Yorkshire and Humber Neonatal ODN (South) Clinical Guideline

Title: Coagulopathy in the neonate

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This clinical guideline has been developed to ensure appropriate evidence based standards of care throughout the Yorkshire and Humber Neonatal ODN (South). The appropriate use and interpretation of this guideline in providing clinical care remains the responsibility of the individual clinician. If there is any doubt discuss with a senior colleague.

Best practice recommendations represent widely used evidence-based practice and high quality standards that all Neonatal Units across the Network should implement. Subsequent suggested recommendations may be put into practice in local units. However, alternative appropriate local guidelines may also exist.

Summary

Treatment: Age and gestation specific ranges should be used (see 4.2.2).

	Fibrinogen g/L	PT (s)	APTT (s)
<28/40 gestation	<0.7	21	113
28-34/40 gestation	<0.9	20	80
Term (birth)	<1.0	20	64
Term day 5	<1.0	19	64
Term day 30	<1.0	18	61
Action-bleeding/high risk of haemorrhage	Cryoprecipitate	vitamin K +- FFP	FFP
Evidence strength/category	4D	3C	3C

DIC/liver disease- if bleeding or at risk of bleeding from an invasive procedure

FFP 10-20ml/kg over 30 mins

Cryoprecipitate (consider if fibrinogen low) 5-10ml/kg over 30 mins

Consider treatment for DIC even in the absence of bleeding if coagulation times of PT and APTT are >1.5 times normal in the absence of heparin contamination

B. Full guideline

1. Background

Clotting abnormalities are commonly seen on the neonatal intensive care unit.

2. Aim

The aim of this guideline is to advise on the initial management and investigation of the neonate with coagulation abnormalities.

3. Areas outside remit

Management of infants with suspected/known congenital haematological disorder. Expert advice should be sought from a consultant haematologist/ refer to guideline.

4. Core guideline

4.1 Coagulopathy

4.1.1 Clotting screen

PT- prothrombin time
This assesses the function of factors II, V, VII and X- which includes the vitamin K dependent factors, hence is prolonged in vitamin K deficiency and with warfarin usage. It is also abnormal in fibrinogen deficiency.

APTT- activated partial thromboplastin time.
This measures the activity of factors II, V, VIII, IX, X, XI and XII. It is also abnormal in fibrinogen deficiency.

TT- Thrombin time
This tests for fibrinogen deficiency/dysfunction, such as in disseminated intravascular coagulopathy (DIC). Also prolonged with heparin.

4.1.2 Reference ranges

Coagulation problems are common in preterm infants, however there remains a scarcity of data on the acceptable normal ranges. It is known that the components of the coagulation system vary widely from adult ranges across different gestations for example fetal fibrinogen is known to be more active. Table 1 lists some published ranges used[1,2,3]. Andrew and co-workers measured the levels in 137 preterm "well" infants with the gestational ages 30-36 weeks[1]. Further studies have now been performed. Christensen[2] took cord blood samples from 168 infants <34 weeks gestation and Neary[3]

retrospectively studied 183 infants <27 weeks gestation who had routine coagulation profiles taken on day 1 of life.

In view of the small numbers involved in the Christensen study <28 weeks (24 infants), it would appear pragmatic to use the larger Neary study for infants <27 weeks, the Christensen data for infants 28-34 weeks and the older Andrews data for infants 34-term and term. There is also limited data for infants beyond day 1 of life, but using corrected gestational age has some theoretical support. Using this, the reference ranges suggested are as below.

Corrected Gestational age	Age	PT (s)	APTT (s)	Fibrinogen (g/l)
23-27[3]		14.4-36.7	40.5-158.5	0.7-4.8
28-34[2]		13.9-20.6	30-57	0.87-4.7
34-36[1]	1 day	10.6-16.2	27.5-79.4	1.5-3.7
	5 days	10-15.3	26.9-74.1	1.6-4.2
	30 days	10-13.6	26.9-62.5	1.5-4.1
Term[1]	1 day	11.6-14.4	26.8-48.7	2.3-3.4
	5 days	10.9-13.9	34.0-51.2	2.4-3.9
	30 days	10.6-13.1	33-47.8	2.2-3.2

4.1.3 Clotting abnormalities in term infants

A specific bleeding disorder should be suspected in infants with bleeding in healthy term or late preterm infants, such as oozing from umbilical stump, bleeding following capillary heel prick sampling, attempts at cannulation, excessive cephalohaematoma or an unexplained intracranial haemorrhage. A family history may be helpful, however 1/3 of infants with severe haemophilia have no previous family history.

Expert haematology advice may be required for further investigation and treatment. Although rare, a congenital bleeding disorder must be considered (and appropriate tests requested before blood product support) in a bleeding infant or with an unexplained severe coagulopathy. The infant should not be discharged until the results are available.

Table 2[4] below gives some differential diagnoses of abnormal clotting findings, however expert haematological advice should be sought.

For mild conditions, testing may be required at a later date as definitive diagnosis may not be possible until the haemostatic system has matured.

Clotting abnormality	PT alone	APTT alone	TT alone	PT and APTT	PT, APTT, TT	All normal
Factor abnormality	Factor VII def	Factor VIII, IX, XI, XII def	Low fibrinogen	Factor II, V, X def	Fibrinogen deficiency	XIII def,
	Vitamin	Haemophilia	Heparin	Liver	DIC	platelet

Diagnosis	K def	A or B. Von Willebrand disease	contamination	disease,		defects
	Warfarin	Heparin			Severe liver disease Heparin	

4.1.4 Clotting abnormalities in preterm infants

There is no evidence to support the routine testing of coagulation in preterm infants, or literature to suggest which infants should be tested. It would be reasonable to perform a coagulation profile in infants at high risk of abnormalities eg those who may have a consumptive coagulopathy (DIC, sepsis especially gram negative infections, necrotising enterocolitis), or who have suffered a significant haemorrhage (eg severe bruising, pulmonary haemorrhage, grade IV intraventricular haemorrhage) or those undergoing surgical procedures such as laparotomy.

It should be noted that the wide ranges for "normal" clotting times quoted for preterm infants overlap with values that could occur in neonates with congenital bleeding disorders e.g. haemophilia. The possibility of a bleeding disorder should therefore still be considered if there is a family history or if there is bleeding symptoms even if the clotting screen is normal. Specific factor assays may be required which should be discussed with a haematologist.

Due to the difficulties with defining normal ranges as described above, it is challenging to describe management of this common problem. There have been a few studies looking at routine correction of "prolonged" coagulation profiles with the hope of reducing the rate of intraventricular haemorrhage; however these are all observational studies using historical controls. Dani et al[5] suggested using FFP (10ml/kg over 2 hours repeated until clotting in range) reduced the incidence of IVH (predominantly grade I) in the subgroup 23-26 week gestation (RR 1.61), however these infants received a mean of 2.8 "doses" ie almost 30ml/kg, which is a significant fluid load, which is known to increase the risk of IVH itself and were compared to historical controls, managed in 1999-2002. It is known that neonatal care in general has improved over that time, and may also contribute to the observed reduction in IVH rate. A subsequent study demonstrated that abnormal coagulation results predicted severe IVH, however those treatment with FFP did not change the incidence of IVH or mortality.[6]
A further study noted that preterm infants with "abnormal" cord coagulation profiles did not predict bleeding in the first week of life, and infants with bleeding in the first week of life were not likely to have had abnormal coagulation profiles at birth.[2]

Summary
There is no evidence for routine "screening" coagulation profiles or prophylactic administration of FFP.[8]

4.1.5 Treatment

Empirical blood product support may be indicated if there is bleeding or the clotting times are significantly prolonged (more than 1.5 times the mean normal range) and the infant is considered to be at higher risk of bleeding eg bruised, septic, has suffered a recent haemorrhage (eg significant IVH or pulmonary haemorrhage) or is to undergo an invasive procedure[8]. This table is based wherever possible on values 1.5 above the mean (for PT and APTT) and <5th centile for fibrinogen. For infants below 28/40 the reference ranges are very wide leading to high thresholds. It may be appropriate to use the 95th centile for PT (as per table) in this case, and treat lower APTT in the case of haemorrhage.

When interpreting coagulation results, take into account heparin contamination as this will falsely prolong APTT and in some cases PT. This can be done by taking a venous sample or inferred from the laboratory results (discuss with your local laboratory as some may be able to correct/remove heparin contamination).

Suggested treatment threshold/action[1,2,3]

	Fibrinogen g/L	PT (s)	APTT (s)
<28/40 gestation	<0.7	21	113
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4.1.5a FFP- Fresh Frozen Plasma
This is a blood product containing fibrinogen, factors II, VII, VIII IX, X, XII, XIII. Due to concerns regarding vCJD, for all neonates imported FFP is used and pathogen inactivated using methylene blue[9] or solvent-detergent treated.[10]

There is evidence that routine use of FFP for fluid boluses/blood pressure support for prophylaxis of IVH does not offer benefit in the short or long term and therefore cannot be recommended. See above for discussion regarding preterm infants with abnormal clotting.

The dose of FFP is 10-20ml/kg delivered over 30 minutes.[7]

4.1.5b Cryoprecipitate[7]
This is precipitate that forms following the thawing of FFP. It contains a high concentration of factor VIII, von Willebrand factor, fibrinogen factor XIII and fibronectin.

Cryoprecipitate is often used for infants with low fibrinogen due to DIC, however there is no neonatal evidence to support this use.

The dose used is 5-10ml/kg infused over 30 minutes.

4.1.5c *Specific factor concentrates factor VIII, IX and VWF containing concentrates*
Stocks of specific factor concentrates are only held at centres with haemophilia centres and therefore delivery of infants potentially affected with severe haemophilia or type 2 or 2 VWD should be referred to tertiary centres. Unexpected new diagnoses must be discussed with a consultant paediatric haematologist who will advise on management and/or transfer.

4.1.5d Recombinant factor VIIa (Novoseven)
Factor VII is a pivotal trigger for activating the final pathway in the coagulation cascade.
There are a growing number of small trials of the use of activated FVII in non-haemophilic adults and children with intractable bleeding which including some reports in neonates.[11,12,20]

Doses used were 40-300micrograms/kg. References suggest a dose of 50-90micrograms/kg as a start dose. Note this use is entirely off licence and use is associated with an increased risk of thrombotic complications. In the majority of case reports, it has been used in life threatening situations when all standard therapies have failed. Treatment of the underlying cause and correction of coagulopathies with blood products should always be the priority before considering the use of this product.

4.1.6 Specific Coagulopathies

4.1.6a Vitamin K deficiency[13]
This is a common acquired cause of coagulopathy which can result in vitamin K deficiency bleeding (VKDB). It occurs due to low bacterial colonisation of the gut leading to low endogenous supply, and low intake of vitamin K due to the low quantities in breast milk.

There are 3 subtypes:
Early VKDB- this presents within the first 24 hours, in infants of mothers on vitamin K inhibitors such as anticoagulants, anticonvulsants and anttuberculosis drugs.

Classical- occurs between days 1 and 7 with GI bleeding and intracranial haemorrhage. Often these infants have not received vitamin K at birth. The incidence of classical VKDB is 0.01-1.5% without vitamin K prophylaxis.

Late- this occurs between 2 and 12 weeks of age. The majority of these infants present with intracranial haemorrhage. The incidence of late VKDB is 4-10 per 100,000 births.

Investigation
Initially PT will be prolonged, however in more severe forms; the APTT will also be increased.

Treatment
Urgent vitamin K is the treatment of choice given by slow intravenous injection unless venous access cannot be established in which case this can be given subcutaneously. The intramuscular route should not be used when there is a coagulopathy. In infants who are bleeding, FFP should be given in addition to Vitamin K.

In the presence of life-threatening haemorrhage or intracranial haemorrhage, the use of Prothrombin Complex Concentrate (Beriplex, Octaplex) should be discussed with a haematologist since it is necessary to normalize the levels of the depleted coagulation factors which cannot be achieved with FFP alone.

It is recommended that all infants receive 1mg vitamin K in the first 6 hours after birth to prevent VKDB. Infants receiving this orally require a further dose to prevent the late form.

4.1.6 b Disseminated Intravascular Coagulation (DIC)
This is the most common form of coagulopathy seen on the neonatal unit. It results from activation of the coagulation cascade leading to consumption of coagulation factors and subsequent haemorrhage. Diagnosis is made in infants with a prolonged PT, APTT, reduced fibrinogen, thrombocytopenia and raised d-dimers. Note, not all parameters may be abnormal especially in early DIC.

Treatment
Supportive
The mainstay of treatment is reversing the underlying condition- this is commonly sepsis or necrotising enterocolitis but can include hypoxia, acidosis or rarely capillary haemangioma or large arterio-venous malformation. Septic infants may need circulatory support (as per guideline).

Blood products
Beyond supportive care there are no clear guidelines on the optimal management of neonatal DIC and a virtual absence of recent randomized controlled trials addressing the available treatment options. Blood product support may be indicated if there is bleeding or the infant is at risk of bleeding from an invasive procedure and the clotting times are significantly prolonged. Those more than 1.5 times the mean normal range would usually trigger empirical therapy[7, 8]. This can be seen in the table 4.2.2. Mild DIC usually does not warrant blood product support.

Platelets- thrombocytopenia should be treated as per guideline, aiming for a platelet count of 30-50x10^9/l.

FFP- 10-20ml/kg of FFP can be given to improve coagulation tests by about 30%.

Cryoprecipitate 5-10ml/kg- this can be used for infants with low fibrinogen levels, however this is practice extrapolated from adult literature as there are no trials of this in newborns.

6. Audit criteria
Use of blood products compared to guideline indications

7. References

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