Approach to the Hospitalized Patient With Thrombocytopenia

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Abstract

During the 2020 JADPRO Live Virtual conference, Laura J. Zitella, MS, RN, ACNP-BC, AOCN®, educated the audience on the most important causes of thrombocytopenia in hospitalized patients and diagnostic approaches to employ.

With up to 50% of hospitalized patients experiencing low blood platelet count, thrombocytopenia is a very common condition. During JADPRO Live Virtual 2020, Laura J. Zitella, MS, RN, ACNP-BC, AOCN®, of the University of California, San Francisco, discussed the most important causes of thrombocytopenia in hospitalized patients and reviewed the basic diagnostic approach using key clinical and laboratory parameters.

As Ms. Zitella explained, thrombocytopenia is traditionally defined as a platelet count less than 150,000/µL (Ali & Auerbach, 2017). For some people, however, a platelet count between 100,000/µL and 150,000/µL is normal.

"If the platelet count has been stable for more than 6 months at a level between 100,000/µL and 150,000/µL, it's probably normal for that patient and not indicative of disease," said Ms. Zitella, who noted that there's minimal risk of bleeding with a platelet count greater than 50,000/µL.

Although platelets may seem like simple cells, Ms. Zitella noted their extraordinary qualities. Platelets are managed by the hormone thrombopoietin, which is constitutively secreted, and they autoregulate. Because thrombopoietin is secreted at a constant rate regardless of physiological demand, the platelet count remains remarkably stable in an individual patient over time.

Thrombocytopenia is very common among hospitalized patients but is usually mild, said Ms. Zitella, who noted that a platelet count less than 10,000/µL is highly unusual, except in acute leukemia. Thrombocytopenia is also nearly always a secondary cause, and it's usually discovered incidentally.

Although the morbidity and mortality rate from thrombocytopenia is very low, it usually portends a poor prognosis because it results from an underlying disorder.

"It's not the low platelet count itself that portends the poor prognosis, but the fact that a low platelet

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count was caused by some other serious disorder," said Ms. Zitella, who noted that new-onset thrombocytopenia in a hospitalized patient is nearly always caused by increased platelet destruction due to sepsis, drug-induced thrombocytopenia, immune thrombocytopenia, or surgery.

DIAGNOSTIC APPROACH

Step 1: Thrombocytopenia Should Always Be Confirmed by Examination of Peripheral Smear

One important reason to look at the peripheral smear is that there is a phenomenon called pseudothrombocytopenia, which occurs when platelets clump. To determine if it is pseudothrombocytopenia, said Ms. Zitella, repeat the blood draw using a blue top tube with sodium citrate or heparin in it, and see what the platelet count is.

Step 2: Initial Labs

The next step is drawing an initial set of lab values. You should check the following labs: electrolytes, liver function tests, creatinine, and a disseminated intravascular coagulation (DIC) screen, which includes fibrinogen, D-dimer, international normalized ratio (INR) and partial thromboplastin time (PTT), lactate dehydrogenase (LDH), and blood cultures, if appropriate. These initial labs will guide you to the cause of thrombocytopenia, said Ms. Zitella.

Step 3: Rule Out Life-Threatening Causes

Ruling out life-threatening causes is the most important step, said Ms. Zitella, who noted that it can be complicated to figure out why a patient in the hospital has thrombocytopenia because there are so many potential causes. Although the exact diagnosis of thrombocytopenia may never be determined and the platelet count may resolve spontaneously, the following conditions need to be ruled out immediately:

- Sepsis-induced thrombocytopenia (check blood cultures and lactate)
- Heparin-induced thrombocytopenia
- Thrombotic thrombocytopenia purpura or hemolytic uremic syndrome (which leads to fragmented red blood cells and an increased LDH)
- Drug-induced immune thrombocytopenia
- Primary immune thrombocytopenia (ITP) with bleeding (very unusual in a hospitalized patient who doesn't have a previous diagnosis of ITP)
- Acute leukemia
- Posttransfusion purpura (very rare)

Step 4: Determine Clinical Context

The clinical context will help focus the differential diagnosis. For example, the patient may have had recent surgery, chemotherapy, or been admitted with an infection or with sepsis. The patient could also be on drugs that can cause drug-induced ITP like piperacillin or they may have liver disease (Table 1).

Step 5: Assess Severity of Thrombocytopenia

Most of the time, moderate thrombocytopenia is seen in the hospital. There are a wide variety of causes, including thrombotic thrombocytopenic purpura (TTP), heparin-induced thrombocytopenia, sepsis, cirrhosis, postsurgical, or hemodilutional. If a patient has a low or very low platelet count, then it's generally ITP, a drug-induced ITP, or DIC, said Ms. Zitella. Very rarely, in cases of very severe sepsis, such a low platelet count can be seen.

Step 6: Assess Timing in Relation to Exposures

The next step is to assess the timing and relation to exposures. A drop in the platelet count within 24 hours is usually dilutional or postoperative. Within 1 to 5 days, a drop in platelet count is associated with an acute thrombosis thrombocytopenia, septic thrombocytopenia, DIC, or TTP. If the platelet count drops between 5 and 10 days, on the other hand, this is "classic timing" for heparin-induced thrombocytopenia, a drug-induced thrombocytopenia, or posttransfusion purpura, said Ms. Zitella.

Step 7: Assess for Bleeding or Thrombosis

The last step is to assess for bleeding and thrombosis. In a patient who has thrombocytopenia, bleeding rarely causes serious consequences, but thrombosis associated with thrombocytopenia can be very serious. If a patient is thrombocytopenic and bleeding, that's usually associated with a drug-induced thrombocytopenia or DIC.

Table 1. Most Common Causes of Thrombocytopenia in Hospitalized Patients

Medical patients/ICU	Cardiac patients
• Infections • Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS) • Drug-induced thrombocytopenia (DITP) • Disseminated intravascular coagulation (DIC) • Liver disease • Heparin-induced thrombocytopenia (HIT) • Macrophage activation syndrome • Bone marrow disorders • Chemotherapy-induced thrombocytopenia	• Heparin-induced thrombocytopenia (HIT) • Cardiac bypass • Glycoprotein IIb/IIIa inhibitors • Drug-induced thrombocytopenia (DITP) • Dilutional

Note. Information from Ali & Auerback (2017).

"If thrombosis is present in the setting of thrombocytopenia, that's usually worrisome for heparin-induced thrombocytopenia, TTP, sepsis, or DIC," said Ms. Zitella. "In DIC, you can have either bleeding or thrombosis, or both at the same time."

HEPARIN-INDUCED THROMBOCYTOPENIA

One of the most important and catastrophic complications of drug therapy, heparin-induced thrombocytopenia (HIT) is moderate thrombocytopenia that starts at least 5 days after heparin. Mean platelet count is approximately 40,000/µL and is rarely less than 20,000/µL (Greinacher, 2015). Bleeding is rare, but thrombotic complications are very serious. The paradoxical prothrombotic state makes early recognition of HIT critical, said Ms. Zitella, who noted that there are two types of HIT.

The first is a nonimmune HIT also called type 1. This is not immune-mediated but is a direct effect of heparin binding to the platelets and causing the platelets to clump. Type 1 HIT is fairly common and is not clinically significant. In fact, said Ms. Zitella, many experts believe that this clinical scenario shouldn't be called HIT because the clinical features are so distinct from a classic autoimmune HIT.

A true HIT or type 2 HIT is clinically significant and is potentially life threatening due to autoantibodies to heparin/platelet factor 4 (PF4) complex, referred to as "HIT antibodies" or "PF4/heparin antibodies." The main physiologic concern is activation of the clotting cascade that can cause a series of thrombotic complications.

"If you suspect that a patient has HIT, there is a scoring system called the 4Ts that incorporates the level of thrombocytopenia, the timing of the platelet count, thrombosis, and the possibility of other causes," said Ms. Zitella. "This is a really helpful tool in order to determine if you should pursue further testing for your patient to determine if they have HIT."

Treatment of HIT

The most critical step in treating heparin-induced thrombocytopenia is stopping the heparin and starting an alternative anticoagulation due to high risk of thrombosis. Traditionally, argatroban has been used, said Ms. Zitella, but there are emerging data showing efficacy of direct oral anticoagulants in this situation. Once the heparin is stopped and a nonheparin anticoagulant is introduced, the platelet count should respond within days.

"Extended anticoagulation is really important because the risk of thrombosis with HIT is approximately 50% in one month, so patients need prolonged anticoagulation," Ms. Zitella added. "If patients are refractory to initial treatment, there has been some benefit to using high-dose intravenous immunoglobulin."

IMMUNE THROMBOCYTOPENIA

Immune thrombocytopenia is characterized by production of antiplatelet autoantibodies that target platelets for destruction by macrophages in the spleen, liver, or both through activation of Fcγ receptors. This condition may be idiopathic, drug induced, or secondary to an underlying inflammatory condition.

"Antiplatelet autoantibodies are not detected in up to 50% of patients, so there may be alternate mechanisms such as T cells," said Ms. Zitella.

The peripheral smear (Panel A) will reveal thrombocytopenia, while the bone marrow (Panel B) will reveal increased numbers of megakaryocytes in a response to produce additional platelets (Cooper & Ghanima, 2019).

With drug-induced ITP, platelets are generally below 20,000/μL, which causes severe thrombocytopenia and is often associated with bleeding. The onset is approximately 5 to 10 days after exposure, and the diagnosis and the treatment are to stop the drug.

"If the thrombocytopenia gets better, then in retrospect, you can conclude that it was a drug-induced thrombocytopenia," Ms. Zitella observed. "This condition is difficult to prove with serology."

DISSEMINATED INTRAVASCULAR COAGULATION

Disseminated intravascular coagulation is the most common acquired hypercoagulable state in hospitalized patients. Because it's life threatening, said Ms. Zitella, it's really important to recognize it immediately.

Disseminated intravascular coagulation is characterized by systemic activation of the coagulation system followed by activation of the fibrinolytic system, which leads to bleeding and thrombosis.

"DIC is not a disease in and of itself," said Ms. Zitella. "It's always due to an underlying disorder, and so it's often seen in situations where tissue factor is released, which triggers the coagulation cascade."

Because it takes a combination of laboratory tests to determine if a patient has DIC and because no single test can lead to the diagnosis, there is a scoring system that can be helpful in determining a high probability for DIC. However, the algorithm is not recommended for patients who do not have an underlying disorder known to be associated with overt DIC.

If the patient has active bleeding, there are a number of helpful supportive care measures, such as platelet transfusions to keep the platelets greater than 30 to 50 K/μL, or plasma and/or factor concentrate if there's a prolonged prothrombin time. Vitamin K supplementation can be helpful if there is a suspected/known deficiency, said Ms. Zitella, and antifibrinolytic treatment may be considered for severe hyperfibrinolysis but is usually not necessary (Levi & Scully, 2018).

If a patient has no major bleeding or thrombosis, a prophylactic anticoagulant can be used, but if a patient has overt thromboembolism or organ failure, even if there is some minimal bleeding, a therapeutic anticoagulant like unfractionated heparin is recommended.

"Unfractionated heparin has a very short half-life, so you're able to turn it on and turn it off if you need to if there's excessive bleeding," said Ms. Zitella. ●

Disclosures

Ms. Zitella has served on an advisory board for Merck.

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