COMMENTS AND RESPONSES

Delayed-Onset Heparin-Induced Thrombocytopenia

TO THE EDITOR: There are 2 forms of heparin-induced thrombocytopenia. Type 1 is common and trivial. The incidence of heparin-induced thrombocytopenia type 2, which causes serious thrombosis in patients receiving full doses of heparin for therapy (not for hip replacement prophylaxis), is unknown (1). Heparin-induced thrombocytopenia type 2 is associated with platelet factor 4 antibodies and delayed thrombosis. Rice and colleagues (2) did not describe these 2 forms of heparin-induced thrombocytopenia. They indicated an incidence of approximately 3% for heparin but cited a reference for prophylactic heparin, not therapeutic heparin. I think they have muddied the waters. The **Figure** illustrates these issues as they pertain to the more than 300 000 patients with end-stage renal disease who may receive up to 20 000 U of heparin over a 3-hour period.

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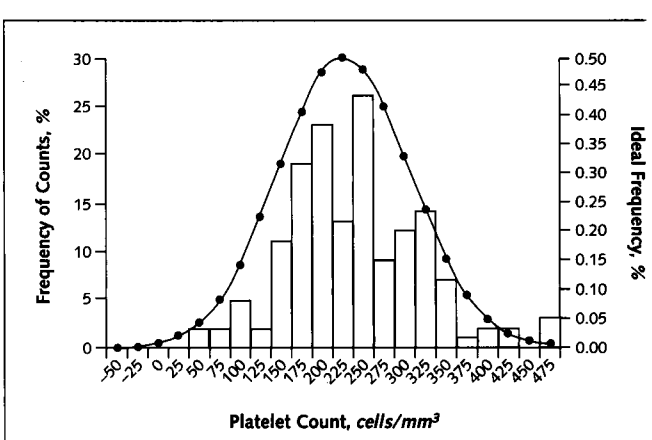
2. Rice L, Attisha WK, Drexler A, Francis JL. Delayed-onset heparin-induced thrombocytopenia. Ann Intern Med. 2002;136:210-5. [PMID: 11827497]

TO THE EDITOR: Rice and colleagues (1) highlighted an important distinction in patients who experience a thromboembolic event in the days or weeks after a medical intervention: Is this event related to a disease process or to treatment with heparin? How often does this occur as a delayed event in patients after a course of heparin? Is this a possible cause of "warfarin resistance"? Does a decline in platelet count of a certain amount or at a certain time predict heparin-induced thromboembolism? If heparin-type therapy is to be restarted after a previous medical intervention that included heparin, what additional monitoring might be useful? How long after previous heparin exposure can heparin-induced thromboembolism develop? When is pharmacologic therapy of heparin-induced thrombocytopenia warranted to attempt to prevent heparin-induced thromboembolism? What is the discriminant value of a positive test result for heparin-induced antibody? I'd guess the frequency of a positive antibody titer would be much higher than the frequency of a clinical event (low specificity?). As Gilbert and Sullivan wrote, "Things are seldom what they seem; skim milk masquerades as cream."

Figure. **Platelet counts in July 2001 for approximately 600 patients receiving dialysis who were treated by Hemodialysis, Inc.**



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Reference

1. Rice L, Attisha WK, Drexler A, Francis JL. Delayed-onset heparin-induced thrombocytopenia. Ann Intern Med. 2002;136:210-5. [PMID: 11827497]

IN RESPONSE: We deserve no credit for the muddied waters of heparin-induced thrombocytopenia terminology. The concept of early, mild, nonimmune, clinically inconsequential heparin-induced thrombocytopenia was advanced years ago as heparin-induced thrombocytopenia type 1 (1). In fact, low platelet counts in some hospitalized patients may often be unrelated to heparin and may be due instead to infection, surgery, other drugs, and stresses. The recommendation to designate this as "heparin-associated thrombocytopenia" to distinguish it from serious heparin-induced thrombocytopenia (2) has not gained wide favor. Furthermore, separating heparin-induced thrombocytopenia from heparin-induced thrombocytopenia with thrombosis syndrome is artificial and misleading, since isolated heparin-induced thrombocytopenia presents an extreme risk for thrombotic complications (Rice L. Heparin-induced thrombocytopenia: myths and misconceptions that will get you into trouble. In preparation). In our paper, the term *heparin-induced thrombocytopenia* signified the serious, immune clinicopathologic syndrome. We usually refer descriptively to early thrombocytopenia that may or may not be heparin related, its import being that it can be confused with heparin-induced thrombocytopenia at the bedside or in clinical studies.

Dr. De Palma questioned the frequency of heparin-induced thrombocytopenia. Prospective studies finding frequencies of 3% to 5% have been reviewed and re-reviewed (3). The 26% reported by Bell and Royall (4) illustrates how nonimmune thrombocytopenia can contaminate results. Our paper's reference 2 found antibody to heparin-induced thrombocytopenia in 3.3% of orthopedic patients receiving subcutaneous unfractionated heparin prophylaxis (8 of 9 affected patients developed venous or arterial thromboembolism) (5). That study found no heparin-induced thrombocytopenia with low-molecular-weight heparin. However, others have observed heparin-induced thrombocytopenia with low-molecular-weight heparin in about 0.5% of patients (3), as in our patient 1. A similar frequency of heparin-induced thrombocytopenia has been caused by heparin leaching from coated pulmonary artery catheters (3, 6). Our group has highlighted the risks for heparin-induced thrombocytopenia from catheter flushes and even from an oral pentasaccharide glycosaminoglycan used for interstitial cystitis (7, 8).

Delayed-onset heparin-induced thrombocytopenia clearly explains some cases of a condition that has been ascribed to early

"warfarin resistance" (see our patient 2). We are aware of delayed heparin-induced thrombocytopenia presenting at as late as 46 days. Disease-related factors beyond heparin must affect the risk for developing antibodies to heparin–platelet factor 4 or for the full-blown heparin-induced thrombocytopenia syndrome. For example, a high rate of positive results by enzyme-linked immunosorbent assay is seen after heart surgery in the absence of the clinical heparin-induced thrombocytopenia syndrome, but this is much less common in other clinical situations (9).

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Laboratory Monitoring of High-Dose Factor VIIa Therapy

TO THE EDITOR: Recombinant factor VIIa (FVIIa) is approved as a "bypassing" agent to promote hemostasis in congenital or acquired hemophilia with inhibitors. Factor VIIa has also been used off-label in thrombocytopenia, platelet function defects, and liver transplantation and after trauma or surgery. Deveras and colleagues (1) examined the use of FVIIa to reverse excessive anticoagulation. The authors reported that the prothrombin time and international normalized ratio decreased after FVIIa therapy. In addition, bleeding patients stopped bleeding and nonbleeding patients did not bleed following invasive procedures. The juxtaposition of clinical efficacy with an improvement in the prothrombin time and international normalized ratio suggests that these variables reflect the therapeutic effect of the drug and are a useful means of monitoring.

Our studies (2, 3) and those of others (4) suggest that high-dose FVIIa acts independently of its usual cofactor, tissue factor, to enhance platelet-surface thrombin generation. A platelet-dependent mechanism of action probably explains why FVIIa does not cause systemic activation of coagulation, since the activated platelets on which FVIIa acts localize it to sites of injury.

Shortening of clotting times does reflect the enzymatic activity of FVIIa but does not reflect the therapeutic mechanism of FVIIa action (5). Thus, the prothrombin time can be used as an indication that the patient has received the intended dose of drug but cannot indicate that a "therapeutic" level has or has not been achieved.

The lack of a good laboratory test for monitoring FVIIa therapy has not been a major impediment in treating persons with hemophilia. In this setting, the dose has been safely escalated until hemostasis is attained, without regard for the fact that the prothrombin time starts out normal and may be shortened to "supranormal" levels after FVIIa administration.

I caution clinicians who consider using FVIIa off-label that shortening of the prothrombin time into the "normal" range does not mean that the hemostatic system is "normal" in the patient.

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Hope for the Best, and Prepare for the Worst

TO THE EDITOR: I am grateful to the authors of "Hope for the Best, and Prepare for the Worst" (1). Strategies to enhance communication are crucial to strengthening the patient–physician relationship and improving outcomes. As a patient with a recent diagnosis of advanced lung cancer, I've experienced perspectives on dying that never occurred to me in nearly 20 years of practice.

Making a will and the other suggestions made by the authors are sensible goals. What more is there in preparing for the worst? Tonight I think about the worst, and I pray for the strength to face it. I pray for acceptance; then I pray for a "win." Tomorrow I want my doctor to help me in every practical way there is. My fear is death. My wish is to live. Exploring life closure means little. The patient–