

# Interpretation of clotting tests in the neonate

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## ABSTRACT

There are significant differences between the coagulation system in neonates compared with children and adults. Abnormalities of standard coagulation tests are common within the neonatal population. The laboratory tests of activated partial thromboplastin time (aPTT) and prothrombin time (PT) were developed to investigate coagulation factor deficiencies in patients with a known bleeding history, and their significance and applied clinical value in predicting bleeding (or thrombotic) risk in critically ill patients is weak. Routine screening of coagulation on admission to the neonatal intensive care unit leads to increased use of plasma for transfusion. Fresh frozen plasma (FFP) is a human donor plasma frozen within a short specified time period after collection (often 8 h) and then stored at  $-30^{\circ}\text{C}$ . FFP has little effect on correcting abnormal coagulation tests when mild and moderate abnormalities of PT are documented in neonates. There is little evidence of effectiveness of FFP in neonates. A large trial by the Northern Neonatal Nursing Initiative assessed the use of prophylactic FFP in preterm infants and reported no improvement in clinical outcomes in terms of mortality or severe disability. An appropriate FFP transfusion strategy in neonates should be one that emphasises the therapeutic use in the face of bleeding rather than prophylactic use in association with abnormalities of standard coagulation tests that have very limited predictive value for bleeding.

## BACKGROUND

Abnormalities of standard coagulation tests are common within the neonatal population. But the relationship between these abnormalities and clinical features such as thrombus formation or increased bleeding tendency is far from clear.<sup>1</sup> When evaluating the clotting tests used in the neonatal population, it is important to recognise the inherent differences in the neonatal coagulation cascade compared with that of the adult or older child. Although neonates have similar bleeding times to adults,<sup>2</sup> there are significant differences when we compare the neonatal with the adult coagulation system. Despite these physiological differences, healthy term and preterm babies do not tend to have problems with coagulation, indicating that these differences represent normal development of the human coagulation system.

Many conditions can alter this delicate balance, however, and lead to abnormal clotting with an increased tendency towards either haemorrhage or thrombus formation. As a result, abnormalities in the coagulation system are relatively common in a neonatal intensive care setting. Multiple factors such as infection, respiratory distress, necrotising enterocolitis, the presence of intravascular catheters, surgical procedures, dehydration and liver

disease can all affect the haemostatic balance.<sup>1</sup> Some disease processes can affect production alone, whereas others may affect consumption or both. Routine screening of this high-risk population does not appear to be the answer. Although we know that screening of coagulation on admission to the neonatal unit demonstrates 'laboratory' coagulopathy in a significant number of admissions, we also know that routine screening can lead to greater use of blood products to correct this 'coagulopathy' without evidence of apparent benefit.<sup>3</sup>

In order to target treatment for coagulation disorders appropriately, we need to have established normal reference ranges, understand the pathophysiology of conditions affecting the coagulation system and the risks and side effects of blood product administration. There is currently a lack of evidence surrounding the assessment of coagulation abnormalities within neonates, with recent studies<sup>4</sup> demonstrating different 'normal' ranges for coagulation tests depending on gestational and postnatal age. There is also evidence that 'abnormal' coagulation tests are not associated with increased risk of bleeding, and there has been a move to reset the bar for transfusion in order to minimise risk of blood product administration.

## WHAT ARE THE DIFFERENCES IN THE NEONATAL COAGULATION SYSTEM?

There are many differences between the neonatal and adult coagulation systems; bleeding times of healthy neonates are shorter than their mothers,<sup>5</sup> indicating a more rapid overall thrombin generation. Foetal production of coagulation proteins begins at 11 weeks' gestation, and these cannot cross the placenta because of their size as macromolecules.<sup>6</sup> The levels of most coagulation factors are approximately 50% the adult levels, with most reaching adult levels by 6 months of age. The activity of vitamin K-dependent clotting factors is approximately 50% (between 37% and 100%) of the adult values, and reduced further in preterm infants; to 30% in 24–29 weeks' gestation (25–79%) and 20% in 19–23 weeks (11–39%).<sup>6</sup> The naturally occurring anticoagulants (antithrombin, protein S+protein C) are synthesised in the liver dependent on vitamin K. Plasma concentrations of these anticoagulants are significantly lower at birth than in adults (60%, 39% and 36%, respectively). Activity of the protein S is higher due to low levels of C4b-binding protein (which acts as an inhibitor for the natural anticoagulants and the complement system).

Levels of fibrinogen are similar to adult ranges, although comprising a foetal variant that is used clinically in the foetal fibronectin test. Foetal fibrinogen is more active than adult variant, caused by a post-translational modification leading to a



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larger molecular weight.<sup>7</sup> It is also thought that this polymerisation of fibrinogen may confer some thromboprotective mechanism within neonates.<sup>7</sup> Early studies by Andrew *et al*<sup>8</sup> demonstrated that neonates had 30–50% thrombin activity. More recent studies by Cvirn *et al*<sup>9</sup> have demonstrated that activation with smaller amounts of activation factor is needed and results in shortened coagulation times and quicker thrombin generation compared with adults, most likely as a result of the reduced level of inhibitory factors in neonates.

## COAGULATION SCREENING

Haemostasis *in vivo* results from the complex interplay of vascular endothelium, platelets, a series of soluble coagulation factors known as the coagulation cascade, anticoagulation mechanisms and the fibrinolytic system. A typical routine 'coagulation' profile assesses a component of these pathways and consists of an activated partial thromboplastin time (aPTT), prothrombin time (PT), fibrinogen and platelet count. Blood samples that are tested for coagulation studies are collected with anticoagulants to prevent blood clotting. Most routinely used anticoagulants function by binding calcium and preventing the coagulation protein binding. EDTA irreversibly binds and chelates calcium and is commonly used in full blood count testing, and therefore the assessment of platelet count. Citrate is often used for the standard coagulation tests and is added to transfusion bags. Citrate binds calcium less strongly than EDTA, and this is reversible with the addition of calcium.

aPTT, PT and fibrinogen levels are measures of the intrinsic, extrinsic and the final common clotting pathway, respectively, although our current understanding of these pathways suggests much more functional inter-relationship. The intrinsic pathway is activated by exposed collagen. The extrinsic pathway is activated by tissue factors released from damaged cells. Both pathways lead to the activation and generation of clotting factors, and finally lead to fibrin formation via a common pathway. Platelets are required for clot formation and repair of damaged endothelium, and play a role in coagulation by releasing calcium (which promotes activation of clotting factors), and binding of fibrinogen.

The laboratory tests of aPTT and PT were developed to investigate coagulation factor deficiencies in patients with a known bleeding history, and their significance and applied clinical value in predicting bleeding (or thrombotic) risk in critically ill patients remains open to debate. Both PT and aPTT results are dependent on reagent and laboratory quality controls and may be abnormal for a number of reasons not associated with bleeding risk, including normal variation of coagulation factor levels or the presence of a lupus anticoagulant. Coagulation results also vary in sensitivity with reduced levels of different coagulation factor levels. For example, aPTT will be significantly prolonged with only small reductions in the levels of some intrinsic coagulation factors, and PT, in particular, is sensitive to mild (but not clinically significant) deficiencies of multiple procoagulants, as is often seen in clinical practice.

aPTT and PT are reported in seconds, as the time taken for blood to clot under various conditions, assessing each of the systems and by extension-regulating factors. Lower time for coagulation is not associated with risk of thrombus formation in neonates, although sometimes noted in association with thrombophilic factors such as protein S deficiency, FV Leiden heterozygosity or antiphospholipid antibodies.<sup>10</sup> Abnormally high coagulation times are sometimes considered to be associated with risk of bleeding; in this setting, therefore it is the upper

limits of the ranges that are more clinically important within the neonatal population.

The international normalised ratio (INR) was devised in 1983 to overcome the interlaboratory variability due to the thromboplastin (reagent) sensitivity during measurement of PT by dividing PT by a control level. The extrapolation of PT to INR is really only valid for those patients stably anticoagulated with vitamin K antagonists and may not be a valid measure of coagulation for many patients in critical care. An INR of 1.5 is not equivalent to a PT of 1.5× midpoint of reference range, although it may approximate to this measure as the international sensitivity index value (a measure of 'sensitivity' of the laboratory coagulant reagents) moves closer to a standard of 1.0. PT depends on levels of vitamin K and the dependent clotting factors.<sup>11</sup> PT is known to be prolonged in cord blood samples normalising over a few weeks; therefore, selection of a control group poses challenges within the neonatal population. INR is commonly used within adults when monitoring warfarin therapy. Warfarin is only occasionally used within neonates when treating thrombosis<sup>10</sup> because of the narrow therapeutic range, interactions with other medications (such as antibiotics and antiepileptic medications), effects of serum lipid concentrations, effects of vitamin K levels and the need for frequent monitoring.<sup>12</sup>

Measurements of the natural anticoagulant levels are performed as part of the thrombophilia screen in neonates. Clotting factor assays may also be performed in the presence of abnormal coagulation tests or bleeding. The normal levels of these differ compared with adults and with gestational age, therefore these should be interpreted with the appropriate reference range (see below).

## WHAT ARE THE REFERENCE RANGES IN NEONATES?

There are significant differences between the coagulation system in neonates compared with children and adults.

The reference ranges for healthy moderate preterm and term infants were primarily established by Andrew *et al*<sup>8 13</sup> over 30 years ago during the early 1980s. The initial study included 118 term infants in 1983 and 1984, with serial testing at various times between day 1 and day 180 of life using venous samples.<sup>13</sup> This enabled the formation of reference ranges for term infants. A subsequent study assessed the clotting function in neonates from 30 to 36 weeks' gestation with a similar methodology.<sup>8</sup> Both studies also demonstrated changes in the normal ranges of the standard coagulation tests with postnatal age for both preterm and term infants; for example, aPTT has a trend of starting at a higher level and then reducing towards the adult range over 6 months, PT remains relatively stable over time and fibrinogen demonstrates a trend of increasing in the first few days of life and then reducing towards adult levels.

Subsequent studies by Christensen *et al* published in 2014<sup>4</sup> sought to determine the reference ranges for infants below 34 weeks' gestation and those of extreme prematurity (table 1). This was a prospective study using cord blood samples (N=175). 95% CI was calculated at various gestational age groups at birth, including below 28 weeks; however, a lower-end cut-off is not quoted. This change in the reference ranges has significant effects in terms of both numbers of transfusions and also assessment of efficacy of fresh frozen plasma (FFP) (measured as correction of laboratory values towards 'normal'). The authors advise caution with use of the reference ranges, pending further studies to support the creation of evidence-based protocols.

**Table 1** Infant reference ranges of common coagulation tests

Gestational age	<28 weeks <sup>4</sup>	28–34 weeks <sup>4</sup>	30–36 weeks <sup>8</sup>	Term infants <sup>13</sup>
Reference range—PT (s) 95th centile	>21	>21	>16	>16
Reference range—aPTT (s) 95th centile	>64	>57	>55	>55
Fibrinogen level (5th–95th centile, g/dL)	0.71–5.35	0.87–4.70	2.25–3.41	1.50–3.73

Reference ranges are taken from the Christensen *et al*<sup>4</sup> paper for neonates <34 weeks' gestation and from the Andrew *et al*<sup>8, 13</sup> paper for those 30–36 weeks' gestation and term infants.

aPTT, activated partial thromboplastin time; PT, prothrombin time.

## HOW CAN CLOTTING ABNORMALITIES PRESENT IN NEONATES?

Coagulation abnormalities can present in various ways within the neonatal population; from asymptomatic results on blood tests to severely unwell neonates with thrombi or bleeding. The clinical consequences of clotting abnormalities depend on several factors. First, the type of event, such as bleeding or thrombus. Second, the location and severity of the abnormality. Within normal babies, bleeding in itself will trigger further secondary changes in the coagulation balance; for example, birth trauma and intracranial haemorrhage.<sup>1</sup> Bleeding in the neonatal period can occur relatively frequently; for example, intraventricular haemorrhage (IVH) in 29–44% of preterm infants<sup>14–15</sup> and pulmonary haemorrhage in 8%.<sup>16</sup> The overall incidence of venipuncture site oozing, umbilical cord bleeds or gastrointestinal bleeds in the absence of necrotising enterocolitis has not been reported. Treatment of neonatal bleeding is supportive and may require replacement of lost volume with fluids or blood products to correct coagulation abnormalities.

Thrombi can be arterial or venous, and 90% of cases are catheter related.<sup>1</sup> Catheter-related thrombi may present with signs of venous obstruction depending on the location such as facial or upper chest congestion in superior vena cava obstruction or respiratory compromise in pulmonary thromboembolism. Renal vein thrombosis accounts for up to 20% of all neonatal thromboembolism and is the most common non-catheter-related thromboembolism in neonates.<sup>17</sup> This usually presents within the first week of life with loin mass, haematuria and proteinuria and is associated with factors affecting blood flow such as hypercoagulability, polycythaemia and hyperviscosity, stasis or vessel injury. Idiopathic thromboembolism is relatively rare within the neonatal population and is usually associated with risk factors such as maternal disease (systemic lupus erythematosus, diabetes, antiphospholipid syndrome), placental pathology (vasculopathy, infarct), growth restriction or neonatal illness (dehydration, infection, acidosis or deficiency in natural anticoagulants).<sup>18–19</sup> Neonatal stroke commonly presents with seizures but may present with non-specific symptoms such as apnoea and poor feeding.

## TREATMENT OF THROMBUS

Treatment of thrombi is either supportive or with thrombolytic agents or anticoagulants. Therapeutic ranges used are based on adult target ranges as there is a paucity of neonatal trials in this area. The differences in neonatal physiology (higher volume distribution and rapid clearance) mean that high doses of anticoagulant drugs are often required. There is no causal link between coagulation tests and non-inherited thrombotic events (ie, those not associated with a thrombophilia).<sup>1</sup> There are also no trials in neonates to demonstrate the efficacy or safety of thrombolytic agents. Despite this, the current practice is to treat thrombi with anticoagulants and monitor for complications such as bleeding. The American College of Chest physicians recommends

3 months of low-molecular weight heparin following proven cardioembolic stroke.<sup>20</sup> Further studies are therefore needed to define neonatal therapeutic ranges for antithrombotic treatment, define therapy and also assess long-term outcomes for neonates with thrombosis.

## TREATMENT OF BLEEDING

It is widely accepted that standard coagulation tests have significant limitations as predictors of bleeding in any patient group, including neonates, and that use of FFP has little effect on correcting abnormal coagulation tests when mild and moderate results are recorded.<sup>21–22</sup> Despite this, FFP is frequently administered to neonates.<sup>3–23</sup>

FFP is a human donor plasma frozen within a short specified time period after collection (often 8 h) and then stored at a defined temperature, typically  $-30^{\circ}\text{C}$ . FFP is typically given at a dose of 10–20 mL/kg over 30 min and may be given for two indications: to prevent bleeding (prophylaxis) or to stop bleeding (therapeutic). FFP contains proteins, clotting factors, immunoglobulins and vitamin K-dependent factors. The common uses of FFP within the UK have been identified in a recent prospective study by Stanworth and colleagues assessing the transfusion practices of blood products.<sup>3</sup> Four per cent of FFP transfusions occurred within infants (defined as <1 year). Within neonatal units, the indications for transfusion with FFP are laboratory evidence of coagulopathy, correction of disseminated intravascular coagulopathy (DIC) and prevention of IVH. Forty-two per cent of FFP transfusions were given to children with no evidence of bleeding.<sup>3</sup> Previous common uses of FFP that are now considered inappropriate include volume replacement, correction of hypoalbuminaemia, nutritional support and immunoglobulin replacement.

Routine screening of coagulation on admission to the neonatal intensive care unit (NICU) leads to increased use of FFP. A retrospective study by Catford *et al*<sup>24</sup> demonstrated that this policy led to a fivefold increase in FFP use in NICU with no evidence of clinical benefit in non-bleeding patients. Many of the babies treated will have had mild or moderate isolated 'laboratory coagulopathy', and the side effects of FFP (see below) may well outweigh any theoretical advantage.<sup>25–26</sup>

Reference ranges will also affect measurement of efficacy of FFP. The study<sup>24</sup> mentioned above evaluated the coagulation tests from two tertiary neonatal units within the UK, and the correction of abnormal clotting values depended on the reference ranges used. For example, by using the reference ranges devised by Andrew *et al*,<sup>8</sup> this ranged from 10% to 15% success rate for aPTT and PT, respectively. If the more recent reference ranges suggested by Christensen *et al*<sup>4</sup> are used, then the normalisation following FFP was 59% and 68% for 28–24 weeks and under 28 weeks, respectively.

Currently, there is very limited evidence surrounding the use of FFP in the neonatal population, especially with respect to

changes in clinical outcomes. There have been small prospective randomised studies published by McCall *et al*<sup>27</sup> in 2004 (N=20) in babies under 8 kg undergoing heart surgery with half receiving FFP before surgery, with no significant difference in bleeding from chest drains or frequency of transfusions post-operatively. Four other studies compared FFP to colloid before cardiobypass surgery in neonates and children. The primary outcomes in these studies were clotting profile, thrombin generation and other laboratory variables. Overall, there were no significant differences between the groups receiving FFP and colloid.<sup>28</sup> A systematic review and meta-analysis of trials (including those with adult patients) demonstrated no significant improvement in clinical outcomes in using FFP compared with colloid or no transfusion.<sup>28</sup> There have been few trials of FFP within neonates specifically. A trial by the Northern Neonatal Nursing Initiative in 1996 (NNNI) assessed the use of prophylactic FFP in preterm infants (N=776) that were randomly assigned to receive prophylactic FFP (N=257), a gelatin-equivalent infusion (N=261) or an infusion of 10% dextrose (N=258) as a control.<sup>29</sup> There was no improvement in clinical outcomes in terms of mortality or severe disability.<sup>29</sup> There have been a small trial of 10 preterm infants with supplementation of FFP and recombinant factors demonstrating no decrease in incidence of IVH, though treatment with the factor appears safe.<sup>30</sup> In patients with DIC, there have been few trials completed. Three trials conducted show no improvement in survival or clotting test results if FFP was given in these cases.<sup>31</sup> Although the current evidence demonstrates an improvement in the coagulation tests following FFP administration, there is currently a lack of evidence to support any difference in outcomes.<sup>32</sup>

### COMPLICATIONS OF BLOOD PRODUCTS AND FFP

There is little evidence of adverse effects of FFP in the neonatal population. Interpretation of the data from the UK Serious Hazards of Transfusion (SHOT) National Haemovigilance Scheme against a population-based epidemiological study of transfused patients has suggested that a disproportionate number of all adverse events occur in children compared with adults, and more so in infants and neonates.<sup>33</sup> The reasons for these differences are unclear; it seems likely that many risks may be underrecognised in a neonatal intensive care setting, managing sick patients. A significant proportion of all SHOT reports in infants and children were related to transfusion errors, including transfusion of an incorrect blood component.

There are slight differences in the complications of FFP compared with red cells and platelets, with fewer studies reporting the complications of FFP transfusions. Viral infections (such as HIV, hepatitis B virus, hepatitis C virus, parvovirus B19) have been reported following FFP transfusion, although these risks are very low with current technologies for screening infection in blood donations. Allergic reactions resulting in urticaria have been reported in 1–3% of transfusions; however, anaphylaxis is rare. Transfusion-associated lung injury (TRALI) is a serious initial reaction to an FFP transfusion.<sup>34</sup> TRALI incidence is higher following FFP transfusions compared with platelet (1.3:1) or packed red cell transfusions (9:1)<sup>33</sup> with an increased risk of occurrence with the critical care setting with a risk of 5–8% in adults.<sup>35</sup> The incidence of TRALI in children is controversial, with reported incidence in the USA and Canada of 1/5–10 000 and much lower in the UK at 1/26–55 000.<sup>36</sup> The incidence may vary due to a lack of consensus on definition and potential underreporting in the UK, including the neonatal population.<sup>37</sup> <sup>38</sup> Transfusion-associated circulatory overload

(TACO) is also likely to be underreported following neonatal transfusions and is caused by high fluid infused over a short time. The incidence of TACO is higher within the intensive care unit population, with a recent prospective adult study (N=910) finding an incidence of 6% with larger volume of plasma and faster rate of infusion.<sup>39</sup>

### CONCLUSIONS

Coagulation abnormalities are a common and clinically important problem within the neonatal population. The neonatal coagulation system shows different levels of clotting factors, cofactors and functionality compared with the older child or adult. These changes represent normal development of the human coagulation system. Coagulation abnormalities may present with either thrombi, bleeding or asymptomatic laboratory findings.

Routine coagulation screening usually consists of PT, aPTT, fibrinogen and platelet count. Measurements of clotting factors and anticoagulant levels may be performed subsequent to either abnormal test results or clinical signs of thrombi or bleeding. The reference ranges for neonates differ compared with adults and vary with gestational and postnatal age.

There are few neonatal trials exploring the treatment of coagulation abnormalities in terms of indications as well as therapeutic targets. Thrombi may be treated with thrombolytic agents using adult target ranges, but with no evidence from neonatal trials regarding efficacy, safety or change in outcomes. In practice, an appropriate FFP transfusion strategy in neonates should be one that emphasises the therapeutic use in the face of bleeding rather than prophylactic use in association with abnormalities of standard coagulation tests that have very limited predictive value for bleeding. Further trials are needed to support the development of evidence-based guidance for the assessment and treatment of abnormal coagulation within the neonatal population.

**Competing interests** None.

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