patients are considered heparin resistant. It is useful to measure anti-factor Xa levels in heparin-resistant patients because many will have a therapeutic anti-factor Xa level despite a subtherapeutic aPTT. This dissociation in test results occurs because elevated plasma levels of fibrinogen and factor VIII, both of which are acute-phase proteins, shorten the aPTT but have no effect on anti-factor Xa levels. Heparin therapy in patients who exhibit this phenomenon is best monitored using anti-factor Xa levels instead of the aPTT. Patients with congenital or acquired antithrombin deficiency and those with elevated levels of heparin-binding proteins may also need high doses of heparin to achieve a therapeutic aPTT or anti-factor Xa level. If there is good correlation between the aPTT and the anti-factor Xa levels, either test can be used to monitor heparin therapy.

DOSING For prophylaxis, heparin is usually given in fixed doses of 5000 units SC two or three times daily. With these low doses, coagulation monitoring is unnecessary. In contrast, monitoring is essential when the drug is given in therapeutic doses. Fixed-dose or weight-based heparin nomograms are used to standardize heparin dosing and to shorten the time required to achieve a therapeutic anticoagulant response. At least two heparin nomograms have been validated in patients with venous thromboembolism and reduce the time required to achieve a therapeutic aPTT. Weight-adjusted heparin nomograms have also been evaluated in patients with acute coronary syndromes. After an IV heparin bolus of 5000 units or 70 units/kg, a heparin infusion rate of 12–15 units/kg per hour is usually administered. In contrast, weight-adjusted heparin nomograms for patients with venous thromboembolism use an initial bolus of 5000 units or 80 units/kg, followed by an infusion of 18 units/kg per h. Thus, patients with venous thromboembolism appear to require higher doses of heparin to achieve a therapeutic aPTT than do patients with acute coronary syndromes. This may reflect differences in the thrombus burden. Heparin binds to fibrin, and the amount of fibrin in patients with extensive DVT is greater than that in those with coronary thrombosis.

Heparin manufacturers in North America have traditionally measured heparin potency in USP units, with a unit defined as the concentration of heparin that prevents 1 mL of citrated sheep plasma from clotting for 1 h after calcium addition. In contrast, manufacturers in Europe measure heparin potency with anti-Xa assays using an international heparin standard for comparison. Because of problems with heparin contamination with oversulfated chondroitin sulfate, which the USP assay system does not detect, North American heparin manufacturers now use the anti-Xa assay to assess heparin potency. The use of international units in place of USP units results in a 10% reduction in heparin doses, which is a difference unlikely to affect patient care because monitoring will help to ensure that a therapeutic anticoagulant response has been achieved.

LIMITATIONS Heparin has pharmacokinetic and biophysical limitations (Table 143-2). The pharmacokinetic limitations reflect heparin's propensity to bind in a pentasaccharide-independent fashion to cells and plasma proteins. Heparin binding to endothelial cells explains its dose-dependent clearance, whereas binding to plasma proteins results in a variable anticoagulant response and can lead to heparin resistance.

The biophysical limitations of heparin reflect the inability of the heparin-antithrombin complex to inhibit factor Xa when it is incorporated into the prothrombinase complex, the complex that converts prothrombin to thrombin, and to inhibit thrombin bound to fibrin. Consequently, factor Xa bound to activated platelets within platelet-rich thrombi has the potential to generate thrombin, even in the face of heparin. Once this thrombin binds to fibrin, it too is protected from inhibition by the heparin-antithrombin complex. Clot-associated thrombin can then trigger thrombus growth by locally activating platelets and amplifying its own generation through feedback activation of factors V, VIII, and XI. Further compounding the problem is the potential for heparin neutralization by the high concentrations of PF4 released from activated platelets within the platelet-rich thrombus.

SIDE EFFECTS The most common side effect of heparin is bleeding. Other complications include thrombocytopenia, osteoporosis, and elevated levels of transaminases.

Bleeding The risk of bleeding rises as the dose of heparin is increased. Concomitant administration of drugs that affect hemostasis, such as antiplatelet or fibrinolytic agents, increases the risk of bleeding, as does recent surgery or trauma. Heparin-treated patients with serious bleeding can be given protamine sulfate to neutralize the heparin. Protamine sulfate, a mixture of basic polypeptides isolated from salmon sperm, binds heparin with high affinity, and the resultant protamine-heparin complexes are then cleared. Typically, 1 mg of protamine sulfate neutralizes 100 units of heparin. Protamine sulfate is given IV. Anaphylactoid reactions to protamine sulfate can occur, and drug administration by slow IV infusion is recommended to reduce the risk.

THROMBOCYTOPENIA Heparin can cause thrombocytopenia. Heparin-induced thrombocytopenia (HIT) is an antibody-mediated process that is triggered by antibodies directed against neoantigens on PF4 that are exposed when heparin binds to this protein. These antibodies, which are usually of the IgG isotype, bind simultaneously to the heparin-PF4 complex and to platelet Fc receptors. Such binding activates the platelets and generates platelet microparticles. Circulating microparticles are prothrombotic because they express anionic phospholipids on their surface and can bind clotting factors and promote thrombin generation.

The clinical features of HIT are illustrated in Table 143-3. Typically, HIT occurs 5–14 days after initiation of heparin therapy, but it can manifest earlier if the patient has received heparin within the past 3 months. A platelet count below 100,000/μL or a 50% decrease in the platelet count from the pretreatment value should raise the suspicion of HIT in those receiving heparin. HIT is more common in surgical patients than in medical patients and, like many autoimmune disorders, occurs more frequently in females than in males.

HIT can be associated with thrombosis, either arterial or venous. Venous thrombosis, which manifests as DVT and/or PE, is more common than arterial thrombosis. Arterial thrombosis can manifest as ischemic stroke or acute MI. Rarely, platelet-rich thrombi in the distal aorta or iliac arteries can cause critical limb ischemia.

TABLE 143-2 PHARMACOKINETIC AND BIOPHYSICAL LIMITATIONS OF HEPARIN

Limitations	Mechanism
Poor bioavailability at low doses	Binds to endothelial cells and macrophages
Dose-dependent clearance	Binds to macrophages
Variable anticoagulant response	Binds to plasma proteins whose levels vary from patient to patient
Reduced activity in the vicinity of platelet-rich thrombi	Neutralized by platelet factor 4 released from activated platelets
Limited activity against factor Xa incorporated in the prothrombinase complex and thrombin bound to fibrin	Reduced capacity of heparin-antithrombin complex to inhibit factor Xa bound to activated platelets and thrombin bound to fibrin

TABLE 143-3 FEATURES OF HEPARIN-INDUCED THROMBOCYTOPENIA

Features	Details
Thrombocytopenia	Platelet count of ≤100,000/μL or a decrease in platelet count of ≥50%
Timing	Platelet count falls 5–10 days after starting heparin
Type of heparin	More common with unfractionated heparin than low-molecular-weight heparin
Type of patient	More common in surgical patients and patients with cancer than general medical patients; more common in women than in men
Thrombosis	Venous thrombosis more common than arterial thrombosis