Paediatric Haematology

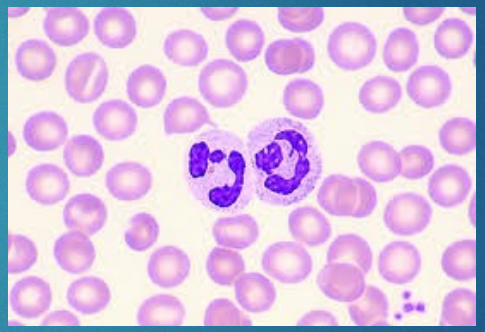
DR BETHANY MITCHELL & DR CATHERINE MARK

CONSULTANT PAEDIATRIC HAEMATOLOGISTS RBHSC

Neutropenia

Definition

- Technically…..
  - < 1 x 10^9/L in under 1s
  - <1.5 x 10^9/L in over 1s
- In reality…..
  - <1 x10^9/L
  - Particularly <0.5 x 10^9/L (Severe)



Neonatal period

- 6-8% of babies in NICU
  - 3% term babies > 2500g
  - 13% < 2500g
  - 38% < 1000g
- Causes
  - Infection – sepsis, TORCH
  - Antenatal – placental insufficiency, HTN, perinatal asphyxia
  - Allo/iso/autoimmune
  - Genetic – SCN, IBMFS, metabolic

Neonatal period

- Persistent neutrophils 0.5 x 10^9/L
- Significant sepsis/pyogenic infection
- Other anomalies – eg dysmorphic features, hepatosplenomegaly
- Consider alloimmune

Infants and children

- Very common!
- Really only consider if < 1 x 10^9/L
- Special care if severe - < 0.5 x 10^9/L

Most common causes?

Post –infection

Autoimmune/idiopathic

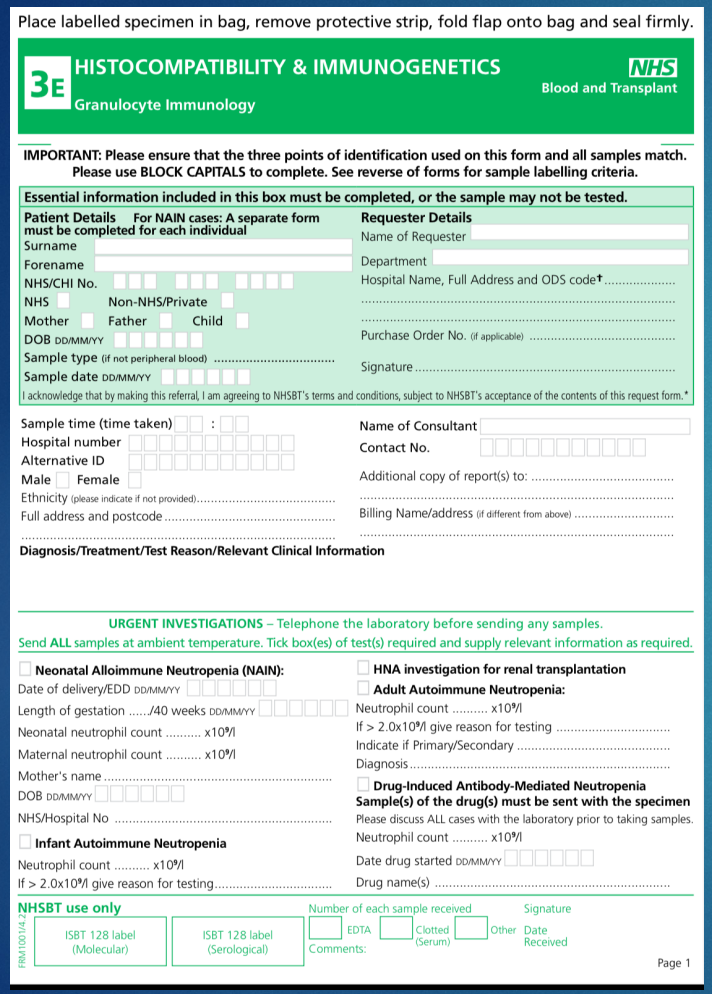
Infants and children – other causes

- Malignancy
- Nutritional deficiency
- Other pathology – hypersplenism
- Genetic
  - Ethnicity
  - Cyclical neutropenia
  - SCN
  - Immunodeficiency
  - IBMFS

Investigations

- FBP &film
- Consider if any worrying symptoms on hx or exam or if any other cell lines affected – if concerns consider referral
- If not meeting criteria for referral repeat FBP in 4-6 weeks and consider haematinics
- Safety net advice re febrile neutropenia

- Currently refer General Paeds unless red flag symptoms
- Virology (HIV/CMV/EBV/Parvo)
- Granulocyte immunology



Place labelled specimen in bag, remove protective strip, fold flap onto bag and seal firmly.

3E HISTOCOMPATIBILITY & IMMUNOGENETICS
Granulocyte Immunology
NHS Blood and Transplant

IMPORTANT: Please ensure that the three points of identification used on this form and all samples match. Please use BLOCK CAPITALS to complete. See reverse of forms for sample labelling criteria.

Essential information included in this box must be completed, or the sample may not be tested.

Patient Details For NAIN cases: A separate form must be completed for each individual
Surname
Forename
NHS/CHI No.
NHS Non-NHS/Private
Mother Father Child
DOB DD/MM/YY
Sample type (if not peripheral blood) .....
Sample date DD/MM/YY

Requester Details
Name of Requester
Department
Hospital Name, Full Address and ODS code† .....
.....
.....
Purchase Order No. (if applicable) .....
Signature .....

I acknowledge that by making this referral, I am agreeing to NHSBT's terms and conditions, subject to NHSBT's acceptance of the contents of this request form.*

Sample time (time taken) :
Hospital number
Alternative ID
Male Female
Ethnicity (please indicate if not provided).....
Full address and postcode .....
.....

Name of Consultant
Contact No.
Additional copy of report(s) to: .....
.....
Billing Name/address (if different from above) .....
.....

Diagnosis/Treatment/Test Reason/Relevant Clinical Information

URGENT INVESTIGATIONS – Telephone the laboratory before sending any samples.
Send **ALL** samples at ambient temperature. Tick box(es) of test(s) required and supply relevant information as required.

☐ **Neonatal Alloimmune Neutropenia (NAIN):**
Date of delivery/EDD DD/MM/YY
Length of gestation ...../40 weeks DD/MM/YY
Neonatal neutrophil count x10⁹/l
Maternal neutrophil count x10⁹/l
Mother's name .....
DOB DD/MM/YY
NHS/Hospital No .....

☐ **Infant Autoimmune Neutropenia**
Neutrophil count x10⁹/l
If > 2.0x10⁹/l give reason for testing.....

☐ **HNA investigation for renal transplantation**

☐ **Adult Autoimmune Neutropenia:**
Neutrophil count x10⁹/l
If > 2.0x10⁹/l give reason for testing .....
Indicate if Primary/Secondary .....
Diagnosis.....

☐ **Drug-Induced Antibody-Mediated Neutropenia**
Sample(s) of the drug(s) must be sent with the specimen
Please discuss ALL cases with the laboratory prior to taking samples.
Neutrophil count x10⁹/l
Date drug started DD/MM/YY
Drug name(s) .....

NHSBT use only
ISBT 128 label (Molecular)
ISBT 128 label (Serological)
Number of each sample received ☐ EDTA ☐ Clotted (Serum) ☐ Other
Comments:
Signature
Date Received

FRM10014.2

Page 1

[H&I test request forms - Hospitals and Science - NHSBT (blood.co.uk)]

- Form 3E Granulocyte immunology

Autoimmune neutropenia

- High rate of spontaneous remission
- Generally “benign”
- If significant infections rethink
- If febrile needs assessment and consideration given to IV abx
- Open access is helpful

When should I refer/contact haematology?

- Persistent > 6 months and no antineutrophil antibodies found
  - Or antineutrophil antibodies but significant infections/other concerns
- Discussion of severe neutropenia (< 0.5)
- Other cell lines affected
- Concerning history (infection etc)
- Other abnormalities (liver, spleen, congenital abnormalities, liver, spleen)
- Other signs of immunodeficiency

Other causes

- Genetic causes
  - Cyclical neutropenia
  - Severe congenital neutropenia
    - ELANE mutation
    - Kostmann syndrome (HAX1)

Case - ELANE/ELA-2 mutation

- Acinetobacter sepsis at birth
- Empyema at 18m – CD and abx
- Recurrent tonsillitis – removed aged 3
- Prolonged gastro illness requiring admission
- Neutropenia but can mount a response to infection
- Brother and mum carry same mutation
- Potential rx with GCSF but MDS/AML risk

Other causes

- Immunodeficiency syndromes
  - Wiskott Aldrich
  - WHIM syndrome
  - GATA2
  - DiGeorge/22q
  - Cartilage hair hypoplasia

Case – GATA2

- 7yo boy peri-orbital cellulitis , Hb 90 WCC 4.5 plts 100 neuts 0.2
- Transformed to high risk MDS secondary to GATA2, now 18m post SCT

- 14yo boy with lymphoedema
- GATA2 diagnosed by genetics
- For SCT due to immunodeficiency

- 16yo boy, HR MDS secondary to GATA 2, presented with anaemia
- Post second SCT

Case WHIM syndrome

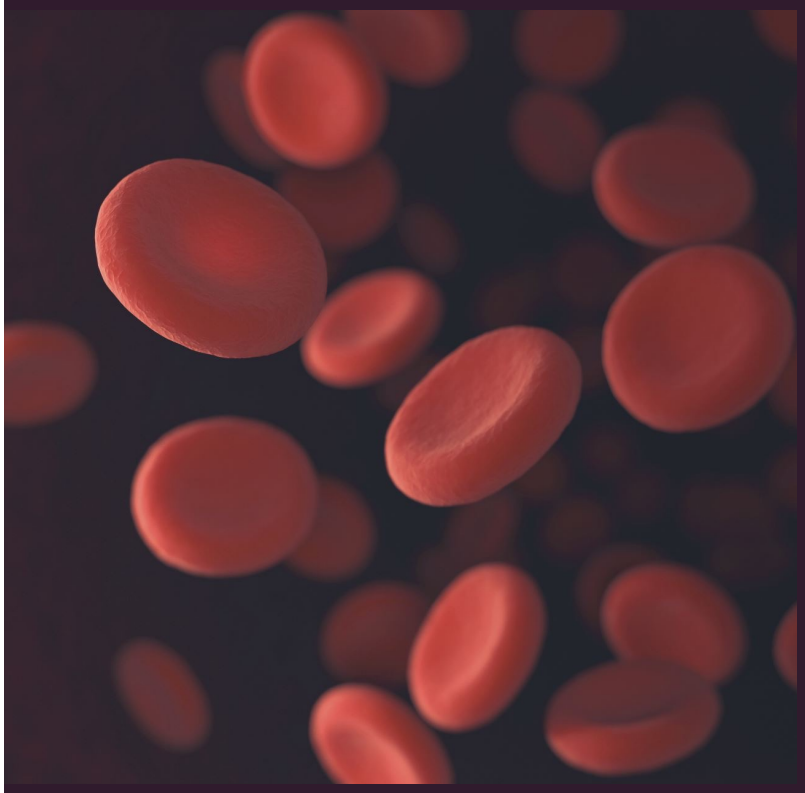
- 5yo girl, recurrent RTI, numerous admissions
- Persistent lymphopenia(0.2) and neutropenia (0.1), hypogammaglobulinaemia
- Heterozygous for pathogenic CXCR4 nonsense variant – WHIM syndrome
- Warts, Hypogammaglobulinaemia, Immunodeficiency, Myelokathexis
- Phenotype varies
- IVIG replacement, co-trimoxazole prophylaxis
- HPV vaccine – no hx of warts so far
- ?SCT

Case – cartilage hair hypoplasia

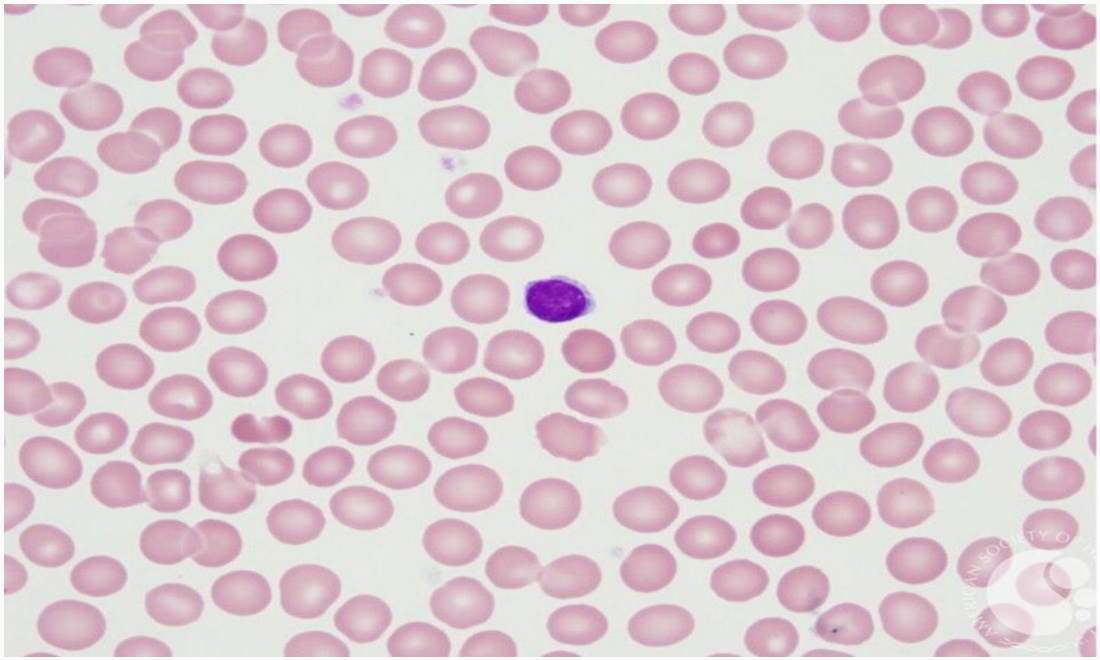
- 3yo girl with recurrent infection and skeletal dysplasia
- Developed autoimmunity – plts and neutrophils
- Now 2 years post SCT

Other causes

- IBMFS
  - Fanconi
  - Schwachman diamond
  - Dyskeratosis congentia
- Metabolic
  - Pearsons
  - Glycogen-storage disorders

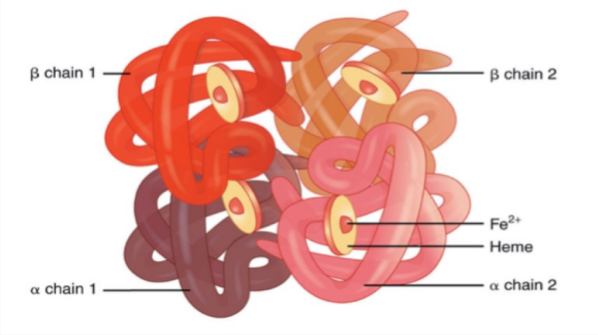


A GENERAL PRACTITIONERS GUIDE TO: ANAEMIA



Haemoglobin

- Ring-shaped ‘Haem’; an iron containing compound
- Most of your body’s iron stores are in the Haem portion of red blood cells (RBCs)
- Attached to ‘Globin’ polypeptide chains
- Most people have HbA (2 Beta globin chains, 2 Alpha globin chains)



Function

- Haemoglobin is the primary O2 carrier in humans (also facilitates transport of ‘waste’ CO2)
- Four binding sites for O2 (each Haem group) in a Hb molecule
- We need O2 delivery to all metabolically active cells in the body
- Impaired O2 carrying capacity in severe anaemia → tissue hypoxia



Anaemia



- Decreased building blocks for RBC production: iron, B12, folate
- Building of RBCs occurs but blueprint is incorrect or inefficient: Thalassaemia or Sickle Cell Disease
- RBC membrane defect results in secondary anaemia, due to decreased ‘life expectancy’: Spherocytosis
- As sequelae of another, non-haematological, process: ‘anaemia of chronic disease’, trauma, GI blood loss etc.

Meet B



- B is 7, Caucasian, and has ASD
- B’s diet consists of crackers, cheese, milk and a single brand of chocolate cookies
- Presents to your afternoon clinic with fatigue + ’frequent napping after school’, increased shortness of breath on exertion
- Soft systolic murmur on exam, pale
- Lengthy history; mum reports ‘has looked pale for months’
- Reasonable to check a CBC, at minimum

Blood Results

- Hb: 54 g/L
- MCV: 52 fL (74-91)
- MCH: 22 pg (25-29)
- RBC: 3.6×10^{12}/L
- WBC: 7×10^{9}/L
- Platelets: 1000×10^{9}/L
- (Total Bili: 6 umol/L)
- (LDH: Normal)

- Caucasian patient
- Consistent clinical history → please ask about haemoglobinopathy in the family
- CBC as shown
- **Diagnosis could almost be made from CBC alone, an iron profile + reticulocyte count is a reasonable next step**
- Microcytic (MCV) < normal parameters (microcytic anaemia: thalassaemia vs iron deficiency vs lead poisoning vs anaemia of chronic disease (vs sideroblastic anaemia)
- Hypochromic (MCH) < normal parameters
- Thrombocytosis; no inhibition of platelet production

Mentzer Index

- Take MCV/RBC
- >13 IDA likely
- <13 could still be IDA but consider other diagnoses (Thalassaemia)

- In IDA, RBC is low due to decreased production and MCV is low
- In Thalassaemia, RBC is normal/elevated as RBC production is not deficient but defective, MCV remains low
- For Thal trait patients, there can be concurrent IDA—it may be helpful to treat these patients with iron supplementation if iron deficiency proven. Not so for Thalassaemia major patients, as they have a much lower Hb and are often transfusion dependent and prone to iron overload.

Iron profile + reticulocytes

- **Ferritin** — **low**
- **Serum Iron** — **low**
- **Transferrin** — **Often elevated**
- **Transferrin Saturation** — **low (<20%)**

(serum iron divided by 2 x transferrin will give you % saturation)

- **TIBC** — **high**

- **Reticulocytes** — **Often normal/low**

When should B have Hb electrophoresis?

- Family History
- African, Mediterranean, Middle East, South-East Asia origin
- Findings on blood film; basophilic stippling, poikilocytosis, nucleated RBCs etc that suggest more significant pathology than IDA

- Thal trait patients are usually well with a normal/slightly low Hb and degree of microcytosis. There is no need for chronic transfusion program or Haematology follow-up
- Thal major patients require regular Haematology input; unless recent migrant to NI, many (but not all) of these patients should be identified via newborn screening

	Genotype	HbA	HbA2	HbF
Unaffected	Beta/Beta	97%	2%	1%
Beta-thalassemia minor	Beta(0)/Beta Beta(+)/Beta	Remainder	Variably increased (2-8%)	Variably increased (up to 30%)
Beta-thalassemia major/intermedia	Beta(+)/Beta(+) Beta(0)/Beta(+)	Remainder	Over 2%	30-90%

B Thal Electrophoresis; for alpha Thalassaemia a low MCH may be the only indicator & molecular testing is required.

Quick note:

4 genes controlling synthesis of alpha globin chains

Carrier→Trait→HbH→Hb Bart's

Hb Bart's patients are severely unwell; foetal hydrops

2 genes controlling synthesis of Beta globin chains

Trait→ Intermedia vs Major

What to do with B?

- Iron supplementation: 2-3mg/kg/day elemental iron BUT up to 6mg/kg/day is reasonable in severe deficiency
- Any preparation is acceptable
- One dose per day
- Take with orange juice-high in vitamin C and encourages absorption
- Stop high milk consumption or, at least, do not take iron concurrently (casein inhibits gut absorption of iron)
- These children need support to aid compliance
- Dietitian



Should I transfuse PRBCs?

Paediatr Child Health. 2023 Feb; 28(1): 30–36.
Published online 2022 Oct 28. doi: 10.1093/pch/pxac095
PMCID: PMC9971582
PMID: 36865758

Severe iron deficiency anemia in the paediatric emergency department: A retrospective study

Matthew Speckert, MD, Lana Ramic, BScH, Nicholas Mitsakakis, PhD, Vid Bijelić, MSc, Mira Liebman, MD, and Elaine Leung, MD

- 57 patients with severe IDA Hb <70 g/L; median Hb was 51 g/L
- Most managed with oral iron (95%)
- 13 (23%) also received iron sucrose—IV iron, at 14/7 these patients had the same Hb levels as transfused patients. No severe reactions to IV iron.
- 16 (28%) received PRBCs-3 mild reactions, 1 TACO (25%)
- No return visits to ED within 30 days

What if Bob had a high MCV?

- Macrocytic anaemia is unusual in children:
- B12/folate deficiency
- Hypothyroidism
- Liver disease
- Bone marrow failure syndromes

- Avoid sending B12/Folate, routinely, on children without an elevated MCV

Take Home Messages:

- We are always happy to discuss difficult cases!
- Consider the most likely differential and complete a relevant work-up
- Most children that attend hospital with anaemia have a nutritional deficiency and/or anaemia secondary to other co-morbidities
- Not all children with IDA need paediatric input but, those who do not respond to supplementation and/or with an atypical presentation, do

Lymphadenopathy (and how do I avoid missing a blood cancer)

-Up to 50% of children develop lymphadenopathy at some point

Most reactive in nature

-If overlying erythema / fever → suspect infective aetiology (lymphadenitis), this might require IV antibiotics but, if mild, could attempt PO first with short-interval review

Worry about:

Persistent lymph nodes > 1 cm diameter (>2 cm cervical)

Characteristics of lymphadenopathy

- Location
- Duration
- Pain
- Redness

Associated symptoms

- Fatigue
- Weight loss
- Fever
- Bleeding or easy bruising
- Joint pain or swelling
- Rash
- Pallor (looking very pale)
- Cough or shortness of breath

Recent infections

- Upper respiratory tract infection
- Dental infections
- Skin infections
- Sexually transmitted infections

Other

- Foreign travel
- Exposure to TB (contact/travel)
- Immunisations and medications

Red Flags

- Respiratory compromise; cannot lie flat, exertional dyspnoea over minimal distance, new wheeze in an older child
- Night sweats (drenching, change of bed clothes)
- Weight loss
- Pallor, bruising / bleeding, fatigue
- Persistent fever >38

Who should be referred to the on-call paediatrician?

Children with red flag symptoms

Cervical LN >2 cm; particularly if increasing in size and/or persistent for > 7 days

Unexplained non-cervical lymphadenopathy > 1 cm (special note that supraclavicular LNs are almost always pathological and axillary LNs are unusual in children)

Best reviewed, in the first instance, via Rapid Access Clinic and then discussed with Haematology

Easy bruising, epistaxis

Easy Bruising



- Difficult presenting sign
- Can be very subjective
- Consider NAI
- Can be non-haematological
  - Connective tissue
  - Vasculitis/Dermatology

Epistaxis



- Common
- Can be a sign of bleeding disorder – generally frequent, profuse, drop Hb, iron deficiency
- Can be hayfever related – consider antihistamines, vaseline/naseptin, nasal sprays
- Nose picking!
- ENT

Menorrhagia

- Can be a real problem in young women with bleeding disorders
- Not all menorrhagia is in the context of a bleeding disorder
- Management
  - Mainly hormonal manipulation with some
  - Adjunctive haemostatic medications
  - Iron
- Extremely challenging
  - Haematology
  - Gynaecology
  - MDT including psychology



Investigations

- History – family history, bleeding pattern, bleeding challenges
- In General Practice reasonable to do FBP and baseline coag screen
- In Hospital setting could also consider first line investigations such as FVIII, FIX, VWF and blood group

Potential bleeding disorders

- Haemophilia A and Haemophilia B
  - FVIII/FIX deficiency
  - Joint and muscle bleeds
- Von Willebrands disease
  - Primary haemostatic defect
  - Mucous membrane bleeding
- Others
  - Platelet dysfunction disorders
  - Non-specified bleeding disorders

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Coagulation testing in investigation for possible physical maltreatment

Northern Ireland regional paediatric guidance (haematology)

No laboratory investigations are required in the majority of cases who present with bruising, particularly older children. Consider laboratory investigations when

- There is bruising in a pre-mobile child
- There is an unusual bruising pattern and/or bleeding that is out of proportion to the purported mechanism
- There is bleeding at a critical site (eg intracranial haemorrhage, retinal haemorrhage, gastrointestinal haemorrhage, intraspinal haemorrhage, haemarthrosis) with no correlating history of trauma or other explanation that adequately accounts for the bleeding
- There is suspicion of bleeding disorder from the personal history, family history and/or examination

Important Note: where there are concerns regarding the safety of a child, please consider discussion with the Safeguarding Team

First line haematological investigations

- Full blood count
- Coagulation screen (APTT, PT and fibrinogen)

If results of these tests are normal, and if ongoing clinical concern about the presence of a bleeding disorder see "Second line haematological investigations"" below.

Second line haematological investigations

Please alert and/or discuss with paediatric haematology

These may be performed at the same time as first-line tests if;

a. An inherited bleeding disorder is suspected
b. And/or there is unexplained bleeding at a critical site eg intracranial haemorrhage

- Von Willebrand screen (antigen and activity)
- Factor assays – (II, V, VII, 1-stage and chromogenic FVIII, FIX, FX, FXI and FXIII)
- Platelet flow cytometry (0.5 ml EDTA to BCH flow lab 028 95040913) to test for Glanzmanns and Bernard Soulier platelet function disorders

Practical points regarding samples

- **State on form** **NAI screen and site of bleeding (if applicable)**
  This will ensure sample is processed urgently and plasma stored for future additional tests which may be requested as part of child protection investigation. Please also include as

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much clinical information as possible, including relevant medications and any family history of bleeding disorder

- Ideally two, 2.7 ml blue coagulation bottles (citrate sample) should be sent and a 0.5ml EDTA sample
- **Contact the BCH Coagulation Laboratory at BCH 028 95040910 to alert the lab of the sample and BCH flow lab 028 95040913 to alert them of the platelet flow cytometry test**
- Bloods should be venous NOT arterial as this can affect the results
- Ensure bottle is filled correctly
- Sample must be transported immediately to your local laboratory(can be stored in local lab and transported next morning to BCH coagulation lab)
- Results should be interpreted with reference to paediatric ranges (contact CHU for advice)

Other tests (only on advice of paediatric haematology)

- Platelet nucleotide studies
- Platelet aggregometry (requires 12-20 mls of citrated blood so not often practical)
- Platelet function analyser (PFA) is not recommended unless no access to other platelet tests
- α2 antiplasmin
- PAI-1 deficiency
- Vitamin C level
- PIVKA – Vitamin K deficiency

Reference

Haematological evaluation of bruising and bleeding in children undergoing child protection investigation for possible physical maltreatment: A British Society for Haematology Good Practice paper. Biss et al. British Journal of Haematology 2022;00:1-9

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