Venous Thromboembolism in the ICU and Reversal of Bleeding on Anticoagulants

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Patients in intensive care units are at high risk for venous thromboembolism; studies have documented a venous thrombosis rate of 12%–33% in this patient group [1–5]. Certain patients are at particularly high risk [6,7]. For example, trauma patients have venous thrombosis rates of up to 60%, 60% of stroke patients will develop thrombosis, and in patients with traumatic spinal cord damage, thrombosis rates approach 100%. Venous thromboembolic disease is one of the most common challenges ICU doctors face.

Prevention

Given the high rates of venous thrombosis in ICU patients, and the fact that clinical signs of deep venous thrombosis (DVT) are unreliable, it is better to attempt to prevent venous thromboembolism in ICU patients than to treat it when it presents clinically [8]. Only 10%–20% of patients with DVT are symptomatic in most large screening studies, and the first sign of pulmonary embolism (PE) in 10%–30% of patients is sudden death. Many ICU patients also have risk factors that place them at higher-than-normal risk of bleeding should they require full anticoagulation therapy. Multiple methods exist to prevent venous thromboembolism, which makes it possible for the clinician to tailor a specific regimen to a particular patient’s clinical situation [6,9]. Studies have consistently shown that aspirin alone does NOT prevent venous thrombosis, despite its widespread use for this purpose. Use of other thromboprophylactic modalities is, therefore, mandatory. Table 1 summarizes suggested methods to prevent venous thrombosis.
in particular clinical settings. Intermittent compression stockings are a mechanical means of preventing DVT by squeezing the patient’s calves, which leads to increased blood flow through the venous system. This compression also stimulates fibrinolysis by stimulating the endothelium [10,11]. Although the use of compression stockings is particularly useful in patients unable to tolerate any degree of anticoagulation, the disadvantages include patient discomfort, noncompliance, and risk of mechanical breakdown.

Unfractionated heparin in the dose of 5000 units two to three times a day is the traditional prophylactic regimen [12], and has proven efficacy in surgical patients at average risk of thrombosis [13], in patients with medical illness, and in critical care patients [6]. In high risk surgical patients, low molecular weight heparin (LMWH) is currently the standard for prevention of thrombosis [14]. LMWH has also been proven very effective for this purpose when studied in medical patients [15].

Fondaparinux is a synthetic pentasaccharide that binds to antithrombin. It has been shown to be effective in thromboprophylaxis in both medical and surgical patients [16]. Fondaparinux is renally cleared and should not be used in patients with renal insufficiency or failure.

There have been multiple trials of all the above mentioned agents for prevention of DVT [6,8,9], most of which have been in the surgical, rather than the ICU setting. However, the data do allow for some specific recommendations in critical care patients (see Table 1).

It is clear that prophylaxis should be considered in all ICU patients [6,8,17]. In surgical ICU patients at high risk for thrombosis (neurosurgery, orthopedics, trauma, and so forth), LMWH is superior to other forms of prophylaxis and should be used [6,18,19]. LMWH is also the most effective method of thrombosis prevention in stroke patients. Medical ICU patients have been less well studied, but trials exist confirming the efficacy of low molecular weight heparin,

<table>
<thead>
<tr>
<th>Clinical setting</th>
<th>Methods of prevention</th>
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<tbody>
<tr>
<td>Medical patient</td>
<td>Unfractionated heparin 5000 units BID</td>
</tr>
<tr>
<td></td>
<td>Low molecular weight heparin&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Intermittent compression stockings&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Trauma</td>
<td>Low molecular weight heparin&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Intermittent compression stockings&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Lower extremity</td>
<td></td>
</tr>
<tr>
<td>Orthopedic surgery</td>
<td>Low molecular weight heparin&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Fondaparinux</td>
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<tr>
<td>Hip fracture</td>
<td>Fondaparinux</td>
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<td></td>
<td>Low molecular weight heparin&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Stroke</td>
<td>Low molecular weight heparin&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Intermittent compression stockings&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> Dose varies with the specific LMWH.

<sup>b</sup> Patients at high risk of bleeding.
fondaparinux, and standard heparin for thromboprophylaxis in these patients [5,6].

**Diagnosis**

Diagnosis of DVT is normally best accomplished by venous ultrasound [20]. In patients with suggestive symptoms, doppler ultrasound has a sensitivity of 95% [21,22]. However, dopplers will miss sites of some thrombosis, especially iliac vein and vena cava thrombosis [23]. Further imaging of the abdomen and pelvis with computed tomographic (CT) angiography is suggested in patients with clinical signs of thrombosis but negative doppler exam.

Newer testing methodologies have been recently introduced to try to simplify the problem of diagnosing PE [24,25]. For outpatients, it has been clearly established that a negative high sensitivity D-dimer assay alone rules out the diagnosis of PE. Unfortunately, there is less data on D-dimer and PE in the setting of sick inpatients, and this test appears to be far less useful in this population. One difficulty is that most sick patients (including patients in the perioperative setting, those with liver disease, with malignancy, with obstetric issues, and so forth) will have a positive sensitive D-dimer assay caused by their underlying disease, which greatly lessens the usefulness of D-dimer testing for PE in ICU populations.

In the past several years, CT angiography has become the first line imaging procedure for diagnosis of PE [26–28]. Although studies in outpatients have shown that a negative CT angiogram essentially rules out PE [25,29], there is less inpatient data on CT angiogram, especially in the ICU setting. Study rates of inadequate or uninterpretable CT angiograms range from 1% to 10%, and rates are likely to be even higher in the ICU. A negative poor quality CT angiogram cannot rule out the diagnosis of PE, and given ambiguous results, further testing such as a pulmonary angiogram should be pursued.

In summary, given the lack of an ideal testing approach, the diagnostic evaluation of an ICU patient suspected of having a PE must be individualized. A lower extremity doppler performed at the bedside may rapidly confirm deep venous thrombosis, eliminating the need to transport the patient to the radiology department. A CT scan may be useful in evaluating respiratory failure and can be extended to examine other areas of the body. However, if diagnosis of PE appears at all ambiguous, pulmonary angiography may still be required in many patients.

**Treatment**

There is now abundant evidence that full-dose LMWH is as effective as full-dose unfractionated (or standard) heparin for treatment of all types of venous thrombosis, from sub-massive PE to superficial thrombophlebitis [30–35]. There
is also a fair amount of data supporting the efficacy of fondaparinux in treatment
of all forms of venous thrombosis. However the long half-life and renal clearance
of fondaparinux may be concerns in complex patients [36].

There are a variety of LMWHs on the market. All differ from standard heparin
in their pharmacokinetics and in binding to plasma proteins. For most patients
receiving full anticoagulant doses of any LMWH, laboratory monitoring is not
required. Dose adjustment and monitoring of LMWH is, however, necessary in
renal failure (see later discussion). Also, the partial thromboplastin time (PTT) is
usually insensitive to the effect of LMWHs. Therefore, monitoring the antico-
agulant effect of LMWHs, when necessary, should be done by a special LMWH
assay (which measures anti-factor Xa activity). Laboratories doing such assays
may prefer to have the assays ordered according to the specific LMWH involved
(eg, enoxaparin level rather than anti-Xa level) and will specify the normal
therapeutic range for the results they report. Because LMWH is given sub-
cutaneously (SQ), timing of the assay draw is important in assuring accurate
levels. Normally LMWH levels are drawn 4–6 hours post the second or third
SQ injection.

LMWH is cleared by a renal mechanism and will accumulate in patients with
renal failure, so dosing should be reduced by 50% and levels monitored. How-
ever, the use of low molecular weight heparin is not associated with additional
risk of bleeding when compared with standard heparin [38]. Monitoring should
also be considered for patients who are very obese (>2 times ideal body weight),
who have severe liver or heart failure, who are pregnant, or who require long-
term therapy. Very obese patients still require actual body-weight-based dosing
without “capping” the dose at an arbitrary level; checking a level the second day
of therapy is prudent [37].

Thrombolytic therapy for PE remains controversial [39–41]. No prospective
study has shown meaningful clinical benefit in patients who have received
thrombolytic therapy for PE versus those who have been treated with standard
anticoagulant regimens. Furthermore, the intracranial hemorrhage rate is sub-
stantially higher in patients receiving thrombolytic therapy for PE than for cardiac
indications [42]. Thrombolytic therapy may be considered for the patient with
documented PE who remains hypotensive despite maximal medical management.

Another contentious treatment modality is the use of inferior vena cava (IVC)
filters to prevent PE [43,44]. In the sole clinical trial in which high-risk patients
with venous thrombosis were randomized to treatment with or without IVC fil-
ters, the IVC filter patients had less PE but no reduction in mortality [45].
Conversely, it does appear that an indwelling IVC filter will double long-term
thrombosis risk [43,46]. Reasonable indications for filters would include lower
extremity DVT in patients with an absolute contraindication to anticoagulation,
or very ill patients with DVT in who even a small embolism might be fatal. The
use of retrievable or temporary IVC filters has increased in recent years [47].
However, this technology is new and there is very limited clinical data on these
devices [48] regarding their efficacy, and how long they may be left in place
before removal becomes impossible.
Catheter thrombosis

Central venous catheters are common in ICU patients. The incidence of symptomatic thrombosis of central venous catheters is estimated to be 5%–30% [49–52]. The signs of catheter thrombosis are non-specific and the incidence of thrombosis is underestimated since catheters are often coated with sheaths of fibrin soon after introduction [53,54].

Therapy of catheter thrombosis is not well defined. Intuitively removing the catheter will remove the nidus of thrombosis and should be done if possible. If the patient is stable, anticoagulation for 4–6 weeks should be considered. Given the low risk of long-term sequela, there is little indication for thrombolytic therapy.

A particular high-risk situation for thrombosis is placing catheters in the femoral vein, and use of this site should be avoided if at all possible [55]. Use of a femoral site versus other sites appears to be associated with a substantially increased thrombotic rate (as much as 14 times higher risk in one study [56]). Catheter-related femoral thrombosis can appear as early as one day after catheter placement. If circumstances dictate a femoral vein placement for a catheter, it should be removed as quickly as possible.

Prevention of catheter thrombosis is difficult. Two trials with long-term tunneled catheters did show that low-dose unmonitored warfarin (1 mg/d) or LMWH may prevent thrombosis [57,58]. However, more recent studies have failed to confirm these findings [59,60]. The applicability and safety of using low-dose anticoagulation to maintain catheter patency in ICU patients is unknown, especially since 5%–20% of patients in the warfarin trials developed high international normalized ratios (INR) [61] and this practice cannot be recommended at this time.

Reversal of bleeding caused by antithrombotic therapy

Bleeding on antiplatelet agents

For patients on aspirin with emergency bleeding, platelet transfusions can be given. There are reports that desmopressin will reverse aspirin inhibition and may be effective for emergency surgery in patients on aspirin therapy who bleed [62–64].

Few data exist on specific therapy of bleeding complications in patients on either ticlopidine or clopidogrel. For severely bleeding patients, platelet transfusions may be useful.

Therapy for bleeding complications seen with glycoprotein IIb/IIIa (GpIIb-IIIa) inhibitors is guided by the agent received. Most infused abciximab binds to the IIb/IIIa receptor and very little is found free in the plasma [65,66]. For abciximab related bleeding, treatment is to give a platelet transfusion which will lead to redistribution of the abciximab over a wider number of receptors and
return of platelet function. Tirofiban and eptifibatide do not bind as tightly, so platelet transfusion may not fully restore platelet function. In vitro studies suggest that the addition of fibrinogen may help restore platelet function [67]. Based on this study, severely bleeding patients receiving tirofiban or eptifibatide should be transfused 10 units of cryoprecipitate as a fibrinogen source. In addition, infusion of desmopressin 0.3 \( \mu \text{g/kg} \) may be beneficial [62,68].

Severe thrombocytopenia has been reported in 0.5%–7.0% of patients receiving GpIIb-IIIa blockers [62,69,70]. The incidence is higher in patients previously exposed to GpIIb-IIIa blockers [66]. The onset of the thrombocytopenia is rapid and can occur within 2 hours after the drug is started. Experience with abciximab has shown that infusion of immune globulin or steroids is not helpful. Platelet transfusions result in a prompt rise in platelet count [70–72].

**Bleeding on warfarin**

The key to management of an elevated INR is use of vitamin K (Table 2) [73,74]. Both oral and intravenous vitamin K offer significant advantages over the use of subcutaneous vitamin K or plasma infusion. In fact, because of its erratic absorption and delay in INR reversal, the use of subcutaneous vitamin K is discouraged [73–77]. Often only small doses of vitamin K in the range of 0.5–3mg are needed to reverse warfarin effect [73,76,78,79]. Intravenous vitamin K, even infused slowly, is associated with a slight risk of anaphylaxis (3:10,000) [80] and should be reserved for life-threatening bleeding or a need for rapid reversal [81,82]. For most situations, the oral route will result in more consistent reversal than will the subcutaneous route, and will begin acting within 12 hours [76]. If the patient requires rapid full reversal because of bleeding or need for surgery when the INR is 5–10, 2.5–5 mg of vitamin K can be given orally with the anticipation that the INR will be lowered in 24 hours. Intravenous vitamin K will result in shortening of the INR within 4–6 hours [73,83]. If the INR is over 10, 5–10 mg of vitamin K should be given. For rapid reversal of anticoagulation, both vitamin K and fresh frozen plasma (FFP) should be given. Since one unit of

<table>
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<th>INR</th>
<th>Action</th>
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<tbody>
<tr>
<td>Not bleeding</td>
<td></td>
</tr>
<tr>
<td>3–3.45</td>
<td>Hold dose until INR decreased</td>
</tr>
<tr>
<td>4.5–10</td>
<td>1–2.5 mg vitamin K PO</td>
</tr>
<tr>
<td>&gt;10</td>
<td>2.5–5.0 mg vitamin K PO</td>
</tr>
<tr>
<td>Bleeding</td>
<td></td>
</tr>
<tr>
<td>2–4.5</td>
<td>1 mg vitamin K ± FFP</td>
</tr>
<tr>
<td>4.5–10</td>
<td>2.5–5 mg vitamin K ± FFP</td>
</tr>
<tr>
<td>&gt;10</td>
<td>5–10 mg vitamin K ± FFP</td>
</tr>
</tbody>
</table>

Consider intravenous route for vitamin K if faster effect desired.
Consider prothrombin complex concentrates or rVIIa for life-threatening bleeding.

*Abbreviation:* FFP, fresh frozen plasma.
plasma on average raises coagulation factors by only 5%, large doses (15 mg/kg or 4–5 units) must be given to attempt to correct the INR.

Warfarin reversal in the patient with life-threatening bleeding immediate management is to rapidly reverse the warfarin effect [84,85]. This can be done by giving both vitamin K (10 mg intravenous slowly over one hour) and 15 mL/kg of FFP. It is important to give the vitamin K with the plasma because the effect of plasma is only transient and the patient may have a rebound rise in the INR if vitamin K is not given.

If available, patients with intracranial hemorrhage (ICH) or other life-threatening bleeding should receive prothrombin concentrates. Clinical data has shown these products (which contain all the vitamin K-dependent clotting factors) result in a more rapid correction of coagulation than plasma [86–88]. Patients suffering intracranial hemorrhages should receive prothrombin concentrates such as Konyne or Prophylnine at a dose of a 50 units/kg [87,89–91]. Unfortunately, these products are not often readily available. They are also associated with increased risk of thrombosis and are costly.

There are recent data showing that the use of recombinant factor VIIa (rVIIa) can reverse warfarin-induced bleeding [92–95]. The exact dose of rVIIa needed for effective warfarin reversal is uncertain; the author’s approach is to err on the side of using a larger dose of 40 μg/kg given the need for prompt and complete reversal. Very recently rVIIa has also been shown to limit hemorrhage size and improve outcomes in spontaneous ICH. This agent should, therefore, also be considered in non-warfarinized patients with this clinical presentation [96,97].

**Bleeding on heparins and anti-Xa agents**

Standard heparin has a short (30–60 minute) half-life so in most situations reversal is not required. Low molecular weight heparins have a half-life of several hours, so reversal may be required for serious bleeding soon after drug administration.

Protamine is used to immediately reverse standard heparin and LMWHs [98]. The dose for heparin reversal is dependent on timing of the last heparin dose. For immediate reversal (≤30 minutes since the last heparin dose), 1 mg of protamine should be given for every 100 units of heparin. A suggested nomogram is given in Table 3. One should avoid giving over 50 mg of protamine at one time and ensure that the infusion does not exceed 5 mg/min [99].

Protamine does not fully reverse LMWH (which has enhanced anti-Xa versus anti-thrombin activity when compared with standard heparin), but can neutralize the anti-thrombin effect [99–102]. Because of the longer half-life of LMWH, sometimes a second dose of protamine is required. The dose is 1 mg/100 units of dalteparin or tinzaparin or 1 mg/mg of enoxaparin. In the case of reversal of large doses of standard heparin, if the activated partial thromboplastin time (aPTT) is prolonged 4 hours later (reflecting continued thrombin inhibition), one-half of the initial dose should be given. The PTT does not normally prolong with most LMWHs and cannot, therefore, be used to monitor reversal of the anticoagulant
effect of the LMWHs. LMWH levels by anti-Xa activity may give some index of residual anticoagulant effect, but protamine does not neutralize anti-Xa effect. It is unclear how further protamine dosing should be optimally guided. If there is clinical evidence of ongoing coagulopathy and measurable anti-Xa activity, it would appear reasonable to give an additional half dose of protamine 4 hours after the first dose. If bleeding is severe, and attempted reversal of the anticoagulant effect of LMWH with protamine has been clinically unsuccessful, there is anecdotal data that rVIIa may be helpful, although the clinical efficacy of this approach is unproven [103]. Heparinase is a drug in clinical development, which can dissolve heparin and, if ultimately approved and licensed for clinical use, should be useful for more effectively reversing the anticoagulant effects of the heparins [104]. Currently, no specific antidote exists for the antithrombin-dependent anti-factor Xa anticoagulants danaparoid, fondaparinux, or idaparinux. Given the prolonged half-life of these agents (26, 18, 72 hours, respectively), severe bleeding represents a major challenge. There are data that rVIIa may reverse the coagulation defect induced by fondaparinux and idraparinux but the clinical utility of this is unknown [105–108]. Another concern is that since rVIIa half-life is only 2–3 hours, repeated dosing may be necessary.

**Bleeding on direct thrombin inhibitors**

All direct thrombin inhibitors (DTI) share certain properties (Table 4) [109–111]. They raise both the INR and aPTT since thrombin is part of the

| Table 4 |
| Direct thrombin inhibitors |

<table>
<thead>
<tr>
<th>Agent</th>
<th>Half-life</th>
<th>Renal disease</th>
<th>Liver disease</th>
<th>Antibody formation</th>
</tr>
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<tbody>
<tr>
<td>Argatroban</td>
<td>40 min</td>
<td>Not effected</td>
<td>150 min</td>
<td>No</td>
</tr>
<tr>
<td>Bivalirudin</td>
<td>20 min</td>
<td>Increases to 3.5 h</td>
<td>Not effected</td>
<td>Cross reacts with anti-hirudin</td>
</tr>
<tr>
<td>Hirudin</td>
<td>40 min</td>
<td>Increases to 50 h</td>
<td>Not effected</td>
<td>Yes</td>
</tr>
<tr>
<td>Ximelagatran</td>
<td>2.5–3.5 h</td>
<td>Increases</td>
<td>Not effected</td>
<td>No</td>
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common pathway of blood coagulation. Clinically, the effects of DTIs are monitored by the aPTT, usually aiming for a goal of 2 to 2.5 times the normal control. In patients with normal renal function, the half-life of these agents is short, and range from 20 minutes to 4 hours for ximelagatran. However, with the exception of argatroban, most DTIs are renally cleared and can have dramatic increases in their half-life with renal failure. No specific reversal agent exists for DTIs. Anecdotally rVIIa has been reported to be useful and could be considered for immediate treatment of life-threatening hemorrhage [112]. In vitro data suggest that doses of activated prothrombin concentrates at 50 units/kg may also be useful.

Lepirudin poses special issues concerning bleeding risk. The half-life of lepirudin increases with even modest decreases in renal function and in renal failure the half-life can increase to 50–100 hours [113]. Anti-lepirudin antibodies can be seen in 50%–80% of patients receiving the agent for more than 5 days, which in some patients can increase the antithrombotic activity of the drug [114]. Lepirudin can be removed by hemofiltration using hiﬂux membranes; polysulphone is the most efficient [115–117]. However, the presence of anti-lepirudin antibodies may hinder the ability of hemofiltration to remove lepirudin.

**Bleeding on fibrinolytic agents**

The major complication of thrombolytic therapy is bleeding. Rates of major bleeding range from 4% to 6% [65,118]. Patients bleed at sites of previous injury because of lysis of previously formed thrombosis. Also patients may have bleeding caused by underlying vascular problems. For example, patients who suffer intracranial hemorrhage with thrombolytic therapy often have underlying cerebral vascular amyloid [119]. The most devastating complication is ICH, which can have a mortality rate of up to 60% [120,121]. Incidence rates appear to vary by indication for thrombolytic therapy. ICH occurs in approximately 1%–2% of acute myocardial infarction patients [120,122,123]. Patients receiving thrombolytic therapy for PE or DVT have ICH rates of 1%–2% [124–126]. The highest rates of ICH are seen in patients receiving thrombolytic therapy for stroke: rates of 3%–15% have been reported [127]. Older patients (over age 75), smaller patients, patients with previous stoke, and hypertensive patients appear to be at increased risk of bleeding [120,128]. Analysis of trials of bolus thrombolytic therapy versus continuous infusion suggest a slightly higher rate of ICH with bolus therapy, but this may be offset by a lower likelihood of dosing error [129,130].

Thrombolytic therapy, when given systemically in clinically effective doses, can affect every aspect of the hemostatic system. Patients will normally have a low fibrinogen, and an elevated PT-INR and aPTT (caused by destruction of factors V and VIII as well as to the low fibrinogen). Platelet dysfunction will also occur, because of fibrinogen fragments binding to and blocking platelet receptors and because of plasmin cleavage of platelet receptors. Finally, there will lysis of formed thrombi.
Patients who suffer severe bleeding after thrombolytic therapy should immediately have a PTINR, aPTT, fibrinogen, and platelet count performed [131,132]. Ten units of cryoprecipitate should be infused to replace fibrinogen and factor VIII. If the PT-INR and aPTT remain elevated after infusion of cryoprecipitate, two units of plasma should then be infused. If bleeding persists platelets should be given. If the patient is having an intracranial hemorrhage or other immediately life-or limb-threatening bleeding, empiric therapy with cryoprecipitate, platelets, and plasma should be given.

Although reversal of the fibrinolytic state can be achieved with the use of antifibrinolytic agents, this is rarely required. The fibrinolytic state, especially with tPA, is short-lived. Infusion of fibrinogen and plasma will shorten the duration of the fibrinolytic state. Finally, reversal of fibrinolysis may result in reformulation of the culprit thrombus which may then be refractory to lysis.

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