



Saint Luke's Regional Laboratories Clinical Laboratory Letter



February 2007

RBC Transfusion Trigger

The Transfusion Requirements in Critical Care Trial (TRICC) was a multi-center prospective randomized controlled clinical trial conducted in Canada in 1999, which compared the clinical outcomes in intensive care patients randomized to a restrictive versus a liberal transfusion strategy (NEJM 1999; 340: 409-17). Patients in the restrictive cohort were transfused when their hemoglobin concentration fell below 7 g/dL and their hemoglobin was maintained between 7–9 g/dL, while patients in the liberal transfusion group were transfused when their hemoglobin concentration fell below 10 g/dL and their hemoglobin was maintained between 10–12 g/dL.

Outcomes	Liberal	Restrictive
#Patients	420	418
#RBC units	5.2+/-4.9	2.5+/-3.8
Transfusion avoidance	0%	33%
ICU stay	11.5 days	11.0 days
30 day survival	77%	81%
60 day survival	74%	77%

The TRICC trial demonstrated that a more restrictive transfusion strategy was safe in the ICU patient population and that the liberal use of transfusions increased the risk of death. Multiple other studies have subsequently demonstrated that allogeneic transfusions cause immunomodulation leading to increased ICU and hospital length of stay as well as nosocomial infections and mortality.

In November 2006, an audit of 123 patients who were transfused with RBC at Saint Luke's Hospital was undertaken to determine if the medical staff was following a restrictive transfusion strategy.

Hb	Indications Documented	# Patients	%Patients
<7	-	38	31
>7	Yes	39	32
>7	No	46	37

In 63% of patients, RBC transfusions appeared to be justified because either the hemoglobin was <7 g/dL or the hemoglobin was >7 g/dL and the ordering physician documented the clinical indications for transfusion. In the remaining 37% of patients, the appropriateness of transfusion could not be determined due to the lack of clinical documentation.

Transfusion medicine has evolved over the last few years. Because allogeneic transfusions are a potential risk for patients, physicians should attempt to limit transfusions by aggressively preventing anemia in hospitalized patients. The decision to transfuse RBCs should be based on the entire clinical picture and not solely on the hemoglobin level. Current transfusion guidelines are printed in the Physician Pocket Calendar and in the RBC Transfusion Order Set.

An Overview of New Anticoagulant Drugs

The traditional anticoagulant drugs warfarin, unfractionated heparin (UFH) and low molecular weight heparin (LMWH) have a number of limitations, including issues regarding laboratory monitoring, food and drug interactions (warfarin), and a narrow therapeutic window. Ideal characteristics of new anticoagulant drugs include the following features: good bioavailability, no food or drug interaction, rapid onset of action, a wide therapeutic window, a predictable anticoagulant response making laboratory monitoring unnecessary, availability of an antidote, and effectiveness and safety at least equivalent to the currently available drugs. Whereas the older anticoagulant drugs have an effect on multiple factors in the coagulation pathway, the new drugs selectively inhibit a single coagulation factor, most notably thrombin (factor IIa) and factor Xa.

These new drugs may be classified according to their target coagulation factor, and whether they are orally or parenterally administered (see below). Here follows a brief overview of these agents, and a more detailed discussion of the parenteral factor Xa inhibitor fondaparinux.



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Classification of new anticoagulant drugs (asterisk indicates FDA-approval)

Thrombin inhibitors

- Parenteral -
 - Hirudin (Lepirudin)*
 - Argatroban*
 - Bivalirudin*
- Oral -
 - Ximelagatran (withdrawn from market)
 - Dabigatran

Factor Xa inhibitors

- Parenteral
 - Fondaparinux*
 - Idraparinux
- Oral
 - Rivaroxaban
 - Apixaban
 - Others

The parenteral direct thrombin inhibitors lepirudin and argatroban are approved for the treatment of heparin-induced thrombocytopenia (HIT). They are both administered intravenously and monitored by the APTT (target range 1.5-2 x baseline for lepirudin, 1.5-3 x baseline for argatroban). Lepirudin is excreted by the kidneys, while argatroban is metabolized by the liver. Bivalirudin is approved for percutaneous coronary interventions. All of these drugs have short half-lives (25-60 min).

The promising oral direct thrombin inhibitor ximelagatran, which required no laboratory monitoring, was recently withdrawn from the market due to hepatotoxicity. Dabigatran is another agent in this class, currently undergoing evaluation.

Parenteral factor Xa inhibitors act as indirect inhibitors since their effect is mediated through antithrombin (formerly known as antithrombin III). Fondaparinux is a pentasaccharide obtained by chemical synthesis. It binds to antithrombin resulting in a conformational change in the antithrombin molecule, thereby greatly potentiating its inhibition of factor Xa. It is administered once daily by subcutaneous injection in a fixed dose, and

no laboratory monitoring is required. This drug shows no cross-reactivity with HIT antibodies, and has not been associated with any instance of HIT. The drug is excreted by the kidneys, and has a half-life of 17 hours. No antidote is available.

Fondaparinux has been shown to be effective in the prevention of venous thromboembolism (VTE) following orthopedic surgery. A meta-analysis of four large trials (Arch Int Med. 2002;162:1833-40) showed that fondaparinux was significantly more effective than LMWH in reducing the incidence of VTE after hip replacement, hip fracture surgery and major knee surgery, with an overall 55% decrease in risk reduction compared with LMWH. Fondaparinux was shown in other trials to be at least as effective and safe as LMWH/UFH in the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), in the prevention of VTE after abdominal surgery, and in the treatment of acute coronary syndrome. Fondaparinux is the first selective factor Xa inhibitor to be FDA approved as an anticoagulant. It is currently approved for prevention of VTE following hip fracture surgery, total hip and total knee replacement, and major abdominal surgery. It is also approved for the initial treatment of DVT and PE. The drug in both prophylactic and therapeutic doses prolongs the PT by approximately 1 second, and the APTT by approximately 4-5 seconds, however laboratory monitoring is not indicated.

Oral factor Xa inhibitors (rivaroxaban, apixaban and others) act as direct inhibitors; their effect is not mediated by antithrombin. These drugs also require no laboratory monitoring. They are currently undergoing extensive phase II and phase III studies on prevention and treatment of VTE, and initial reports look promising.

In conclusion, selective inhibitors of specific coagulation factors (thrombin and factor Xa) represent a new class of anticoagulants. They have the potential to be at least as effective and safe as conventional anticoagulants without the need for laboratory monitoring.