Haemophilia 4.03

History of Presenting Illness

USUALLY A YOUNG CHILD

- Presents with bruising
- Complains of bruising easily
- Unstoppable bleeding from insignificant wounds

Mild (50-5% clotting factor) haemophilia presents with:

- Prolonged bleeding from surgery or severe injury
- Rare spontaneous bleeding episodes
- Rare joint pain and stiffness (haemarthrosis)

Moderate (5-1%) haemophilia presents with:

- Prolonged bleeding after minor surgery
- Bleeding following slight injury
- bleeding without injury, approx. once a month

Severe (<1%) haemophilia presents with:

- bleeds occurring spontaneously several times a week
- the development of severe joint problems as a result of repeated haemarthroses

Symptoms of a joint bleed:
- "bubbling" or tingling feeling
- Warmth
- Tightness or Stiffness

Symptoms of an Intracranial Bleed:
- Headache
- Confusion
- Drowsyness

Symptoms among Infants:
- Crying for no obvious cause (??.. don't they all do that??)
- Refusing to use an arm or leg
- Refusing to walk
- Swelling
- Bruising

!! FIND OUT HOW LONG SINCE INJURY!!

List of Differential Diagnoses (DDx)

- **Haemophilia**
- **Thrombocytopenia**
- **Von Willebrands disease**
- **Anticoagulation Medication**
- **Child abuse**
- **Connective tissue disorder**
- **Senile purpura**
- **Immune vasculitis**

50% of child abuse reports are SUBSTANTIATED: do not be afraid to cry wolf

More Pertinent Findings on History and Physical Examination

CHILD ABUSE:
- History of repeated accidents
- Long delay between injury and seeking treatment
- ?Are the injuries compatible with the history?
- ARE THE PARENTS LYING TO YOU??
- Bruises in soft tissue areas?
- Marks of adult fingers?
- Linear bruises, eg. made by some long instrument
- Retinal haemorrhages (suggestive of violent shaking)
- Bilateral orbital haematoma
- Rib fractures

PLATELET DISORDER:
- Mucocutaneous haemorrhages
- Petechiae
- Cutaneous ecchymoses
- Intra and post-operative bleeding

CLOTTING FACTOR DISEASE:
- Deep haemorrhage involving mainly joints
- Palpable ecchymoses
- Delayed post-traumatic and postoperative haemorrhage

Palpable purpura means INFECTIOUS CAUSE or vasculitis- hemostatic purpurae are flat

Tests and Investigations :

PLATELET COUNTS:
<30 = need treatment;
will have sponataneous bleeds
>50 = minor operations are OK
>100 = Normal surgery is OK

FBC :

RBCs, WCCs, platelet count

Blood film

Platelet morphology

(PT) prothrombin test: Factor II, VII, IX and X: EXTRINSIC→ Normal 10-15 secs

Tissue thromboplastin (brain extract) and calcium are added to citrated plasma.
The normal time for clotting is 10-15 secs.
This may be expressed as the international normalized ratio (INR)

(APTT) (Factors VIII, IX, XI, XII,X) INTRINSIC → Normal 25-35secs

Three substances –

- a phospholipid,
- a surface activator
- and calcium

are added to citrated plasma.

Coagulation factor assays for vWF, Factor VIII, Factor IX

Thrombin time

- (Prolongation in abnormality of fibrinogen or inhibition of thrombin by heparin or FDPs)
- Thrombin time is sensitive to a deficiency of fibrinogen or inhibition of thrombin.
- Diluted bovine thrombin is added to citrated plasma at a concentration given a time of 14-16 sec with normal subjects.

XDP – detection D-dimers

(To detect if fibrin has formed and then is degraded)

Platelet function tests

Using fresh citrated platelet-rich plasma;
Using an "aggregometer" to examine the platelet response to clotting agonists
eg **adrenaline, ADP, arachidonic acid**

NOT USUALLY PERFORMED unless all other tests are negative

How is this diagnosis made ?

The factor which is deficient is deduced from the clotting studies.

FBC: Platelets very low? → **Thrombocytopenia; DIC,**

- Suspect thrombocytopenia? → look at bone marrow;
- Marrow shows increased megacaryocytes ?
- Auto-Antibodies to platelets detected by Coombs' test?

→ **Immune Thrombocytopenia Purpura**

Platelets normal in number and morphology= must be clotting factor issue

APTT tests the factors of INTRINSIC pathway, which is relevant to hemophilia A
PT tests the extrinsic pathway

The bleeding time test

roughly reflects vWF function and may be prolonged in vWD.
Specific antibodies are used to detect the von Willeband factor molecule .

The ristocetin co-factor test

measures the agglutination of normal platelets suspended in patient plasma and is diminished in vWD.
Mucosal bleeding and occasional joint bleeds are the hallmark of vWD.

AN X-RAY of the affected joints in haemarthrosis is required to check the integrity of the joint and to check for any traumatic cause to the bleeding

Disease Definition: Haemophilia A

Inherited disorder (abnormality on X chromosome, F VIII gene abnormality) leading to reduced production of Factor VIII protein leading to inadequate coagulation material (Haemophilia A)

Management

transfusion of recombinant Factor VIII
or
transfusion of whole blood (low yield of Factor VIII)
or
transfusion of cryoprecipitate (slightly higher yield of Factor VIII)
Twice daily to be continuously effective (needed in severe disease)

Acute Haemarthrosis: Immobilise and chill (with ice pack)

Long Term: watch for degenerative changes in the joints
Advice to avoid trauma, eg. contact sports

Transfusion guidelines

CLINICAL PRACTICE GUIDELINES

Appropriate Use of Blood Components

- Use of blood components for clinical or laboratory indications not listed here is likely to be inappropriate. Consult the NHMRC/ASBT guidelines (www.nhmrc.gov.au) for further details.
- Clinical and laboratory indications for use should be documented.

Red blood cells

Hb*	Considerations
<70g/L	Lower thresholds may be acceptable in patients without symptoms and/or where specific therapy is available.
70-100g/L	Likely to be appropriate during surgery associated with major blood loss or if there are signs or symptoms of impaired oxygen transport.
>80g/L	May be appropriate to control anaemia-related symptoms in a patient on a chronic transfusion regimen or during marrow suppresive therapy.
>100g/L	Not likely to be appropriate unless there are specific indications.

* Hb should not be the sole deciding factor. Consider also patient factors, signs and symptoms of hypoxia, ongoing blood loss and the risk to the patient of anaemia.

Platelets

Use of platelets is likely to be **appropriate as prophylaxis:**

Indication	Considerations
Bone marrow failure	At a platelet count of $<10x10^9$/L in the absence of risk factors and $<20x10^9$/L in the presence of risk factors (eg fever, antibiotics, evidence of systemic haemostatic failure).
Surgery/ invasive procedure	To maintain platelet count at $>50x10^9$/L. For surgical procedures with high risk of bleeding (eg ocular or neurosurgery) it may be appropriate to maintain at $100x10^9$/L.
Platelet function disorders	May be appropriate in inherited or acquired disorders, depending on clinical features and setting. In this situation, platelet count is not a reliable indicator.

Platelets

Use of platelets is likely to be **appropriate as therapy:**

Indication	Considerations
Bleeding	May be appropriate in any patient in whom thrombocytopenia is considered a major contributory factor.
Massive haemorrhage/ transfusion	Use should be confined to patients with thrombocytopenia and/or functional abnormalities who have significant bleeding from this cause. May be appropriate when the platelet count is $<50x10^9$/L ($<100x10^9$/L in the presence of diffuse microvascular bleeding).

Fresh frozen plasma

Use of fresh frozen plasma is likely to be **appropriate:**

Indication	Considerations
Single factor deficiencies	Use specific factors if available.
Warafin effect	In the presence of life-threatening bleeding. Use in addition to vitamin-K-dependent concentrates.
Acute DIC	Indicated where there is bleeding and abnormal coagulation. Not indicated for chronic DIC.
TTP	Accepted treatment.
Coagulation inhibitor deficiencies	May be appropriate in patients undergoing high-risk procedures. Use specific factors if available.
Following massive transfusion or cardiac bypass	May be appropriate in the presence of bleeding and abnormal coagulation.
Liver disease	May be appropriate in the presence of bleeding and abnormal coagulation.

Cryoprecipiate

Use of cryoprecipiate is likely to be **appropriate:**

Indication	Considerations
Fibrinogen deficiency	May be appropriate where there is clinical bleeding, an invasive procedure, trauma or DIC.

Abbreviations: Hb = haemoglobin; DIC = disseminated intravascular coagulation; TTP = thrombotic thrombocytopenic purpura.

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Epidemiology

- **1:5,000 to 1:10,000 males affected (hemophilia A)**
- Hemophilia B has incidence roughly 1/10th of Hemophilia A
- VWF abnormailities can be detected in approx. 8000 people per million

Genetics

What genetic tests are available for carrier and prenatal testing. When should they be offered?

Carrier females may be identified with reasonable confidence if their factor VIII activity is only half that expected from the level of vWF. However, the normal range of factor VIII is broad and random X chromosome inactivation makes it difficult to exclude the carrier state in many females in affected families. Carrier status is better determined with DNA probes. Restriction Fragment Length Polymorphisms(**RFLP**) within or close to the factor III gene allow mutant allele to be tracked. Known mutations to Factor VIII gene can also be probed directly using DNA probes.

the key features of X-linked recessive inheritance are:

- **the disorder affects principally males;**
- **the gene is virtually never directly passed on from father to son, but is transmitted by a father to all of his daughters;**
- **a carrier female's son has a 50% risk of inheriting the defective gene;**
- **when more than one male is affected in an extended family, the defective gene has been transmitted through females;**
- **heterozygous females are usually unaffected, but occasionally manifest the disease with variable severity**

Daughters and sons of a carrier female have 50% risk of being carriers; but the sons will be affected by the disorder.

Prenatal testing

Chorionic villus sampling from 8-10 weeks can also be detected for mutations through PCR and DNA probes or RFLP.

Ultrasound needle aspiration at weeks 18-20 from the umbilical vein can also provide levels of factor VIII in fetal blood. This antenatal diagnosis is used to provide information to couples wishing to terminate the pregnancy if the fetus is positive for haemophilia.

PLATELETS adhere to collagen
Via VON WILLEBRAND's FACTOR
!! platelet receptor =
GLYCOPROTEIN Ia/IIa [integrin]

DAMAGE TO ENDOTHELIUM
- EXPOSES COLLAGEN

FIBRONECTIN
Is multifunction adhesive glycoprotein
Attaches cells to a variety of matrices
Binds with one end to collagen or fibrin,
and with the other to a suitable receptor

ADHERED PLATELETS
SHAPE-SHIFT [grow pseudopods, thus INCREASE SURFACE AREA]
and **DEGRANULATE:**
FROM α-granules:
- **Fibronectin**
- **Von Willebrands Factor**
- Fibrinogen
- Factor V

→ **Participate in clotting cascade**

- Platelet-Derived Growth factor (**PDGF**)
- Transforming Growth Factor β (**TGF- β**)

PDGF + TGF- β stimulate growth and migration of **FIBROBLASTS** and **SMOOTH MUSCLE CELLS**

TGF- β also stimulates collagen and fibronectin synthesis by fibroblasts

FROM δ-granules (dense body):
- **HISTAMINE**
- **SEROTONIN**
- **THROMBOXANE A2 (TXA_2)**
- **ADRENALINE (Vasoconstrictor)**
- Adenosine Diphosphate (**ADP**)
- **CALCIUM IONS** which are needed for everything in hemostasis

HISTAMINE AND SEROTONIN are preformed **VASOACTIVE AMINES:**
- Dilate arterioles
- Increase vascular permeability of venules
- **CONSTRICT large arteries**
- **Act via H_1 receptors**

ADHERED PLATELETS ALSO
FLIP MEMBRANE SURFACE:
- **THUS negatively charged phospholipids** are now exposed, facilitating tenase and prothrombinase complex attachment
- **PLUS factor receptors now point OUTWARDS**

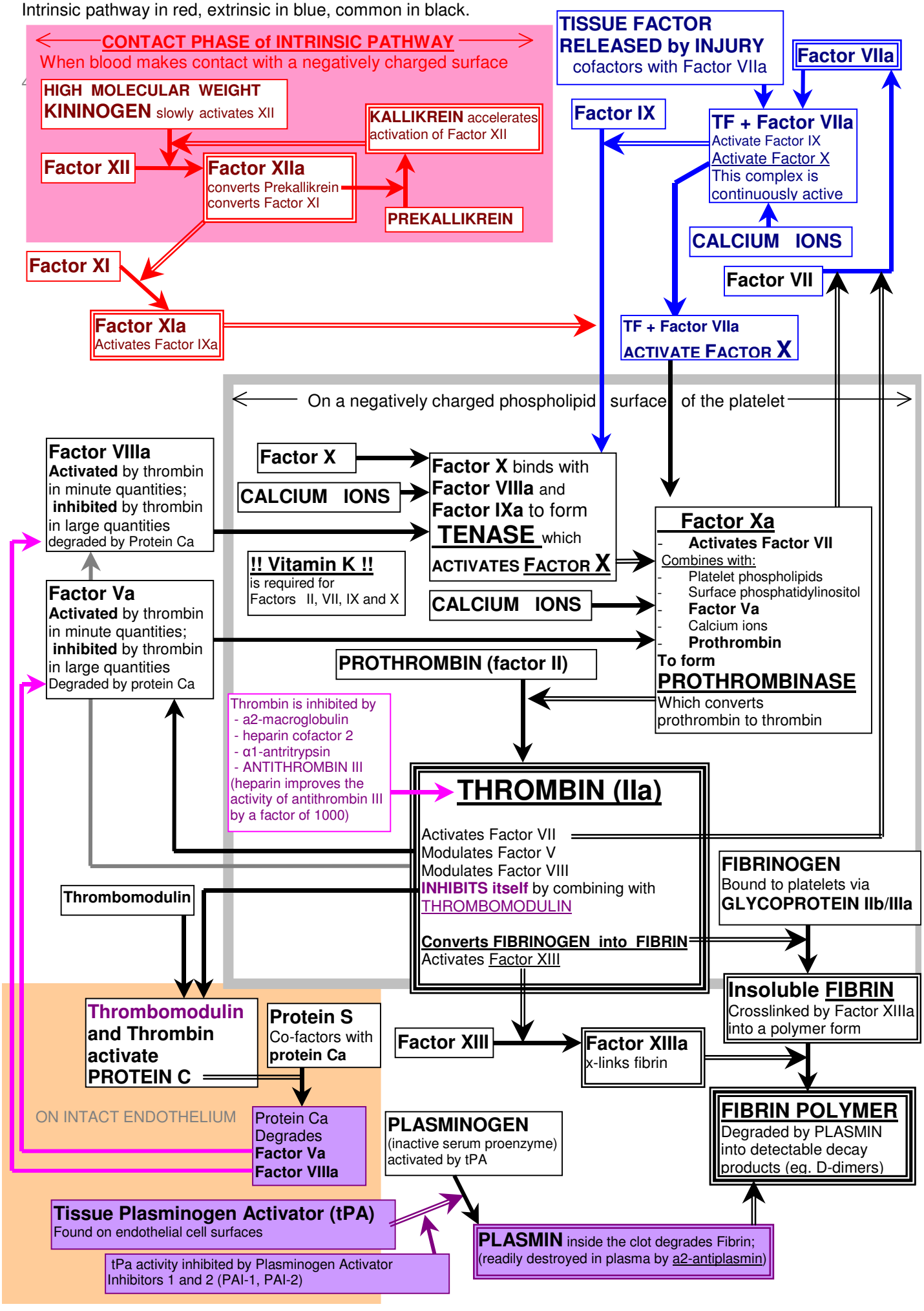
ADP binds purinergic receptors on platelets;
When activated, these change conformation of the **GLYCOPROTEIN IIb/IIIa** so that it **NOW BINDS FIBRINOGEN**
THUS:
platelets adhere to each other via fibrinogen bridges

THROMBOXANE A2
Is an arachidonic acid product, generated by CYCLOOXYGENASE
-CAUSES **VASOCONSTRICTION** and **PLATELET AGGREGATION**

! To coagulate 100 ml of blood you need
- **0.2 mg of Factor VIII,**
- **2mg of Factor X,**
- **15mg of Prothrombin**
- **250 mg of Fibrinogen**

SECONDARY HEMOSTASIS: within minutes to hours [←by Alex→] 4.03

Intrinsic pathway in red, extrinsic in blue, common in black.



Basic Sciences and Comparitive Diseases

risks of transfusions

Haemolytic reactions due to incompatible red cells.

Symptoms may appear from a few minutes to several hours

→ involves the action of the antiA or antiB which bring about complemewnt-mediated lysis

Clinical signs include

- Restlessness
- Fever
- Chills
- anxiety,
- flushing of the face,
- vomiting
- diarrhoea.
- Immediate treatment is diuresis with frusemide.
- Mortality from ABO incompatibility is about 10%.

Pyrexia due to pyrogens and leucocyte antibodies.

- This consists of chills and fever starting 30-60 mins after the onset of the transfusion.
- These febrile reactions are now rare.

Immediate type hypersensitivity to IgA present in donor's blood

- (Severe reactions infrequent 1: 20000)

Bacterial contamination

Circulatory overload by too rapid transfusion of blood, especially in elderly.

- **Restriction of transfusion to 1ml/kgbody weight/hour.**

Citrate toxicity occurs if large volumes of stored blood have to be given very rapidly.

- It is due to the reduction in ionized calcium in the patient's plasma.
- Signs are **gross skeletal muscle tremors and prolongation of QT interval**.
- Parasthesia around lips may also occur

Emerging Infectious Diseases

Examples include

- new HIV variants;
- new hepatitis agents;
- human herpes virus type 8;
- Creutzfeld-Jakob Disease;
- human parvovirus B19;
- MRSA contamination of blood products.

Risk of acquiring a blood-borne infection increases with every exposure,

… and hemophilia patients treated with cryoprecipitate or fresh-frozen plasma (FFP) are exposed to hundreds or thousands of donors during their lifetime.

a person with hemophilia who receives monthly infusions of cryoprecipitate prepared from the plasma of 15 donors over a lifetime of treatment (60 years) is at significant risk of being exposed to HIV.

In the United States the risk was 2% and in Venezuela it was 40%.

Major risk of transfusion remains non viral. They include urticaria, febrile non haemolytic reaction, DHTR, GVHD, wrong unit, bacterial contamination, anaphylaxis and acute haemolytic transfusion reactions

the screening of donors

- Eligibility
- People who are:
- Healthy, not suffering form a cold, flu, or other illnesses at time of donation
- Aged between 16-70
- Weigh more than 45kg
- Not pregnant
- Not on certain medications including antibiotics

Screening questions limiting blood donation

- Any donor who has had recent major dental work
- No alcohol within last 8h
- No tattoos within 12 mths
- No flu within last 2 wks.
- Travel to malarial prone countries within last 3yrs and last year has to been analysed more carefully for malaria

Blood donation

- 1 Unit contains 450mls of blood from donor
- 1 unit of blood can be taken from donor every 10wks – normal blood collection
- 1 unit of plasma can be taken from donor every 2 wks – apheresis

Red cell transfusions are used during massive blood loss from trauma.

Blood groups

ABO blood grouping

Group A blood – contains anti-B in plasma
Group B blood – contains anti-A in plasma
Group O blood – contains anti-A and anti-B

Rh blood grouping

Postive – antigen D present
Negative – antigen D absent

Rh –ve blood is not always available for Rh –ve recipients.
Rh –ve males may receive Rh +ve blood if care is taken to search for anti D if subsequent transfusion of Rh +ve blood is given.
Rh –ve females past menopause is less safe because there is always the possibility that they may have received a primary stimulus with D antigen from an Rh+ve fetus and the anti D in the plasma may be below a detectable level.
Transfusion of Rh +ve would then lead to a delayed transfusion reaction. Rh+ve blood must never been given to Rh-ve women of childbearing age for fear of stimulating anti D production.

Behavioural science

CHILD ABUSE:

The **most accurate ways to tell** if abuse is happening are:

- if a child or friend tells you it is happening,
- if you are present when the abuse occurs
- if you see injuries that concern you and do not have a believable explanation.

Some warning signs that a child might be neglected or abused are:

Physical-

- unexplained and frequent bruises or injuries e.g.
- burns,
- broken bones,
- bruises in soft tissue areas uncommon for normal activities,
- raised intracranial pressure
- retinal haemorrhages from shaking

Emotional-

- the child seems sad most of the time,
- has difficulty making friends
- has difficult behaviour e.g. aggressive

Neglect-

- inappropriate dress for the weather,
- begging or stealing food,
- poor health,
- dirty clothes and unwashed body and hair,
- left alone for long periods of time,
- misses a lot of school

Sexual-

- knows more about sex than appropriate for the age,
- sexual behaviour beyond their years,
- physical signs of sexual practice,
- depression or suicidal tendencies,
- fear of having a nappy changes or being bathed,
- sudden avoidance of familiar adults or places,
- drug and alcohol use

The effects of child abuse depend on a number of risk factors that include:

- age: babies, infants and severely disabled are more vulnerable to abuse
- frequency: the more frequent and severely abused suffer more damage
- relationships with adults: parents who abuse their children damage the child more severely as the child has no support or comfort
- community response: if the family is isolated, the community ignores the abuse or does not speak out against the abuse then there is an increased risk for the child

A link has been found between childhood abuse and neglect and future criminal behaviour. A study in Victoria has shown that 63% of inmates had some form of child abuse. A history of child abuse has been linked to arrests for juvenile crimes, adult crimes and crimes of a more violent nature.

Sexual abuse has been linked to an increase in mental health problems with a reported increase in

- depression,
- anxiety,
- drug and alcohol abuse,
- eating disorders
- post traumatic stress disorders

WHAT TO DO ABOUT CHILD ABUSE

Initially **discuss with a senior staff member** and seek further advice as medical staff are required to report suspected abuse.

Be available to listen to the child and to what they say.

Talking to the child protection services may help stop any further abuse from occurring.

Anonymous reporting via the governments child protection service can occur in each state.
ACT- Family services: 02 6207 1069
NSW- Child protection and family crisis service: 1800 066 777
NT- Crisis line: 1800 019 116
QLD- Dept of families: 07 3235 9999 or 1800 177 135 for non metro callers
SA- Child abuse report line: 13 14 78
Tasmania- Child and family services line: 1800 001 219
Vic- Child protection crisis line: 13 12 78
WA- 08 9223 1111 metro Perth or 1800 199 008 for callers outside Perth

Children can make reports via: www.kidshelp.com.au or phone 1800 551 800
Adults can pledge to stop child abuse: www.stopit.com.au
National child protection week is on from the 7-13 September 2003

How common is child abuse?

In Australia in 2001/02 there were 137,938 reports of child abuse which works out to be one child abused every 4 minutes. The types of abuse reported were: 29% neglect, 27% emotional abuse, 26% physical abuse and 13% sexual abuse.

The abuse of a child occurs in 81% cases by someone the child knows and in 63% of cases by a biological parent.

The number of notifications of abuse rose by 29% from 1999-2002 and the number of substantiated reports rose by 23%. In 1997 there were 15,718 care and protection orders given but in June 2003 there were 20,557. The out of home care has risen to 18,880 in June 2002 when in 1997 it was 14,078.

Indigenous children are 6- 8 times more likely to be on care and protection orders than non-indigenous children. In a recent ABC report (12th Sept 2003) it was reported that nearly 200 children between 4-14yrs of age were diagnosed last year with STD's. These children were abused mostly by older indigenous men.

In June 2002 4.3 children (0-17 yr olds) per 1000 were on care and protection orders and 3.9 per 1000 were in out of home care.

Only 36% of notifications in Victoria are investigated even though the figures indicate abuse and neglect has risen 40% in the past 10 years. The lack of investigation is due to lack of funds to provide adequate resources to investigate the claims of abuse. Most abuse stems from drug and alcohol abuse, domestic violence, mental illness, family isolation and unemployment.