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UNDERSTANDING THE DISEASE

Resistance to unfractionated heparin in the ICU: evaluation and management options

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Because of its rapid onset and offset of action, and its ability to be fully and rapidly reversed with protamine when anticoagulation control is needed, unfractionated heparin (UFH) remains the anticoagulant of choice in many intensive care unit (ICU) patients, particularly those with severe multi-organ failure or extracorporeal circuits, including extracorporeal membrane oxygenation (ECMO).

UFH is a mixture of glycosaminoglycans purified from porcine intestine or bovine lung, which acts as a catalyst for antithrombin, an endogenous inhibitor of thrombin (factor IIa), factor Xa, and several other coagulation factors [1]. Binding of UFH to antithrombin is mediated by a unique pentasaccharide sequence that is present in only one-third of heparin chains [2].

A major drawback of UFH is the large inter-individual variability of its anticoagulant effect [2].

Heparin resistance could be defined as UFH failure to achieve a specified anticoagulation level despite the use of what is considered to be an adequate dose of heparin [3]. In our opinion, the arbitrary definition of the requirement of >35,000 units of UFH per day to maintain an activated partial thromboplastin time (aPTT) within the target therapeutic range reported in patients with venous thromboembolism [3] is inappropriate in ICU patients since it does not take into account body-weight, clinical setting, and the occurrence of thrombotic complications. Furthermore, this definition has not been validated in clinical trials. A weight-based definition (IU/kg/hour) may be more appropriate, but consensus is still lacking. This lack of universally consented and clinically meaningful definition of heparin resistance is illustrated by the heterogeneous definitions at use in each of our 3 institutions (namely, undefined, the need for more than 20 IU/kg/h, or for more than 35,000 IU per day.

During the coronavirus disease 2019 (COVID-19) pandemic, heparin resistance was increasingly reported in critically ill patients [4, 5]. Even though in a small series of patients, heparin resistance was associated with thromboembolic events, the clinical relevance of the laboratory finding of heparin resistance remains unclear [6].

In this article, we discuss the options for UFH monitoring, the mechanisms of heparin resistance and management options for this complex condition in ICU patients.

Monitoring UFH

The aPTT is the most widely used test for UFH monitoring. However, it is affected by numerous pre-analytical and analytical variables unrelated to heparin anticoagulant activity and may be inappropriate for UFH monitoring in many ICU patients. Indeed, high factor VIII levels may shorten aPTT in these patients, while acquired factor XII deficiency, lupus anticoagulant, or low fibrinogen levels may prolong aPTT, independently of heparin [7]. Furthermore, the aPTT therapeutic range is not standardized since aPTT prolongation induced by UFH is highly dependent on the reagent and analyzer used [7].

In this context, chromogenic anti-factor Xa assays are increasingly used for UFH monitoring because of their better specificity [7]. The commonly accepted target therapeutic range is 0.3–0.7 UI/mL. Importantly, results may vary according to the reagent and analyzer used and are susceptible to interference from hemolysis and icterus.

Mechanisms of heparin resistance

Acute-phase reactants, such as von Willebrand factor, factor VIII, and fibrinogen, bind to negatively charged

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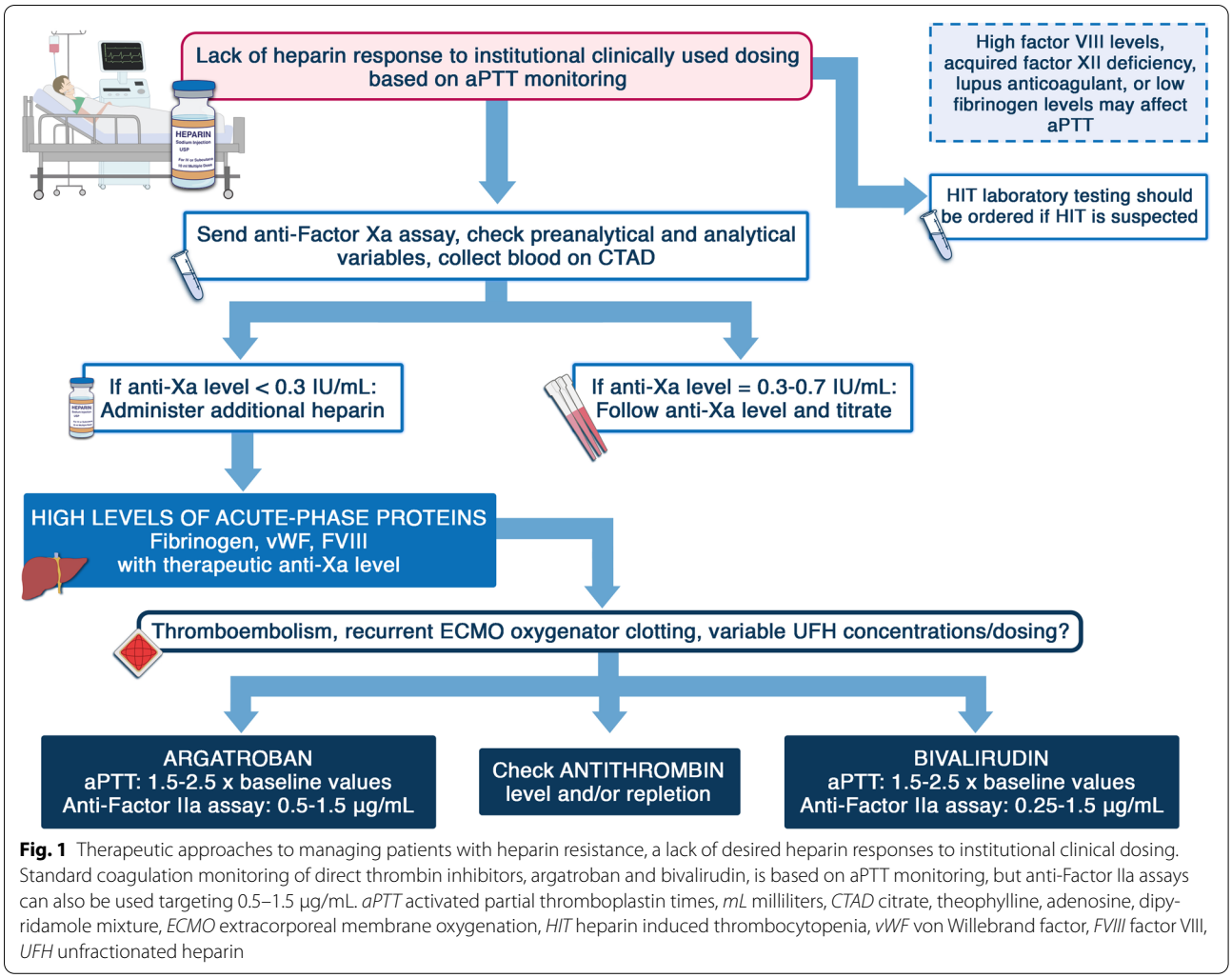

Fig. 1 Therapeutic approaches to managing patients with heparin resistance, a lack of desired heparin responses to institutional clinical dosing. Standard coagulation monitoring of direct thrombin inhibitors, argatroban and bivalirudin, is based on aPTT monitoring, but anti-Factor IIa assays can also be used targeting 0.5–1.5 µg/mL. *aPTT* activated partial thromboplastin times, *mL* milliliters, *CTAD* citrate, theophylline, adenosine, dipyridamole mixture, *ECMO* extracorporeal membrane oxygenation, *HIT* heparin induced thrombocytopenia, *vWF* von Willebrand factor, *FVIII* factor VIII, *UFH* unfractionated heparin

heparin fragments [3]. In ICU patients, increased levels of heparin-binding proteins may therefore result in heparin-reduced bioavailability. Furthermore, extracorporeal circuits and tubing can also bind to UFH.

Acquired antithrombin deficiency which frequently occurs in ICU patients due to sepsis, disseminated intravascular coagulation, ECMO support, or liver disease, is another common cause of heparin resistance [3].

Platelet-factor 4 (PF4) released from activated platelets also binds to UFH. Thrombocytosis can lead to heparin resistance [3]. However, heparin-induced thrombocytopenia (HIT) type II should be suspected in patients with heparin resistance and concomitant falling platelet count and trigger diagnostic and therapeutic algorithms [8].

How to manage UFH resistance in the ICU?

When heparin dose requirement is much greater than expected based on aPTT monitoring in ICU patients, we suggest using chromogenic anti-Xa assays. We recommend checking analytical results before modifying dose or therapeutic strategy and collecting blood on citrate, theophylline, adenosine, dipyridamole mixture (CTAD) to rule out in vitro PF4 release from platelets as the root cause of heparin resistance [7]. In those having a low anti-factor Xa activity (< 0.3 IU/mL), increasing UFH dose should be considered to achieve a 0.3–0.7 IU/mL target (Fig. 1).

In patients with acquired antithrombin deficiency, administration of antithrombin concentrates should be considered, although the benefit of antithrombin supplementation is not clearly established outside of cardiac

surgery. Current Extracorporeal Life Support Organization (ELSO) guidelines recommend daily monitoring of antithrombin if the heparin demand increases, and then to maintain antithrombin levels at 50–80% [9]. In clinical practice, antithrombin supplementation is frequently used during ECMO support [10]. Of note, antithrombin supplementation largely contributes to increased costs associated with UFH anticoagulation in ECMO patients.

Bivalirudin and argatroban are parenteral short-acting director thrombin inhibitors (DTI) that are currently the preferred alternative anticoagulants for patients with HIT. They directly inhibit free and clot-bound thrombin, independently of antithrombin (supplementary Table). In contrast to UFH, they do not cause immune-mediated thrombocytopenia. Argatroban requires dosing reductions in hepatic failure (supplementary Table), while severe renal impairment affects bivalirudin kinetics. Close monitoring of these drugs is of utmost importance since specific antidotes are lacking. Bivalirudin and argatroban are usually monitored with the aPTT. However, aPTT is limited by its linearity within the DTIs therapeutic range. Therefore, additional use of calibrated anti-IIa assays is can also be used for argatroban monitoring [11]. Argatroban has been successfully used off-label in patients with heparin resistance [12]. A recent meta-analysis of observational studies, predominately in patients receiving post-cardiotomy ECMO support, showed improved outcomes with bivalirudin as compared to UFH [13]. In two recent large (570 and 411 patients) prospective observational multicenter studies of ECMO patients, predominately COVID-19 patients, anticoagulation with DTIs achieved nearly comparable clinical outcomes as standard UFH anticoagulation [14, 15]. However, limitations of such observational data, even when using elaborated tools for risk-adjustment should be clearly acknowledged.

Supplementary Information
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Declarations

Conflicts of interest
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