presence of dedicated criteria such as positive cultures and clinical findings
Disseminated Intravascular Coagulation (DIC)	Abnormal laboratory findings (e.g., elevated D-dimer, prolonged PT/aPTT, low fibrinogen)
Massive Blood Loss	Abnormal laboratory findings, clinical evidence of bleeding
Thrombotic Microangiopathy (TTP/HUS)	Schistocytes on peripheral blood smear, clinical findings (e.g., renal failure, neurologic symptoms)
Heparin-Induced Thrombocytopenia (HIT)	History of heparin exposure, positive HIT antibody testing (e.g., PF4 ELISA)
Immune Thrombocytopenia (ITP)	Immunological markers, isolated thrombocytopenia, exclusion of other causes
Drug-Induced Thrombocytopenia	Abnormal findings in bone marrow aspiration, immunological and laboratory findings

Clinical Approach

A structured, stepwise evaluation is crucial [5,6]:

History & Examination

- Prior medical history (CLD, haematological disease, prior ITP).
- Drugs and interventions (heparin, antibiotics, vascular devices).
- Underlying cause of ICU admission (e.g., sepsis, trauma).
- Timing of platelet fall (acute vs delayed).
- Associated bleeding, thrombosis, or organ dysfunction.

Laboratory Evaluation

- Repeat CBC: Exclude pseudo thrombocytopenia.
- Peripheral smear: Platelet clumping, schistocytes.
- Coagulation profile: To differentiate DIC from TTP/HUS.
- Haemolysis labs: LDH, haptoglobin, Coombs test.
- Bone marrow examination: If pancytopenia or unexplained fall.
- Special Tests: HIT ELISA/serotonin release assay, drug-

dependent antibody tests (when available).

Red Flags for Urgent Workup

- Platelet count $<100,000/\mu\text{L}$.
- 30% decline or rapid fall.
- No recovery after 5–7 days of treatment.
- Worsening thrombocytopenia after initial recovery.

Management Principles

- **Treat underlying cause:** Sepsis control, trauma resuscitation, drug withdrawal.
- **Bleeding risk stratification:** Spontaneous bleeding rare $>20,000/\mu\text{L}$.
- **Platelet transfusion thresholds:**
 - $<10 \times 10^9/\text{L}$ (no risk factors).
 - $<20\text{--}30 \times 10^9/\text{L}$ (risk factors: coagulopathy, sepsis, renal/hepatic failure).
 - $<50 \times 10^9/\text{L}$ (before invasive procedures, suspected dysfunction).
 - $<100 \times 10^9/\text{L}$ (neurological bleed, neurosurgery).
- **Avoid unnecessary transfusion** to reduce risks of alloimmunization and transfusion reactions [5].

CHEST 2025 Guideline – Platelet Transfusion in Critically Ill Adults

Category	Principle
Stable, non bleeding patients, at high bleeding risk	Consider transfusion if platelet count is $<30\text{--}50 \times 10^9/\text{L}$.
Critically ill patients with active serious bleeding	Transfuse if platelet count is $<50 \times 10^9/\text{L}$.
Procedure in critically ill patients	Thresholds vary by risk of bleeding with the procedure, but $\geq 50 \times 10^9/\text{L}$ is usually targeted for high-risk invasive interventions (e.g., central line in coagulopathic patients, neurosurgery).
Routine prophylactic transfusion in stable non bleeding patients	Not recommended unless platelet counts are very low ($<10 \times 10^9/\text{L}$) or the patient has additional bleeding risks.

Specific Therapies

HIT – Heparin-Induced Thrombocytopenia (HIT) – Management Principles

- **Immediate discontinuation of all forms of heparin**, including low-molecular-weight heparin, unfractionated heparin, heparin flushes, and heparin-coated catheters.
- **Initiate alternative, non-heparin anticoagulation** promptly to reduce the risk of thrombosis. Options include:
 - **Argatroban** (direct thrombin inhibitor, preferred in renal dysfunction).
 - **Bivalirudin** (alternative in cardiac surgery/ECMO settings).
 - **Fondaparinux** (factor Xa inhibitor, off-label but widely used if renal function is adequate).
- **Avoid platelet transfusions** unless life-threatening bleeding is present, as they may fuel thrombosis.
- Transition to **warfarin or DOACs** only after platelet counts have recovered ($\geq 150 \times 10^9/\text{L}$) and the acute HIT phase is controlled.
- Close monitoring with **serial platelet counts and coagulation parameters** is essential.

Thrombotic Thrombocytopenic Purpura (TTP) Urgent Plasma Exchange (PEX)

- First-line therapy for acquired TTP.
- Removes autoantibodies against ADAMTS13 and replenishes functional ADAMTS13.
- Typically continued daily until platelet count normalizes and LDH decreases.

Immunosuppressive Therapy

- **Corticosteroids** are commonly used in combination with plasma exchange.
- **Rituximab** may be added in refractory or relapsing cases.

Supportive Care

- Manage anaemia and organ dysfunction.
- Avoid platelet transfusions unless life-threatening bleeding occurs, as transfusions can worsen micro thrombosis.

Adjunctive Therapies

- Caplacizumab (anti-vWF nanobody) can be used in severe cases to inhibit platelet-vWF interaction and reduce microvascular thrombosis.

Haemolytic Uremic Syndrome (HUS)

Supportive Therapy (Typical HUS)

- Mainly supportive care, including fluid management, dialysis if needed, and blood pressure control.
- Avoid platelet transfusions unless there is active bleeding.

Atypical HUS (Complement-Mediated):

- Eculizumab (monoclonal antibody against C5) is the treatment of choice.
- Plasma exchange may be used initially if diagnosis is unclear or as a bridge until complement inhibition is started.

Monitoring & Organ Support:

- Frequent monitoring of renal function, haemolysis markers, and platelet counts.
- ICU-level supportive care for multi-organ involvement.

Key Principles Across TTP/HUS:

- Rapid recognition is critical, as delays significantly increase morbidity and mortality.
- Avoid platelet transfusions unless there is life-threatening bleeding.
- Organ support and management of complications are essential components of ICU care.
- **DIC:** supportive management, treat underlying trigger.

Conclusion

Thrombocytopenia is a common and multifactorial complication in critically ill patients, reflecting both the severity of underlying illness and the complex interplay of pathophysiological processes unique to the ICU environment. Its aetiology encompasses a wide spectrum, including **sepsis-associated platelet consumption and dysfunction, trauma and massive transfusion-related dilutional and consumptive losses, immune-mediated disorders such as TTP/HUS, and drug-induced mechanisms including heparin-induced thrombocytopenia**. Each cause not only reduces platelet counts but often impairs platelet function, compounding the risk of bleeding and microvascular thrombosis.

Accurate diagnosis requires careful evaluation of **temporal patterns, clinical context, laboratory markers, and the exclusion of alternative aetiologies**, as thrombocytopenia may

coexist with other coagulopathies like disseminated intravascular coagulation. Management strategies must be individualized, balancing **risk of bleeding, thrombotic complications, and the need for invasive procedures**, guided by contemporary evidence-based thresholds, such as those outlined in the CHEST 2025 guidelines. Specific therapies such as **plasma exchange and immunosuppression for TTP, complement inhibition for atypical HUS, or alternative anticoagulation in HIT**—can be lifesaving when promptly instituted.

Ultimately, thrombocytopenia in the ICU serves not only as a **marker of disease severity** but also as a **modifiable contributor to morbidity and mortality**, emphasizing the importance of early recognition, precise etiological assessment, and tailored therapeutic interventions. A systematic, cause-directed approach, coupled with vigilant monitoring and supportive care, is essential to optimize outcomes in this high-risk patient population.

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