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Review

Differential diagnosis of nontraumatic purpura in the elderly – Have you considered acquired hemophilia?

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This clinical review discusses acquired hemophilia in the context of nontraumatic purpura in the elderly and highlights the most recent published data and guidelines. Acquired hemophilia is a rare bleeding disorder that occurs most frequently in the elderly population, and, is often associated with a high rate of morbidity and mortality. Identifying the underlying cause of bruising or bleeding to make an accurate diagnosis and implement appropriate management strategies can be complicated in the elderly patient where age-related comorbid conditions and use of pharmacologic agents, and sometimes dietary supplements, confound the differential diagnosis process. Delay in treatment can occur due to lack of awareness and challenges with the differential diagnosis. When bruising is not confined over bony prominences or appears in unusual places, it may be worth considering abuse, where bruises are more commonly located on the head, neck, trunk, and buttocks, as opposed to on the extremities. When bruises are larger or more numerous, or develop into hematomas, an underlying hematologic defect should be considered and include such disorders as undiagnosed congenital moderate/mild hemophilia A or an acquired inhibitor against a coagulation factor. Raising awareness of the signs and symptoms of acquired hemophilia and the steps to diagnosis may lead to timely and appropriate treatment of the elderly who present with unexplained bruising or bleeding and have no history of bruising or bleeding.

Key words: Acquired factor VIII inhibitor, Acquired hemophilia, Bruising, Bleeding, Coagulopathy

EPIDEMIOLOGY AND PATHOGENESIS OF BRUISING IN THE ELDERLY

There are several potential reasons for the onset of bruising or bleeding in the elderly, including physical trauma, coagulation disorders, systemic conditions and simple aging of the skin that can lead to alterations of the microvasculature. Hemorrhage, or macrovascular disruption, is often the result of major trauma that leads to alterations in blood volume and commonly presents with pain and shock. Conversely, there is generally no loss of blood volume or pressure associated with microvascular disruption; instead, petechiae and purpura are the most common characteristics at presentation of microvascular disruption [1]. Easy bruising has been estimated to occur in 12% to 55% of healthy adults [2-4]. While the bruising signs of microvascular disruption are fairly obvious, identifying the underlying cause to make an accurate diagnosis and implement appropriate management strategies can be complicated in the elderly patient where age-related comorbid conditions and use of pharmacologic agents, and sometimes dietary supplements, confound the differential diagnosis process. The differential diagnosis should include a patient history, the appearance and location of purpura, and findings from appropriate laboratory tests [1].

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The objective of this review is to provide an overview of purpura in the elderly and identification of the underlying microvascular causes, particularly those that are not obvious based on patient history, with a focus on findings from published data and guidelines on acquired hemophilia. Acquired hemophilia is a rare bleeding disorder that often goes undiagnosed, misdiagnosed, or has a clinically important delay in diagnosis, and, because so, has a high cost and high rate of morbidity and mortality. Increasing awareness of acquired hemophilia among those who care for the elderly may lead to a more timely and accurate diagnosis and appropriate acute and long-term management, especially when referral to an experienced hematologist is considered early in the differential diagnosis process.

The potential underlying causes of purpura are many and varied. Table I provides a summary of each cause, location and appearance of purpura (eg, petechiae or purpura), and any unique characteristics that should be considered in the differential diagnosis in the elderly patient.

In many cases, the underlying microvascular pathology for the observed purpura is unknown. This includes senile purpura also called solar or actinic purpura seen in older adults (Fig. 1). The prevalence is as high as 10 to 12% in patients aged 70-90 year; it is more common

Table I. Potential causes, location, appearance, and diagnostic criterion by classification of purpura in the elderly (from Zumberg, Kitchens, 2007, mod.) [1].

Classification of purpura or microvascular lesion	Appearance and location of bruising	Diagnostic criterion or clues
Purpura with no known underlying microvascular pathology True purpuric lesion – presence of extravasated red cells		
Mechanical causes	• Petechiae on face and neck from increased venous pressure from vomiting or seizures, or hanging upside down (eg, to relieve back pain) • Purpura on palms/soles of feet from traumatic blows, such as falling from a tall ladder	• History of activities prior to appearance of purpura • Formation of petechiae can be seen after choking, asphyxiation, seizure, barotrauma, electrocution • Facial or truncal bruises larger than 5 cm can indicate elder abuse
Factitious and psychogenic purpura	• Purpura is well demarcated; usually in areas readily accessible by the individual	• History that is vague or not credible • Cause is self-infliction with various suction devices, tools etc. • Individuals often have major emotional disturbances and unresolved conflict
Purpura simplex	• Small bruises associated with daily life (eg, being pinched) • Often appear ~ 30 inches above the floor (ie, height of most furniture)	• Nonpathologic normal process • More frequently reported by women
Senile purpura	• Arms and legs; sun-exposed areas • Non-blanching, red to purple	• Age is the greatest risk factor • May occur spontaneously
Bruises and hematomas	• Bruises are not palpable and are flush with the surface of the skin • Can develop into larger bruises or even hematomas in presence of platelet or coagulation defects	• Trauma, location, and appearance of bruising are key considerations • Bruising typically occurs over bony prominences • Unusual bruising: bruises NOT confined to bony prominences or in unusual places (eg, soles or palms) may raise concerns of abuse • Bruises that are larger or more numerous, and especially if palpable: consideration may be given to a hematologic defect as the underlying cause (eg, von Willebrand disease, acquired factor VIII inhibitor)
Progressive pigmented purpuras	• Characteristic collection of progressive purpuric lesions around the legs	• Dermatologic conditions with no known underlying cause • CBC and immunologic test result normal • No known sequelae; treatment is cosmetic • Upon biopsy: absence of leukocytoclastic vasculitis; many display mononuclear pericapillaritis
Purpura associated with abnormalities of platelets Most commonly a result from mild trauma with profound thrombocytopenia (≤ 20,000/μL); also associated with qualitative platelet defects		
Thrombocytopenic purpura (autoimmune)	• Spontaneous purpura and epistaxis most frequently seen in severe thrombocytopenia • Petechial hemorrhage is the clinical hallmark of acute ITP	• Platelet count < 10,000/dL

▶

Classification of purpura or microvascular lesion	Appearance and location of bruising	Diagnostic criterion or clues
Purpura associated with abnormal platelet function	• Purpura or epistaxis due to platelet dysfunction	• Use of antiplatelet agents: aspirin or newer agents used for ischemic heart disease (see **Table III**) • Use of dietary supplements; especially with an underlying platelet defect (see **Table IV**) • Congenital defects: Bernard-Soulier syndrome or Glanzmann's thrombastenia (life-long history of bleeding)
Cutaneous vasculitis	• Palpable purpura	• One of most common causes of nonthrombocytopenic purpura • Frequently associated with significant underlying medical disease • Main clinical attribute is palpable purpura • Histologic hallmark: leukocytoclastic vasculitis • Normal results for nearly all routine labs (eg, CBC, coagulation profile, serum studies for cryoglobulins, serologic studies for ANAs, serum complement levels, and ANCAs); except, sedimentation rate is substantially elevated in most cases. • Causes are many; characterized as rheumatologic in origin and associated with requisite immune complexes • Majority of adult cases are from primary causes: idiopathic, upper respiratory viral or bacterial infection, and hypersensitivity to drugs such as penicillin, iodine, aspirin, antibiotics, analgesics, NSAIDs, thiazides, colchicine • Most common secondary causes in adults include: lupus erythematous, cryoglobulinemia, chronic hepatitis C, Sjögren syndrome, polyarteritis nodosa, Churg-Strauss syndrome, rheumatoid arthritis, subacute bacterial endocarditis
Purpura associated with microbial endothelial damage Caused by residence and proliferation or direct attack by microorganisms		
Rickettsial disease	• Petechial rash may be detected the first day of illness, but more often third or fourth day • Spots become larger (5-6 mm diameter) than most petechiae and may have vague border that blend into erythema • Spots may appear on palms and soles	• Rocky Mountain spotted fever by far the most common cause
Leptospiral disease	• Petechial rash	• Petechial rash, sometimes modest thrombocytopenia, and DIC
Parvovirus B19 Infection	• Self-limiting "socks and gloves" petechial rash	• Skin biopsy shows no evidence of vasculitis
Viral hemorrhagic fevers	• Petechiae • Hemorrhage in multiple organs	• Global distribution in remote areas • Bleeding and accompanied thrombocytopenia or DIC
Purpura associated with decreased microvascular mechanical strength		
Scurvy	• Bleeding is characterized by perifollicular hemorrhage; large-huge, flat, plate-like ecchymoses; and hypertrophic spongy, bleeding gums	• Diagnosed by its appearance
Hypercortisolism	• Purpura seen primarily on the extensor surfaces of the forearms and is the presenting sign in 25% of cases	• Result of hypercortisolism
Senile, atrophic, or actinic purpura	• Purpura on the extensor surfaces of the forearms is characteristic, especially for those who work outdoors without adequate skin protection.	• Hemostasis is normal • Skin is extremely thin in affected areas and if biopsied the dermal-epidermal junction will be thin and flattened • Slight trauma or stretching of the skin can physically rupture the skin with subcutaneous bleeding as a result • Common in older and debilitated individuals • Sometimes seen in healthy individuals with excessive exposure to the sun
Heritable disorders of connective tissue	• Large vessel hemorrhage • Subcutaneous hemorrhage may also occur, but is not of diagnostic importance	• Bleeding as a result of tearing fragile subcutaneous tissues and skin as the result of spontaneous purpuric lesions. • No persistent coagulation or platelet abnormality • Healing is impaired

▶

Classification of purpura or microvascular lesion	Appearance and location of bruising	Diagnostic criterion or clues
Amyloidosis	• Purpuric bleeding with somewhat unusual distribution along pressure points, particularly in the periorbital area	• Coagulation abnormalities are frequent, multiple, and of varying patterns of amyloidosis, which can confound an accurate cause of the purpura (ie, deposition of amyloid)
Purpura associated with microthrombi		
Disseminated intravascular coagulation	• Purpuric skin lesions and frank purpura fulminans	• Fibrin deposition in microcirculation • Multiorgan dysfunction syndrome • Abnormal coagulation studies and platelet count
Warfarin skin necrosis	• Preceded by stinging or burning sensation ~ 2-4 days after initiation of warfarin therapy; site becomes hemorrhagic 1-2 days later • More frequent in women than men (9:1), and develops in areas where generous adipose tissue is found (ie, thighs, buttocks, breasts). • If not promptly treated, site become necrotic and appears as a large burn eschar	• Upon biopsy, fibrin deposition is prominent in dermal microcirculation
Fat embolism syndrome	• Petechiae with unusual distribution scattered about the neck, shoulders, and axillary folds in the upper chest area; occasionally in conjunctivae	• Diagnosed based on presence and location of petechiae (60% of cases); shortness of breath (50% of cases) • Fever is characteristic • Peak incidence ~24-72 h after traumatic event. • Associated with trauma: seen in 10-20% of all trauma cases when sought, specifically in cases of trauma and hypoxemia • Seen in up to 60% autopsies involving blunt trauma
Blue toe syndrome, purple toe syndrome, and cholesterol emboli syndrome	• Purple or blue discoloration of the toes • Necrosis of toes and feet and significant soft tissues areas of the legs, or lower flank and back	• Occur during heparin or warfarin administration, following abdominal trauma or cardiac catheterization, or spontaneously • All patients have significant underlying atherosclerosis and if lesions are biopsied cholesterol crystals in arterioles seen • Differential diagnosis should focus on the arterial system: echocardiography with aortic arch, imaging aorta; ankle-to-brachial pressure index
Purpura associated with vascular malignancy		
Associated with AIDS	• Most common form is Kaposi sarcoma: ecchymotic-appearing macular lesion that progresses to plaque or nodular lesions	• Key to diagnosis: early purpuric Kaposi sarcoma lesion does not blanch on external pressure • Diagnosis may depend on biopsy, and can be done without risk of hemorrhage
Other hematovascular findings of hematologic interest		
Livedo reticularis	• Dusky, ill-defined violaceous reticular pattern seen on legs and occasionally arms; some resemblance to blue/purple fishnet stockings	• May appear transiently in normal individuals in a cool environment; sometimes seen in lupus erythematosus, antiphospholipid antibody syndrome and other rheumatic disorders
Urticarial vasculitis	• Similar appearance to typical urticaria, but with a substantial vasculitic component	• Lasts > 24 hours, painful, sometimes burning sensation; when lesions are clear some residual purpura is seen • Can be associated with hypocomplementemia
Hemangiomas	• Soft bluish tumors common in infants and spontaneously regresses • Some are persistent, huge, cavernous and require aggressive treatment	• Can appear anywhere in the body, most commonly on the scalp, face, chest or back
Cherry angiomas	• Small (1-3 mm), cherry-red, domed papules over upper abdomen and lower chest that occur in second-half of life	• Do not blanch as easily or completely as telangiectasias of HHT syndrome
Spiders	• 1-3 cm legs that radiate from a 1-2 mm central body	• Gentle pressure collapses spider and legs • Seen in aging, cirrhosis, and pregnancy
Erythema	• Redding of skin, notably on the face; no clear borders	• Blanches with pressure or application of cold • May be result of hot environment, hyperthermia, fever, mild viral infection, or emotional reaction

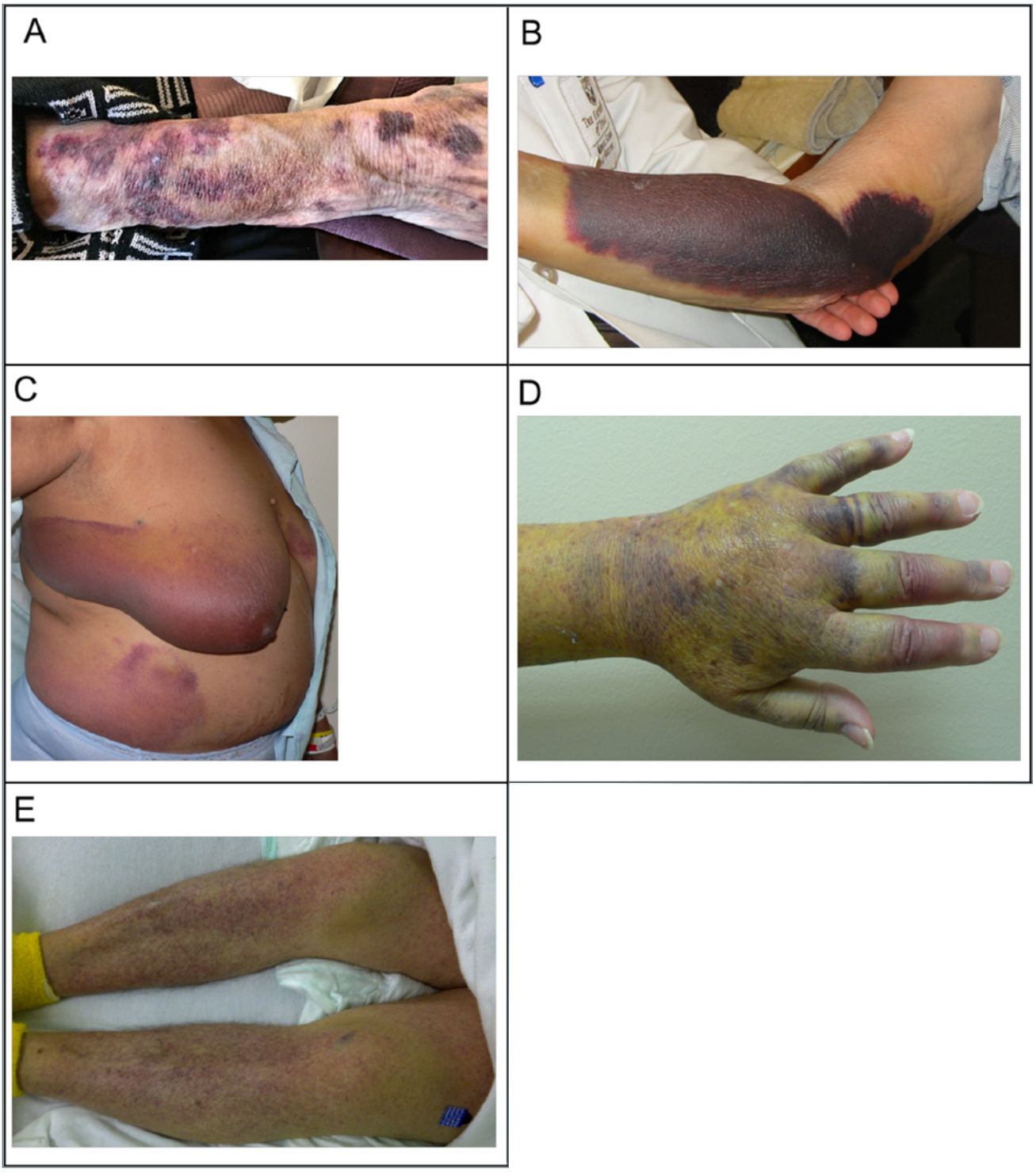

Figure 1. Representative pictures of **A)** Senile purpura. **B)** Typical non-traumatic hematoma of soft tissue in an elderly individual with acquired hemophilia A. **C)** Subcutaneous hematoma from pressure from the brassiere in a patient with acquired hemophilia A. **D)** Extensive hand hematoma after venipuncture in a patient with acquired hemophilia A. **E)** Petechiae in a patient with immune thrombocytopenia (ITP) with platelet count < 10,000.

in women [5,6]. The underlying cause of senile purpura is fragile skin due to aging, although secondary causes include solar damage, genetics, and long-term use of corticosteroids. These lesions may or may not be related to trauma as many older adults do not recall causative events [7]. Recommendations for prevention include protection from the sun, emollients, and adequate protein intake [7].

Purpura simplex is due to blood vessel fragility and medication use irrespective of age. Mild day to day trauma can lead to purpura simplex, where small bruises associated with daily living appear over bony prominences. However, when bruising is not confined over bony prominences or appears in unusual places, it may be worth considering abuse. Abuse is more common when bruises are on the head, neck trunk and buttocks as opposed to extremities. Bruises due to abuse are more likely to be 5 cm or larger. The color of the bruise is not helpful in timing the traumatic event with accidental bruises or those associated with abuse [8]. Notably, when bruises are larger or more numerous, or develop into hematomas, an underlying hematologic defect should be considered and include such disorders as undiagnosed congenital moderate/mild hemophilia A or an acquired inhibitor against a coagulation factor (ie, FVIII or von Willebrand factor).

Acquired hemophilia is a rare (1-1.48 in 1 million [9]), but severe bleeding disorder that occurs when autoantibodies develop against clotting factors [10], the most common of which is directed against FVIII [11]. Patients with acquired hemophilia often present with large areas of subcutaneous hemorrhage (Fig. 1), which can be spontaneous or result from mild trauma or invasive procedures [1]. Compartment syndrome can develop rapidly in acquired hemophilia when bleeding occurs into soft tissues [12]. The bleeding pattern of acquired hemophilia is distinct from that of congenital hemophilia where bleeding occurs mostly in joints and appears in the form of a true hematoma. Acquired hemophilia is seen most commonly in the elderly population, with the exception in younger women of childbearing age [13]. Increasing age has been shown to be an independent predictor of death in people with acquired hemophilia [9,13,14], with those < 76.3 years at 16%, but 43% for those who are > 76.3 years [13]. The mortality rate may even be underestimated because, at least in part, data in the literature largely comes from centers of expertise where mortality rates would be expected to be lower than elsewhere. The European Acquired Hemophilia (EACH-2) registry is by far the largest prospective study of acquired hemophilia to date and included data from 501 patients (53 male, 47% female) with a median age at diagnosis of 73.9 years (IQR, 61.4-80.4 years) from 117 different centers in 13 countries [13]. The most common symptoms of aquired hemophilia in the EACH-2 registry were subcutaneous bleeding (purpura) and soft tissue bleeds, including bleeding into skin (53%), musculoskeletal and retroperitoneal bleeding (50%), and mucosal bleeding (32%) [13]. While most bleeds were spontaneous (77%), some were attributed to trauma (8%), surgery (8%), and the peripartum period (4%) [13]. Similar findings were reported from the Hemostasis and Thrombosis Research Society (HTRS) registry, with the most common site of bleeding being subcutaneous bleeding (40%) followed by mucosal bleeding (33%), and most bleeds were spontaneous (70%), with others associated with trauma (18%), followed by dental (2%), surgical (2%), and other medical procedures (4%) [15]. Finding from the EACH-2 registry showed that a delay in diagnosis can result in subsequent delay in the initiation of hemostatic treatment with up to 35% of patients being diagnosed more than 7 days after the initial bleeding episode; and of these, 67% had severe bleeding [13]. Overall, there is a high rate of mortality (more the 20%) associated with acquired hemophilia in the eldery [12,13,16], which usually occurs within the first few weeks of the onset of bleeding symptoms [12]. Age-related comorbidities, medications, and frailty that are common in elderly patients contribute to the situation [12].

Purpura that is associated with quantitative platelet abnormalities is most commonly a result of mild trauma with profound thrombocytopenia (≤ 20,000 μl). Acute idiopathic thrombocytopenic purpura with a platelet count < 10,000 μl usually presents as petechial hemorrhage. Qualitative platelet defects can also present as purpura because of effects of antiplatelet agents used for ischemic heart disease, use of dietary supplement, mostly in conjunction with an underlying platelet defect, or on rare occasions from congenital defects such as Bernard-Soulier syndrome or Glanzmann's thrombastenia [1].

Side effects of anticoagulants and NSAIDs, both frequently prescribed to older patients, are some of the most common causes of bleeding in the elderly [17,18]. Notably, while newer oral anticoagulants are administered at fixed doses and have some advantages over warfarin, the response between patients is highly variable and there is no reliable method of monitoring their activity [19]. Chronic administration of anticoagulants, especially in combination with antiplatelet agents, has been shown to increase the risk of bleeding that can range from skin bruising to intracranial and fatal hemorrhages [20,21]. Table II provides a list of the common pharmacologic anticoagulant agents with their mechanism of action and parameters for increased risk of bleeding. Approximately half the US adult population regularly consumes a dietary supplement [28], some of which can lead to exacerbate bleeding in combination with other

Table II. Pharmacologic anticoagulant agents and bleeding risk parameters (from Altman, 2014, mod.) [19].

Pharmacologic anticoagulants	Mechanism of action	Increased-risk of bleeding parameters
Warfarin	• Inhibits vitamin K oxide reductase and thereby reduces vitamin K activity	• Narrow therapeutic window • Slow onset/offset of action • Interactions with food and drugs • Unpredictable response, requires systematic monitoring and frequent dose modifications
Antiplatelets		
Aspirin	• Inhibits COX enzymes • Inhibits platelet generation of thromboxane A2 • Weak inhibitor of platelet aggregation	• Increased risk of bleeding when combined with another antiplatelet or anticoagulant • Antiplatelet combinations significantly prolong bleeding time and increase incidence of subcutaneous hematomas and epistaxis
Clopidogrel	• Inhibits ADP receptors on the platelets	
Dipyrimidole	• Inhibits platelet aggregation via inhibition of adenosine deaminase and phosphodiesterase activity	
Anagrelide	• Phosphodiesterase inhibitor [22] • Inhibits maturation of platelets from megakaryocytes [23]	
Ticagrelor	• Inhibits platelet aggregation [24] • P2Y12 receptor antagonist [24]	
Vorapaxar	• PAR-1 receptor antagonist [25] • Inhibits thrombin-related platelet aggregation via inhibition of thrombin-related platelet aggregation [25] • Does not affect ADP-mediated platelet aggregation, coagulation parameters, or bleeding time [25]	• Used in combination with either aspirin or clopidogrel • Increased risk of intracranial hemorrhage [26]
Anticoagulants w/antithrombin activity		
Heparin	• Activates antithrombin, which inactivates thrombin, factor Xa, and other proteases, and thereby inhibits thrombin formation	• Bleeding is a common side effect • Heparin-induced thrombocytopenia is a serious side effect
Dabigatran	• Direct thrombin inhibitor	• Lack of an effective and reliable clotting assay to measure anticoagulation
Rivaroxaban	• Direct inhibitor of free and clot-bound activated coagulation factor X and prothrombinase activity	• Lack of an effective and reliable clotting assay to measure anticoagulation
Apixaban	• Direct inhibitor of free and clot-bound activated coagulation factor X, and prothrombinase activity [27]	• Lack of an effective and reliable clotting assay to measure anticoagulation
Edoxaban	• Inhibitor of activated coagulation factor X, and prothrombinase activity	• Lack of an effective and reliable clotting assay to measure anticoagulation

pharmacologic treatments. Further, many patients do not inform their physicians about their use of supplements. Popular dietary supplements such as fish oil, Ginkgo biloba, ginger, ginseng, and vitamin E can interfere with hemostasis, and adversely affect coagulation alone or in combination with an anticoagulant or antiplatelet medications such as NSAIDS, clopidogrel, or aspirin [29]. Commonly used natural products, dietary supplements, and herbs and their anticoagulant activity and risk of bleeding are show in Table III**.**

The most common cause of nonthrombocytopenic purpura is cutaneous vasculitis, which presents with palpable purpura and has a histologic hallmark of leukocytoclastic vasculitis. The underlying causes are many, but are typically rheumatologic in origin and associated with requisite immune complexes [1].

Other underlying causes of purpura are more readily known or identifiable, and include association with microbial endothelial damage, decreased microvascular mechanical strength, microthrombi (including thrombotic thrombocytopenic purpura), vascular malignancy, and other findings of hematologic interest (see Table I) [1].

DIAGNOSTIC APPROACH

The differential diagnosis for purpura in an elderly patient without a previous history of bleeding or known underlying microvascular pathology should include a detailed review of the patient's medical history along with appropriate laboratory tests. Considerations of the unknown cause of purpura should be given to trauma, complications from anticoagulants or NSAIDs, autoimmune disorders, cancers, and bleeding disorders such as von

Table III. Dietary supplements: mechanism of action and risk of bleeding (from Stanger, 2012, mod.) [29].

Dietary supplements[a]	Mechanism of action on platelets	Increased-risk of bleeding parameters
Ginkgo biloba	• reduced platelet aggregation	• Used in combination with warfarin, anti-platelet agents or NSAIDs: cases of spontaneous intracerebral hemorrhage, retrobulbar hemorrhage, subarachnoid hemorrhage, subdural hematoma, and spontaneous hyphema have been reported
Ginger	• Alters thromboxane synthesis • Inhibits arachidonic acid-induced platelet activation	• No confirmed anticoagulant properties
Ginseng	• Reduced platelet aggregation	• When higher than recommended doses used (rude preparations of dried root powder 1-2 g for up to 3 months) [30] • Used in combination with anticoagulants, anti-platelet agents and NSAIDs
Fish oil	• Reduced platelet aggregation • Increased bleeding time	• Bleeding time may increase when used in combination with NSAIDs or other anticoagulants
Vitamin E	• Reduced platelet adhesion to endothelial cells • Prevents platelet aggregation • Increased bleeding time	• High doses may inhibit platelet aggregation (alpha or gamma-tocopherol)
Curcumin	• Inhibits platelet aggregation [31] • Inhibits formation of thromboxane A2 [31]	• Increase risk of bleeding when used in combination with anticoagulant or in those with bleeding disorders

[a] These supplements can cause bleeding during surgical procedures.

Willebrand disease, moderate and mild congenital hemophilia, acquired platelet disorders, and acquired factor deficiencies like acquired hemophilia A [1]. In the case of malignancy, differential diagnosis is important and can be challenging with several more common reasons for bleeding, such as DIC, thrombocytopenia, and localized bleeding from tumor tissue [32]. The differential diagnosis of purpura should involve consultation with and or referral to a hematologist with expertise in diagnosis of bleeding disorders and other causes of purpura that may complicate an accurate diagnosis and potentially delay effective treatment, which in some cases could result in death. Consult with a dermatologist is also merited as causes of purpura can include dermatologic conditions. The differential diagnosis process should start with a complete blood count and blood smear, along with prothrombin time (PT), partial thromboplastin time (PTT) and thrombin time (TT). Should these initial tests be inconclusive, then additional analyses such as fibrinogen level, platelet aggregation and analyses for fibrin degeneration products and D-dimers should be conducted. In obscure cases, blood cultures, viral studies, and even bone marrow biopsy may be warranted [1]. Determining the underlying cause of purpura in an elderly patient with a malignancy can be difficult due to the number of potential causes [33 34]. The potential underlying causes range from pre-existing conditions to cancer treatments or even the malignancy itself [32]. Causes of purpura due to the malignancy include thrombocytopenia resulting from bone marrow infiltration or trauma to friable and/or highly vascularized malignant tissues [32]. Further, many chemotherapeutic agents are myelosuppressive, leading to thrombocytopenia and conditions (eg, infection and sepsis) that trigger DIC [32]. Notably, DIC is the most common cause of bleeding in the setting of malignancy [32]. On rare occasions, bleeding in patients with cancer results from the development of coagulation factor VIII inhibitors (ie, acquired hemophilia). In approximately 50% of cases, acquired FVIII inhibitors develop in patients with other underlying conditions, including malignancies [35].

In the case of acquired hemophilia A, there are 3 important clues to consider for diagnosis: 1) new onset of bruising or bleeding, 2) no previous history of bruising or bleeding, and 3) an isolated prolonged PTT with normal results for thrombin and prothrombin times and platelet count. Similar test results can be seen with presence of a lupus anticoagulant, except that these patients usually do not present with bleeding symptoms. In the contrary, many of them will have thrombosis and/or miscarriages. The next step after having a prolonged PTT is performing a mixing study of the PTT with normal plasma. This test can be easily done in most laboratories that are performing basic coagulation tests. It is recommended to do an immediate (baseline) PTT followed by a PTT after an hour incubation at 37 C because some antibodies are time and temperature dependent. If the mixing study fully corrects the PTT, it is indicative of a deficiency of a coagulation factor in the intrinsic pathway (eg, FVIII, FIX, FXI, FXII). However, if the PTT does not correct, one

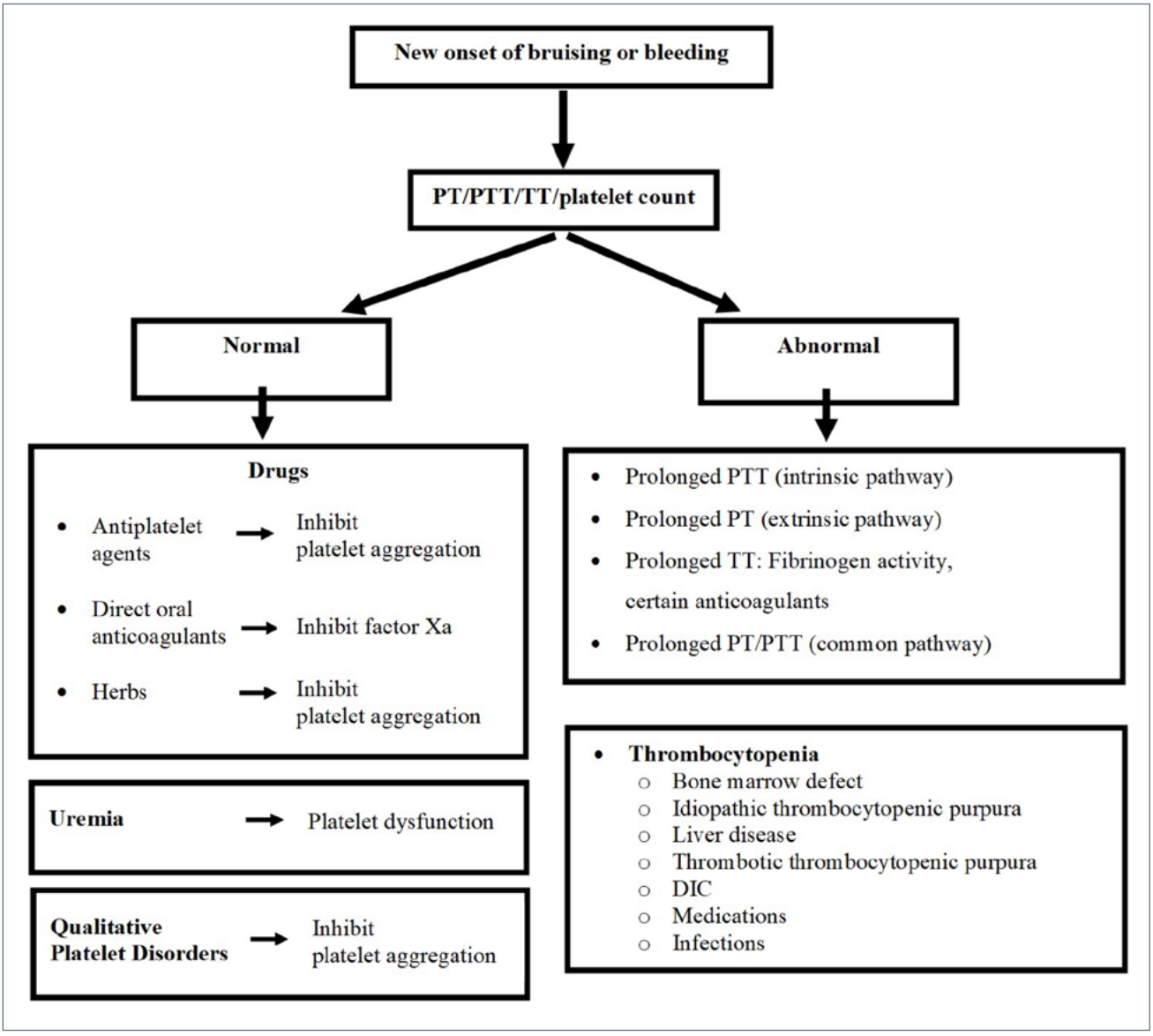

Figure 2. Clinical algorithm.

must consider the presence of an antibody against FXII, FXI, FIX, FVIII or a lupus anticoagulant. At this point in the differential diagnosis, analysis of specific factor levels can be performed. It is not usual for antibodies against FVIII to have a partial correction of the immediate PTT with a prolongation of this test after an hour incubation at 37°C. Lupus antibodies do not usually show this behavior. It should also be noted that heparin and direct oral anticoagulants (see Table II) may interfere with laboratory test results and can resemble FVIII inhibitors, thereby confounding laboratory test results and warrant specialized tests for exclusion [36 37]. Measuring thrombin time may differentiate the effects of direct thrombin inhibitors from acquired FVIII inhibitors [37]. Further, an anti-FXa assay may differentiate the effects of anticoagulants that inhibit factor Xa from FVIII inhibitors [37]. A clinical algorithm can be seen in Figure 2, and differential diagnostic approach when an acquired factor VIII inhibitor is suspected can be found in Figure 3.

THERAPEUTIC INTERVENTION

Treatment for many cases of purpura does not require hematologic intervention, while in other cases it is warranted. Regardless, the appropriate course of treatment requires an accurate diagnosis of the underlying cause of purpura. In many cases, a hematologist and

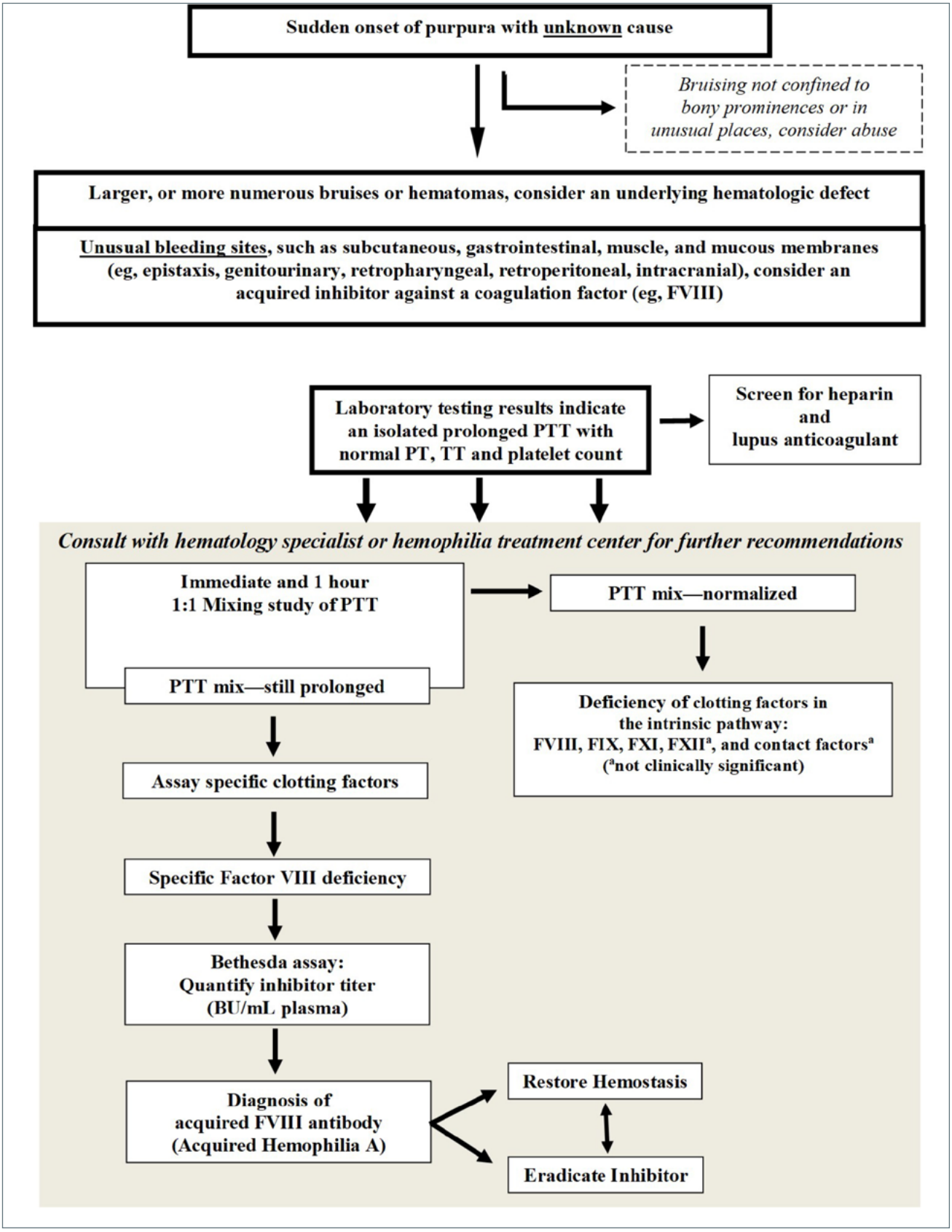

Figure 3. Differential diagnosis of acquired hemophilia A.

Table IV. General treatment approaches to nontraumatic purpura (from Zumberg, Kitchens, 2007, mod.) [1].

Treatment approach	Diagnosis
No hematologic treatment	Purpura simplex, progressive pigmented purpuras, primary cutaneous vasculitis
Hematologic treatment	Immune thrombocytopenic purpura, thrombotic thrombocytopenic purpura, disseminated intravascular coagulation
Nonhematologic treatment *Psychiatric evaluation* *Rheumatologic evaluation* *Antibiotics* *Dietary management*	Factitious purpura Secondary CV RMSF, subacute bacterial endocarditis, meningococcemia Scurvy

dermatologist should be consulted in the differential diagnosis of the underlying cause of purpura. Table IV shows 3 general treatment approaches depending on the diagnosis of purpura.

In a case of acquired hemophilia, there are 2 treatment strategies undertaken. First, bypassing agents (ie, bypass the factors that are blocked by the inhibitor) or recombinant porcine FVIII are used to manage the acute bleeding, and then in most cases immunosuppressive therapy should be used to eradicate the antibody [38]. Care should be taken when undergoing immunosuppressive therapy, as neutropenia is a serious concern in elderly patients who are often susceptible to infection because of underlying comorbidities.

PREVENTION

While purpura itself in many cases cannot be prevented, the morbidity and mortality associated with various causes of purpura can be reduced and even prevented with timely diagnosis and appropriate management. Upon presentation, proper diagnosis of the underlying cause of purpura in the older or elderly patient is often complicated by chronic comorbidities and medications that confound laboratory tests, among other reasons that are inherent in the elderly population. A key to a timely and accurate diagnosis, and prevention of unnecessary morbidity and mortality is awareness of rare conditions, such as acquired hemophilia A, and inclusion of an expert in bleeding disorders when one is suspected [1 12 36].

Generally, coagulation tests are not recommended for routine preoperative screening. A PT and PTT are indicated for patients with a history of bleeding disorders, on medications affecting coagulation like warfarin, or on hemodialysis. According to the American College of Surgery's National Surgical Quality Improvement Project with the American Geriatric Society, preoperative screening is indicated in patients undergoing "high risk procedures that involve arterial reconstruction, cardiac surgery, cancer operations, and ones in which small amounts of bleeding can cause dramatic complications (neurosurgical or orthopedic spine procedures)". In addition, the prothrombin time is also indicated in patients with malnutrition, malabsorption, or liver disease [39].

SUMMARY AND CONCLUSIONS

Diagnosis of the underlying cause of nontraumatic purpura can be challenging in the elderly who often have additional chronic comorbid conditions that may require pharmacologic treatment that can also complicate laboratory testing. A multidisciplinary team of those experienced with identification of the underlying causes of purpura and subsequent treatment include a laboratory specialist, and, if a bleeding disorder is suspected, a hematologist with experience in diagnosing and treating patients with rare bleeding disorders such as acquired hemophilia A. Use of a detailed patient history, appearance and location of purpura, and laboratory findings are all important tools in the differential diagnosis process. Prompt diagnosis and treatment are key to a good outcome, as delays in the diagnosis of acquired hemophilia A often result in severe bleeding and high morbidity and mortality that otherwise could be avoided. Raising awareness of acquired hemophilia A among those who care for the elderly may lead to a more timely and accurate diagnosis and appropriate acute and long-term management.

Conflict of interest

Dr. Escobar has served as an advisory board participant, study investigator, and/or consultant for Bayer, CSL Behring, Genentech, Novo Nordisk, Pfizer, and Shire. Dr. Dyer has no conflicts of interest.

Author's contributions

All authors meet the criteria for authorship stated in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals. Both authors, MAE and CBD, had substantial contributions to conception and design of this manuscript; and, the drafting of the outline and

subsequent drafts of the article, and critically revising it for important intellectual content; and reviewed and approved the final version for submission and to be published.
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