Assessment and Management of Coagulopathies in the Elderly

Anne G. McLeod, MD, FRCPC, Assistant Professor, Department of Medicine, University of Toronto; Staff Physician, Department of Medical Oncology and Hematology, University Health Network, Toronto, ON.

Bleeding in the elderly is a common problem. Careful assessment of a patient’s bleeding history and physical examination is essential to try to establish if a clinically significant bleeding disorder is present. Initial laboratory testing should include a complete blood count, blood film review, PT/INR and PTT. Common etiologies of bleeding in the elderly include thrombocytopenia and medications such as aspirin, non-steroidal anti-inflammatory agents and anti-coagulants. Unfortunately, no single approach to the treatment of coagulopathy exists; rather, a clear understanding of the cause of the bleeding disorder is needed to direct management.

Key words: coagulopathy, elderly, bleeding, hemostasis, clotting.

Introduction

Bleeding is a common clinical problem in the elderly. Age-related changes to the coagulation system do not lead to a higher risk of bleeding, but in fact favour the development of thrombosis. However, many disease states that may lead to bleeding are more common in this patient population, such as malignancy and stroke. Indications for surgery and for the use of anticoagulant medications also are more prevalent in elderly populations. Although severe congenital coagulopathies are unlikely to manifest initially in older age, mild congenital bleeding disorders may be diagnosed only when patients encounter these bleeding stresses, and many acquired bleeding disorders can present in elderly populations.

Pathophysiology

The arrest of blood flow involves a coordinated response by vascular, platelet and plasma coagulation factors to control hemorrhage following blood vessel injury. Hemostasis must be rapid in order to prevent bleeding to death, and must be localized to prevent clotting to death. This necessitates very careful regulation.

Hemostasis can be divided into three main steps (Figure 1). Primary hemostasis occurs immediately in response to endothelial damage to blood vessels. The vessel constricts and platelets adhere to the damaged vessel wall, leading to platelet activation and aggregation to form a temporary plug. Primary hemostasis provides the very rapid response to vessel damage that is necessary to prevent exsanguinations, but it is only a temporary solution.

Secondary hemostasis leads to the production of a more stable fibrin clot by activation of the clotting cascade. Activated platelets provide the procoagulant phospholipid surface needed for the production of fibrin. The fibrin clot that is formed then cements the temporary platelet plug in place, providing a more permanent solution to the bleeding problem. Von Willebrand factor (vWF) plays a crucial role in both primary and secondary hemostasis. In primary hemostasis, vWF acts as a bridge between the endothelium and platelets by binding to collagen on the damaged endothelial surface and platelet glycoprotein Ib at the same time. vWF also functions as the carrier protein for factor VIII, protecting it from degradation in the circulation and ensuring that a plentiful supply of factor VIII will be readily available when secondary hemostasis is turned on.

Fibrinolysis is an often ignored but essential part of the process of hemostasis. The fibrin clot eventually must be resolved to prevent obstruction of the blood vessel and to allow healing of the endothelium; this is the job of the fibrinolytic system.

Changes with Aging

Changes in the clotting system that have been associated with aging include a shortening of the bleeding time and of the partial thromboplastin time (PTT). Levels of factors II, VIII and X tend to increase with age while antithrombin III levels tend to decrease. Furthermore, fibrinogen levels increase and fibrinolysis may be reduced. All of these age-related changes shift the hemostatic system towards thrombosis and away from bleeding.

Clinical Assessment

The mainstay of clinical assessment is the bleeding history. Essential questions in the bleeding history are listed in Table 1. In the elderly a careful medication history of both prescription and non-prescription drugs is essential. Congenital disorders are suspected if there has been a lifelong history of bleeding or bruising or if a family history exists. Acquired dis-

<table>
<thead>
<tr>
<th>Table 1 Essential Questions in the Bleeding History</th>
</tr>
</thead>
<tbody>
<tr>
<td>When did the bleeding start?</td>
</tr>
<tr>
<td>Is there a family history?</td>
</tr>
<tr>
<td>Is the bleeding spontaneous or after trauma?</td>
</tr>
<tr>
<td>If after trauma, is it immediate or delayed?</td>
</tr>
<tr>
<td>Is there petechiae, ecchymoses, mucosal or deep tissue bleeding?</td>
</tr>
<tr>
<td>Is there a history of bleeding with surgery or dental work?</td>
</tr>
<tr>
<td>Any new drugs or over-the-counter medications being taken?</td>
</tr>
<tr>
<td>Any other medical illnesses present?</td>
</tr>
</tbody>
</table>
orders are more likely when a sudden onset of symptoms occurs or when previously normal laboratory investigations become abnormal.

Physical examination is important to corroborate reports of bruising or petechiae and to look for evidence of other systemic disorders. Bruising is notoriously over-reported by patients of all ages. Very extensive bruising or bruising in unusual locations such as the trunk or inner aspects of arms or legs—where trauma is less likely—should heighten suspicion of a significant coagulopathy.

Recurrent bleeding from a single site in the absence of other signs of a bleeding disorder suggests an anatomic defect and warrants treatment of the lesion; for example, cautery for recurrent nosebleed from a single nostril.

Disorders of primary hemostasis usually lead to bruising, petechiae and mucous membrane bleeding. The bleeding also tends to occur immediately after injury, and bleeding from surface cuts or abrasions is prolonged. Spontaneous joint or muscle bleeds are always significant and are usually associated with disorders of secondary hemostasis, such as acquired FVIII inhibitors. Disorders of primary or secondary hemostasis may lead to excessive bleeding with surgical procedures.

The bleeding history and physical examination allow the physician to determine if a clinically significant bleeding disorder is present. Symptoms and signs may suggest a primary or secondary defect and help guide laboratory testing, but are not sufficient to make a final diagnosis.

**Laboratory Assessment**
Initial lab testing should include a complete blood count, blood film review, PT/INR and PTT. The presence of symptoms on history and physical examination that are suggestive of a systemic disorder, such as renal failure...
or liver disease, should prompt additional lab testing. Abnormal CBC results may require further investigation to rule out bone marrow disorders. In young adults with thrombocytopenia, a diagnosis of idiopathic thrombocytopenic purpura (ITP) often can be made in the absence of a bone marrow because of the very low incidence of myelodysplasia (MDS) in this population. However, thrombocytopenia of unclear etiology in a patient older than 60 years should warrant a bone marrow, as MDS may rarely present with thrombocytopenia initially.

A normal platelet count rules out thrombocytopenia as a cause of bleeding but does not rule out a platelet function defect. If symptoms are suggestive of a primary hemostatic defect, then platelet function tests and investigations for von Willebrand disease should be warranted in the absence of an obvious etiology, such as Aspirin use or uremia.

Normal PT and PTT results rule out a disorder of secondary hemostasis. An elevated PT or PTT in the absence of heparin or warfarin use should prompt a mixing study. In this test, 50% patient plasma is mixed with 50% normal plasma and the PT and PTT is repeated. Clotting factor levels of 50% are all that is needed for secondary hemostasis. Therefore, if a clotting factor is deficient in a patient’s sample, a 50:50 mix with normal plasma will be sufficient to replace the missing factor and the test will normalize. If, however, there is an inhibitor present in the patient’s sample, then even on mixing the test will remain prolonged. Correction of the 50:50 mix should lead to testing of individual factor levels and non-correction should lead to testing for a clotting factor inhibitor (Figure 2). An antiphospholipid antibody may prolong the PTT but is not an explanation for a bleeding problem, as these antibodies paradoxically are a risk factor for clotting and not bleeding.

Testing for fibrinolytic disorders often requires specialized testing not readily available outside the hospital setting.

---

**Etiology and Management**

A common approach to any clinical problem is to consider congenital versus acquired causes, and this question should certainly be addressed even among elderly patients. However, it is often more helpful in patients of any age to approach the etiology of bleeding based on the pathophysiology of blood clotting.

**Disorders of Primary Hemostasis**

Clotting starts with primary hemostasis. This involves the vessel wall, platelets and vWF, and abnormalities in any of these may lead to bleeding. A common cause of bruising due to vascular fragility in the elderly is senile purpura. This occurs secondary to a loss of collagen in the supporting tissue around blood vessels and leads to easy bruising, particularly in areas of sun-damaged skin such as the forearms. This is a clinical diagnosis made only in the absence of significant bleeding and abnormal lab testing. It does not predict bleeding from other sites in the patient. Unfortunately, treatment is limited to reassurance, good skin care to prevent skin breakage and avoidance of trauma as much as possible.

Thrombocytopenia is a very common cause of bleeding in the elderly. It should be stressed again, however, that thrombocytopenia does not naturally occur with aging, but that many disorders and medications that can lead to thrombocytopenia are more prevalent in older populations. Thrombocytopenia is not usually symptomatic until counts fall below 50,000/mm³, even in the elderly.

Thrombocytopenia may be secondary to decreased production, sequestration or increased destruction of platelets. Decreased production of platelets is usually secondary to underlying bone marrow abnormalities or bone marrow infiltration. Nutritional deficiencies of vitamin B₁₂ or folate and alcohol abuse are important reversible causes of thrombocytopenia, and should be ruled out. Splenomegaly secondary to causes such as myelofibrosis or portal hypertension may lead to thrombocytopenia through
platelet sequestration. Increased peripheral destruction may be seen with ITP, but in the elderly it is much more likely for the ITP to be secondary to an underlying lymphoproliferative disorder, and this possibility must be investigated. Disseminated intravascular coagulation (DIC) and sepsis are other common causes of thrombocytopenia in hospitalized patients. Medications such as thiazides, furosemide, heparin, phenytoin, valproic acid, ranitidine, ampicillin and penicillin, as well as many others, may lead to thrombocytopenia. Treatment of the underlying cause can hopefully lead to reversal of thrombocytopenia. However, if this is not the case, support with platelet transfusions may be necessary.

Platelet dysfunction secondary to medications such as Aspirin or non-steroidal anti-inflammatories is well documented. These medications also lead to increased risk of gastrointestinal bleeding because of impairment of prostaglandin synthesis in gastric mucosa. Serotonin reuptake inhibitors also have been found to increase the risk of GI bleeding, especially in the elderly who have other risk factors for bleeding. The risks and benefits of these medications in the patient should be carefully assessed. For many elderly patients, the potential benefits may greatly outweigh the risks. However, patient education and physician vigilance to monitor for evidence of bleeding is essential to prevent life-threatening bleeding complications. Uremia and myeloproliferative disorders are other common acquired causes of platelet dysfunction.

Disorders of Secondary Hemostasis

Mild congenital factor deficiencies may go undiagnosed until older patients face stresses such as anticoagulation or surgery. Although very rare, acquired factor inhibitors—specific autoantibodies directed against clotting factors—are more likely to be found in the elderly. Acquired factor inhibitors have been described against each of the coagulation factors, including vWF, but acquired factor VIII inhibitors are by far the most frequently encountered. These autoantibodies directed against factor VIII can occur in association with malignancy, surgery, inflammation or other disease states, but are frequently idiopathic in the elderly. The bleeding seen in these patients is often life threatening and characterised by the development of large hematoma, gross hematuria, retropharyngeal and retroperitoneal hematomas and cerebral hemorrhage. The mortality rate has been reported to be as high as 22% in treated patients. Management of these inhibitors in bleeding patients requires aggressive factor replacement and immunosuppressive therapy in hospital. Overdosage of anticoagulants is an extremely important cause of bleeding in the elderly. Warfarin is used to treat venous thromboembolic disease and arterial thrombosis and to prevent thrombotic complications in atrial fibrillation. These medications can dramatically improve quality of life in elderly patients but require very careful and frequent monitoring to prevent bleeding complications. Bleeding risks are increased among the elderly because older patients may have decreased rates of warfarin metabolism and they are more likely to be on multiple medications that can potentially interact with warfarin. Chronic illnesses that may increase the risk of bleeding also are more common in the elderly, such as GI lesions. However, the strongest predictor of bleeding is not age, but the degree of anti-coagulation, which can be controlled with very careful monitoring of the INR. Therefore, we must be careful not to deny life-improving therapies to older patients simply on account of their age.

Other common acquired causes of coagulopathies in the elderly are vitamin K deficiency, liver disease and DIC. These disorders are more commonly seen in hospitalised patients. Whereas vitamin K deficiency can be treated with ongoing replacement, coagulopathies associated with liver disease and DIC are much more difficult to manage. Treatment of the underlying disease and blood product support are the mainstays of therapy. Abnormal fibrinolysis also plays a role in DIC and liver disease and may also be seen in patients with malignancy. The use of antifibrinolytic agents such as tranexamic acid may help control bleeding in certain circumstances.

Conclusion

Bleeding is never a natural part of aging. All bleeding in the elderly deserves consideration. A thorough history and physical examination, including a careful medication history, need to be carried out. Screening investigations should include a CBC, blood film review, INR/PT and PTT. Unfortunately, no single approach to managing coagulopathies can be taken; rather, an understanding of the cause of the coagulopathy is needed to direct appropriate therapy.

Suggested Reading