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Approach to Thrombocytopenia in Older Adults

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Thrombocytopenia, whether symptomatic or not, is a relatively common finding in clinical medicine. The causes of thrombocytopenia are many, and all of these may be found at all ages. However, just as the frequencies of these causes vary between pediatric and adult age-groups, so too is there variation between younger adults and older individuals. Also, the pathophysiological approach to thrombocytopenia (decreased production, increased destruction, sequestration, dilution) remains just as valid to the seasoned hematologist as to the neophyte. In this article, we provide a suggested approach to the patient with thrombocytopenia, with emphasis on the more common causes in older adults.

Key words: *thrombocytopenia, platelets, bleeding disorders, primary hemostasis, older adults*

Introduction

Thrombocytopenia is defined as a platelet count below the normal range for the population (±2 standard deviations from the mean). In most laboratories, the normal platelet count in adults ranges from 150–450 x 10^9/L, with mean values of 237 x 10^9/L and 266 x 10^9/L in males and females, respectively. Thrombocytopenia is defined as a platelet count less than 150 x 10^9/L, keeping in mind that 2.5% of the normal population will have a platelet count lower than this.

Analogous to the red blood cell system, the major mechanisms for a reduced platelet count are decreased production (e.g., bone marrow failure) and increased destruction (e.g., drug-induced thrombocytopenia). Two additional mechanisms are distributional or sequestration (i.e., hypersplenism) and dilutional (i.e., massive transfusions) thrombocytopenia.

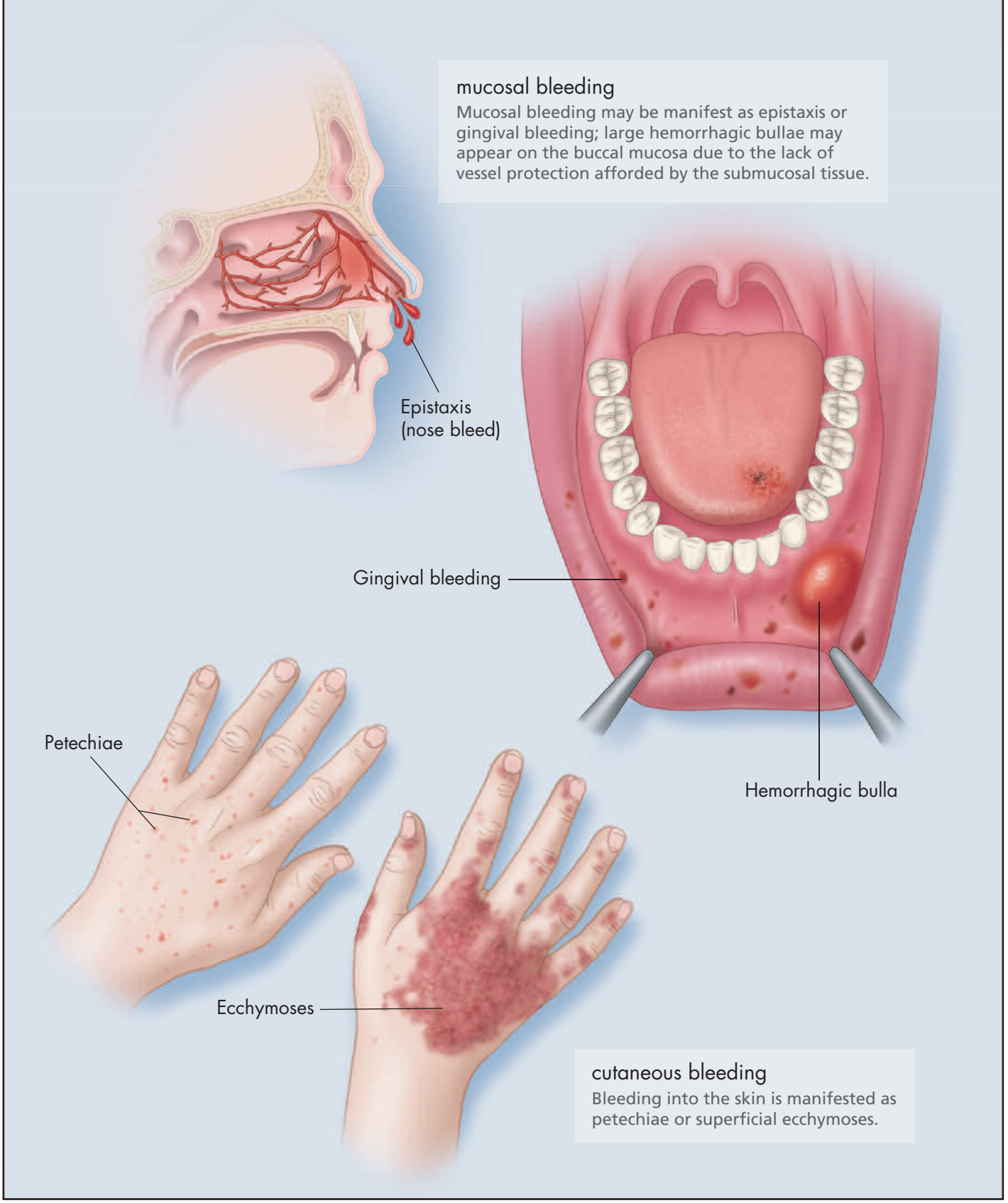
Thrombocytopenia in Older Adults in the Outpatient Setting

The commonest causes of thrombocytopenia in this scenario are listed in Table 1, together with less common or rare causes. Although it may seem surprising to some to see immune or "idiopathic" thrombocytopenic purpura (ITP) listed in the left-hand column, about one-quarter of the patient with ITP in our large hematology practice are over the age of 50.

Diagnostic Approach

Individuals with thrombocytopenia may be asymptomatic and thrombocytopenia may first be detected on a routine complete blood count. The symptomatic presentation of thrombocytopenia is bleeding, characteristically cutaneous and/or mucosal (Figure 1). Bleeding into the skin is manifested as petechiae or superficial ecchymoses. Mucosal bleeding may be manifest as epistaxis or gingival bleeding; large hemorrhagic bullae may appear on the buccal mucosa due to the lack of vessel protection afforded by the submucosal tissue. The pattern of bleeding in patients with thrombocytopenia (and in patients with disordered platelet function) differs from that seen in patients with coagulation disorders such as hemophilia, in that the latter group has delayed bleeding that begins several hours or a day after trauma, because normal platelet function can provide temporary hemostasis. Patients with coagulation disorders also have deep bleeding (into tissues, muscles, and joints), minimal bleeding after minor cuts, more delayed bleeding, more postsurgical bleeding, and tend not to have petechiae Certain drugs that affect the number or function of platelets are listed in Table 2. Of course, many older adults may be taking more than one of these drugs, in which case identifying the culprit may involve a

Figure 1:
Symptomatic Presentation of Thrombocytopenia



combination of good clinical "hunch" with consultation of a pharmacopoeia, or even trial and error. We also recommend the article by George, *et al.,* listed in our references.[6]

When thrombocytopenia is confirmed, a stepwise evaluation should be undertaken to assess the causes and the urgency of treatment. If diagnoses such as thrombotic thrombocytopenic purpura (TTP) or heparin-induced thrombocytopenia (HIT) are suspected, immediate intervention is required. In addition, any patient with severe thrombocytopenia or evidence of hemorrhage should receive immediate attention and possible platelet transfusion.

A detailed comprehensive history can provide valuable diagnostic information. The history should focus on identifying the presence of bleeding with particular attention to critical sites including the head and gastrointestinal tract, as patients with TTP can present with intermittent confusion. A recent viral respiratory illness can sometimes be associated with transient thrombocytopenia. A complete medication history including use of over-the-counter (OTC) products should be elicited. A history of prior low platelet counts or bleeding tendency should be sought and previous blood counts reviewed. Family history of platelet disorders should be elicited (occasionally, congenital thrombocytopenia will be first diagnosed in an adult).

History pertaining to alcohol consumption and HIV risk factors should be obtained. Physical examination should focus on finding the presence of bleeding in the skin, mucous membranes, gastrointestinal tract, brain, urinary tract, and retroperitoneum. The presence of retinal hemorrhage on ocular fundus examination is a predictor of CNS hemorrhage. Typically, patients with thrombocytopenia do not have soft tissue or joint bleeding. Their presence should raise suspicion of additional coagulation problems. Presence of vascular thrombi raises the possibility of HIT or disseminated intravascular coagulation (DIC). A diligent neurologic examination should indicate the need for imaging in patients with a suspected intra-cranial bleed. Patients with TTP can present with mental status changes. The presence of lymphadenopathy and splenomegaly can also provide clues to the diagnosis.

Table 1: Causes of Thrombocytopenia in Older Adults

Common	Uncommon or rare
Drugs	Recent viral illness
MDS (Myelodysplastic syndromes) Other bone marrow disorders (e.g., myeloma, lymphomas, leukemias, solid tumours, etc.)	Liver diseases Hypersplenism (many causes, some of which overlap with others in these columns)
ITP	Ethanol (acute effects)*
Low-grade DIC (e.g., secondary to metastatic prostate cancer)	Heparin-induced thrombocytopenia (HIT) with or without thrombosis* High-grade DIC* Thrombotic thrombocytopenic purpura (TTP)* Familial thrombocytopenia

DIC: disseminated intravascular coagulation; *: these are more likely to be seen in the inpatient than the outpatient setting.

Initial laboratory evaluation should include a peripheral blood film, serum creatinine, DIC panel, lactate dehydrogenase (LDH), total and direct bilirubin, alanine aminotranferease (ALT) and aspartate aminotransferase (AST). This allows an initial determination of whether thrombocytopenia is an isolated abnormality or part of a constellation of abnormalities that may suggest a specific diagnosis. If hemolysis is suspected then a direct antiglobulin test, reticulocyte count, and haptoglobin should be checked. The presence of schistocytes on the film is suggestive of TTP or DIC. Differentiation is usually made by the presence of normal coagulation parameters in TTP and elevated prothrombin time, partial thromboplastin time, fibrin split products, and low fibrinogen in DIC. An HIV test is indicated in patients with any risk factors. Vitamin B_{12} and folate levels can help diagnose nutritional causes of thrombocytopenia. Suspicion of connective tissue disorders should lead to appropriate serologic testing. In considering potential causes of thrombocytopenia, it may be helpful to take a pathophysiology-based approach, keeping in mind that distinct pathogenetic mechanisms are not mutually exclusive.

Finally, the possibility of pseudothrombocytopenia should be mentioned. In some patients, platelet clumping may occur in vitro in the lavender-topped tubes (containing the anticoagulant EDTA) usually used to draw CBCs. This gives rise to a falsely low count produced by the electronic counter. The platelet

Table 2: Drugs Affecting Platelet Function and Number

Drugs affecting platelet number	Drugs affecting platelet function
MYELOTOXIC DRUGS (dose-dependent)	ASA (acetylsalicylic acid)
IDIOSYNCRATIC (not dose-dependent); quinine, quinidine, valproic acid, many others)	NSAIDs (nonsteroidal anti-inflammatory drugs)
Heparin	Clopidogrel (Plavix)

clumps are easily seen on the blood film, and an experienced technologist can estimate the true count as being adequate or not. As a further check, one can have the blood drawn in citrate (blue-topped) or oxalate (grey-topped); the clumping will usually not occur in these.

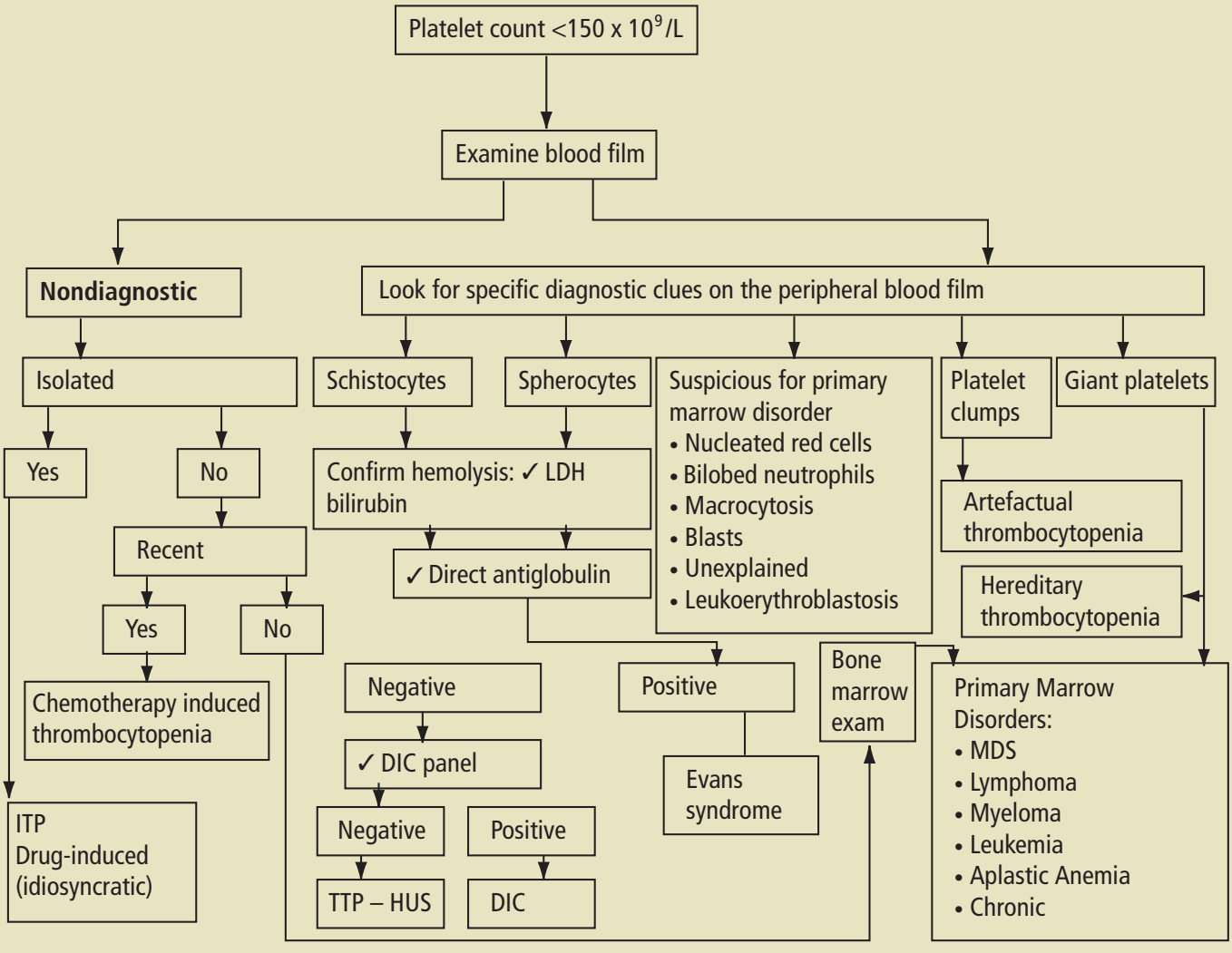
An algorithm for the evaluation of thrombocytopenia in older adults is shown in Figure 2.

Recommendations

While thrombocytopenia can be caused by myriad conditions, including systemic disease, infection, drugs, and primary hematologic disorders, a number of salient points will help the physician in determining its cause.

First, although thrombocytopenia is defined as a platelet count less than 150 x 10^9/L, keep in mind that 2.5% of the normal population will have a platelet count lower than this. A fall in platelet count to levels less than 150 x 10^9/L may be important, and requires active follow-up, although thrombocytopenia is not usually detected clinically until the platelet count has fallen to levels significantly below 50 x 10^9/L. Findings that suggest reduced production of platelets as the cause for the patient's thrombocytopenia include the presence of small platelets, malignant cells, a leukoerythroblastic blood picture (immature granulocytes and nucleated red cells), leukopenia, anemia, and/or large (macrocytic) red cells. Large platelets (megathrombocytes) on the peripheral film without significant bleeding suggest the presence of young, hemostatically active platelets in response to peripheral destruction. However, very large platelets, approaching the size of red cells, suggest either a chronic myeloproliferative disorder or a congenital thrombocytopenia. Other findings that suggest increased peripheral destruction of platelets as the cause of thrombocytopenia include the presence

Figure 2: Evaluation of Thrombocytopenia in Older Adults



DIC=disseminated intravascular coagulation; HUS=hemolytic uemic syndrome; ITP=idiopathic thrombocytopenic purpura; LDH=lactate dehydrogenase; MDS=myelodysplastic syndrome; TTP=thrombotic thrombocytopenic purpura.

Key Points

Thrombocytopenia is common in clinical medicine.

Causes of thrombocytopenia in older adults include all those seen in other age groups, but the frequency distribution is somewhat different.

Drug-induced thrombocytopenia is common among older adults, but because of polypharmacy in this age group, there are often multiple drugs that could be implicated.

The frequencies of most bone marrow disorders, especially MDS and leukemias, increase with age.

Although young people with presumed ITP (i.e., no other obvious cause for thrombocytopenia) are commonly started on treatment without having a bone marrow examination performed, this is not prudent in older adults.

of fragmented red cells, hemolytic anemia, and an increased serum concentration of lactate dehydrogenase (LD or LDH). A presumptive diagnosis of immune thrombocytopenic purpura (ITP) is made when the history (e.g., lack of ingestion of a drug that can cause thrombocytopenia), physical examination, complete blood count, and examination of the peripheral blood film do not suggest other etiologies for the isolated thrombocytopenia. Bone marrow aspiration and biopsy is indicated in virtually all patients with unexplained thrombocytopenia severe enough to constitute a risk for major bleeding. The only valid exclusion to this requirement is the patient less than 60 years of age with a presumptive diagnosis of ITP (see above). In the patient over 60, even with a presumptive diagnosis of ITP, a bone marrow biopsy should be obtained because of the relatively high incidence of other causes of thrombocytopenia in this age group.

Conclusion

A significantly reduced platelet count, whether accompanied by bruising/bleeding or not, demands explanation. The clinician's approach to this problem, as in most areas of medicine, entails a thorough history (including prescribed and over-the-counter medications) and physical examination, coupled with examination of the blood film by an experienced microscopist and other laboratory tests as indicated.

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Clinical Pearls

Readers should familiarize themselves with the article "Drug-induced thrombocytopenia: A systematic review of published case reports"[6] and keep the article close at hand for reference.