# BLOOD TRANSFUSION

- ***Indications for Transfusion***

1. increase the $O_2$ carrying capacity of blood → ↑ $DO_2$
2. increase circulating blood volume, when $DO_2$ is low

***NB:*** Hct at which transfusion indicated is ***age & disease*** dependent, otherwise healthy patients rarely require transfusion at Hct > 30%, whereas transfusion is usually required at Hct < 21% (RDM)

- ***Compatibility Testing***

1. ABO-Rh typing
   - i. **rbc's** tested with commercial anti-A, anti-B and anti-D (***direct Coomb's***)
   - ii. **serum** tested against A-rbc's and B-rbc's (***indirect Coomb's***)
   - iii. ABO: O ~ 45%; A ~ 41%; B ~ 10%; AB ~ 4%
   - iv. Rh(D): positive ~ 85%; negative ~ 15% ~ 60-70% ***anti-D-positive***
2. antibody screening
   - i. trial transfusion between ***recipient serum*** and commercially supplied rbc's
     - looking for commonly occurring rbc antigens other than ABO-Rh
     - same 3 phases and similar length to cross-match
   - ii. also performed on the ***donor serum*** shortly after collection
     - primarily preventing reactions with subsequently transfused units
3. cross-matching
   - trial transfusion between ***donor rbc's*** and ***recipient serum***
   - i. ***immediate phase***
     - donor rbc's mixed with recipient serum
     - conducted at room temperature, complete in ~ 5 minutes
     - detects ***ABO***, plus MN, P, and Lewis incompatibilities
   - ii. ***incubation phase***
     - incubation of first phase reactions at 37°C in albumin for 30-45 minutes, then in low ionic strength saline for 10-20 minutes
     - promotes aggregation of surface Ag, and reduction in surface (-)'ve charge
     - aids detection of ***incomplete antibodies***, especially ***rhesus***, by the 3rd phase,
   - iii. ***antiglobulin phase***
     - polyvalent ***antihuman antiglobulin*** reacts with incomplete antibodies
     - detects most of Rh, Kell, Kidd and Duffy

- ***Effectiveness of Matching***

| | | | |
|---|---|---|---|
| 1. | ABO-Rh typing | ~ 99.8% compatible | 1:500-1000 |
| 2. | + antibody screening | ~ 99.94% compatible | 1:1700 |
| 3. | + cross-matching | ~ 99.95% compatible | 1:2000 |

- ***Emergency Transfusion***

1. type O Rh-negative blood
   - universal donor, uncrossmatched blood
   - some type O donors produce high titres of anti-A,B immunoglobulins

     → ***packed cells*** better than whole blood
   - transfusion of > 2 units of whole type O requires continued use until the blood bank determines levels of anti-A/B have declined (theoretically !)
   - continued use of type O results in minor haemolysis & hyperbilirubinaemia
2. type specific, partially cross-matched blood
   - ABO-Rh typing plus immediate phase X-match ~ 5-10 minutes
   - only **1:1000** patients has an unexpected Ab found in full X-match
   - greater risk in previously transfused patients ~ 1:100 unexpected Ab

## Effects of Blood Storage

- ***Citrate Phosphate Dextrose + Adenine***

a. Citrate - prevents clotting by binding $Ca^{++}$

b. Phosphate - pH ~ 5.5, acts as a buffer against the large fall in $[H^+]$ at 1-6°C
   ? also may increase 2,3-DPG levels

c. Dextrose - allows continued glycolysis & maintenance of ATP

d. Adenine - improves rbc survival by adding substrate for ATP synthesis
   - increases survival from ***21*** ® ***35 days***

***NB:*** duration of storage set by requirement for ³ **70%** rbc survival 24 hours post-$T_X$
storage at 1-6°C slows the rate of glycolysis by ~ 40x

| | | | |
|---|---|---|---|
| i. | whole blood | ~ 430 ml blood & 70 ml preservative | Hct ~ 40% |
| ii. | packed cells | ~ 230 ml blood & 70 ml preservative | Hct ~ 70% |

1. metabolic effects
   - ↓ glucose / dextrose / ATP / 2,3-DPG, and ↑ lactate
   - ↑ $P_{aCO2}$, ↓ pH, ↓ $HCO_3^-$
   - ↓ $Na^+$ / ↑ $K^+$
   - oxidant damage to membranes with ***spherocyte*** formation
   - ↓ 2,3-DPG → ↑ $O_2$ affinity
   - changes occur earlier & to greater extent in whole blood cf. packed cells
2. microaggregates
   - conventional filters remove particles > **170 µm**
   - aggregates of platelets/fibrin/leukocytes range from 20 to > 170 µm
   - clinical significance of microaggregates debated
   - most would no longer use a micropore filter
   - ***no change*** in the incidence of ARDS

## ***Frozen Storage***

- rbc's stored with ***glycerol*** at -79°C survive well
- all glycerol must be removed prior to use & this is difficult and expensive

1. long-term storage of rare blood types
2. safer in patients susceptible to allergic reactions
   - freezing & washing process decreases ***HLA antigens***
3. reduced risk of hepatitis infection ? since questioned
4. low levels of leukocyte & fibrin aggregates safer for massive transfusion
5. normal levels of 2,3-DPG retained, therefore better $O_2$ capacity

## ***Adsol***

- shelf-life extended to 42 days
- contains adenine, glucose, mannitol, and NaCl

## ***Heparin***

- used for priming CPB pumps etc.
- anticoagulant, not preservative as lacks glucose
- antocoagulant effect decreases with time due to liberation of thrombogenic substances from the cellular elements during storage, therefore must be used within 24-48 hours

## ***Classification***

1. ultrafresh < 24 hours
2. fresh < 7 days
3. stored > 7-35 days

## Complications

- ***Hazards of Rapid or Massive Transfusion***

1. impaired $O_2$ transport
   i. defective rbc function
   ii. impaired Hb function
   iii. fluid overload / underload
   iv. DIC
   v. ARDS
   vi. MOSF
   vii. microaggregates
2. haemostatic failure
   i. dilution
   ii. depletion / consumption
   iii. decreased production
   iv. DIC
3. electrolyte & metabolic disturbance
   i. hyperkalaemia / delayed hypokalaemia
   ii. sodium overload
   iii. acid-base disturbances
   iv. citrate toxicity
   v. hypothermia
4. vasoactive reactions
   i. kinin activation
   ii. damaged platelets & granulocytes
5. serological incompatibility
   i. immediate generalised reaction
   ii. delayed transfusion reaction
6. impaired reticuloendothelial function

***NB:*** the majority are related to the type and time of storage
***massive transfusion*** ≥ 1 times the patients blood volume

?? over what time-frame → 1BV per 24 hours
½BV per 2 hours

## ■ ***Oxygen Transport***

• $HbO_2$ dissociation ∝ pH, Temp., $P_{aCO2}$ and 2,3-DPG

1. ***citrate*** is metabolised to $HCO_3^-$ → ***L***-shift
   - WB & FFP have the greatest effect
2. hypothermia → ***L***-shift
3. stored blood deficient in ***2,3-DPG*** → ***L***-shift
4. $CO_2$ / $H^+$ load → ***R***-shift

• good correlation between decrease in rbc 2,3-DPG and $\mathbf{P_{50}}$ after 7 days storage,

i. 2,3-DPG 4.8 µmol/l → 1.2 µmol/l

ii. $P_{50}$ 26.5 mmHg → **18 mmHg**

***NB:*** specific organ hypoxia ***has not*** been demonstrated from low $P_{50}$ transfusion, washed rbc's depleted of 2,3-DPG given to patients with anaemic hypoxia, showed no change in mixed venous $P_{vO2}$ or cardiac output

• recommendations,

1. warm all blood products
2. avoid $HCO_3^-$ administration
3. attempt to use fresh blood in hypoxic, low CO patients
4. use frozen blood if available

• ***microaggregates*** progressively accumulate with storage & potentially decrease gas exchange
• reduced$^{++}$ with micropore filters, however, incidence of ARDS is ***unaffected***

## ■ ***Transfusion Coagulopathy***

***NB:*** most important factors are ***volume of transfusion & duration of hypotension***

***differential diagnosis***,

1. dilutional thrombocytopenia
2. low factor V & VIII activity
3. DIC
4. haemolytic transfusion reaction
5. preexisting coagulopathy
   i. haemophilia, von Willebrand's
   ii. anticoagulant therapy
   iii. aspirin, NSAID's

## ▪ ***Dilutional Thrombocytopenia***

- total platelet activity in stored whole blood ~ 60-70% after 6 hrs
  ~ 5-10% after 48 hrs
- effects of dilution depend upon,
  1. initial platelet count
  2. risk of haemorrhage depends upon acute versus chronic,
     i. acute loss < 50,000-75,000
     ii. chronic disease < 10,000-15,000
  3. volume transfused ~ 2 BV's in children
     - thrombocytopathy with massive transfusion

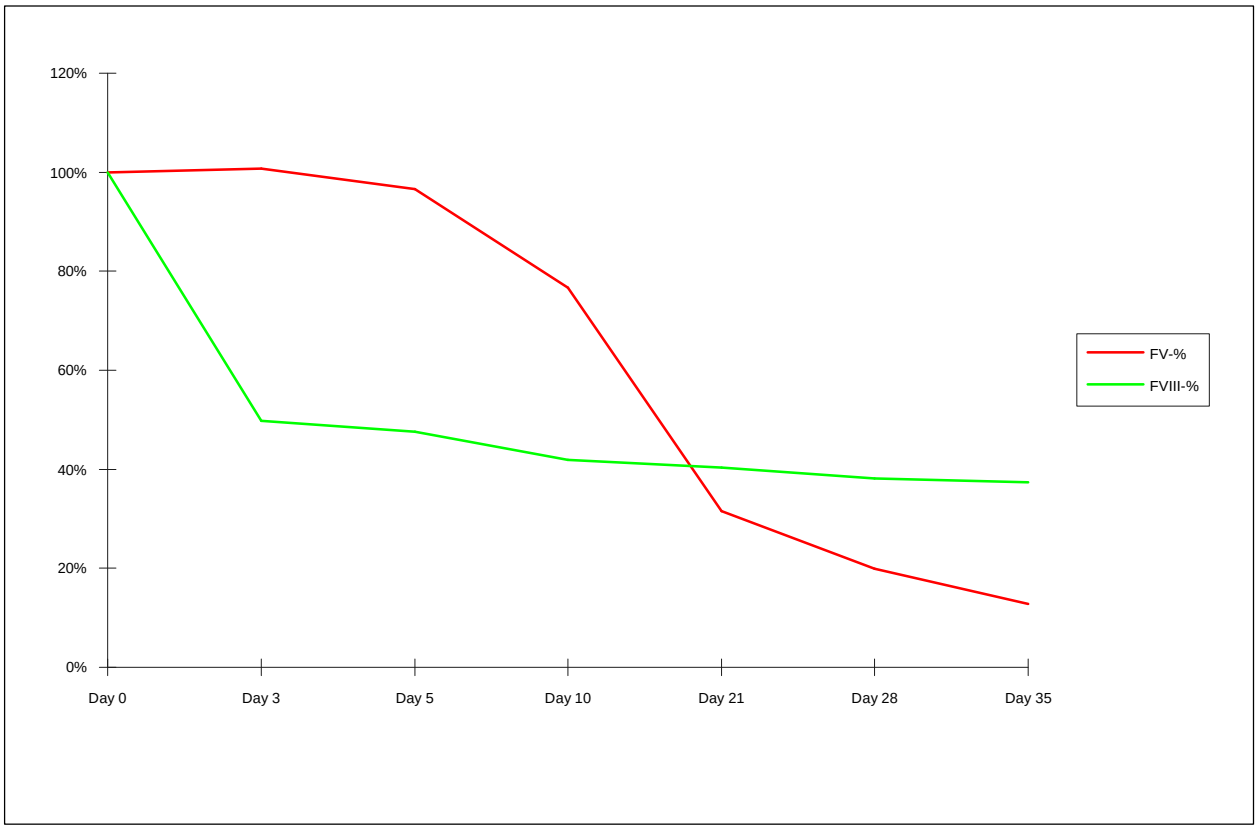
  ***NB:*** → baseline & subsequent ***clotting studies***

- Vietnam war studies & experimental data support,
  1. an increased likelihood of a platelet count < 100,000 with > 10-15 unit transfusion
  2. bleeding becomes increasingly likely at platelets **< 75,000**

- however, counts do not fall as predicted by haemodilution alone, ? release from marrow & RES
- there is ***no benefit*** in prophylactic administration of platelets in massive transfusion
- therapy should be assessed by laboratory data & clinical evidence of disordered coagulation
- higher counts are required in surgery and trauma
- ***platelet concentrates*** ~ 50 ml and contain ~ 70% of the platelets of a unit of whole blood
- in a 70 kg adult each unit will raise the platelet count ~ 7,000-10,000 / $mm^3$
- paediatric doses 0.1-0.3 units/kg ~ 20,000-70,000 / $mm^3$

## ▪ ***Low Factor V & VIII Activity***

- respectively, these decrease to ~ 15% and 50% of normal activity in whole blood after 21 days
- packed cells minimal quantities
- however, only 5-20% $F_V$ and 30% $F_{VIII}$ activity are required for normal haemostasis
- therefore these factors ***rarely*** decrease below those levels required for coagulation
- concomitant reductions may increase coagulopathy from other sources, ie. platelets
- RDM study giving FFP to $15^+$ unit transfusions with disordered coagulation, resulted in ***no improvement*** in coagulopathy, ie. other causes are usually responsible
- criterea for ***FFP administration*** in massive transfusion,
  1. generalised bleeding uncontrollable by surgical means
  2. APTT > 1.5x normal
  3. platelet count > 70,000 ie. correct the platelets first !




***NB:*** data from actual quality control on Red-Cross banked ***whole blood***, Feb '89

- ***Disseminated Intrvascular Coagulation***

1. relatively uncommon entity
2. microvascular ***thrombosis*** occurs rarely
3. rarely results in specific organ damage or infarction
4. accompanying large vessel thrombosis is not uncommon,
   but is probably ***not*** directly a result of DIC (ie. low flow)
5. ***bleeding*** is common, but usually originates from sites of local pathology
6. ***heparin*** is seldom useful and frequently worsens bleeding
7. DIC is associated with a ***high mortality***, 2° underlying disease severity
8. ? may be regarded as an incidental preterminal event in many patients

- ***Metabolic Effects***

1. ***citrate toxicity***
   - citrate itself is nontoxic → ***hypocalaemia***
     ∝ to citrate content of unit
     ∝ rate of infusion, hyperventilation
   - ≤ 1.5-2.0 ml/kg/min rarely a problem (≤ $1^U$/5 min in average adult)
   - FFP has higher % citrate than WB → ≤ 1.0 ml/kg/min
   - decreases in $Ca^{++}$ are ***transient*** and are restored immediately following $T_X$
   - RDM → $CaCl_2$ ***very rarely*** required
     monitor by ***ECG*** at higher rates
   - factors ↑'g citrate toxicity - hypothermia (↓ ~ 50%, 37→31°C)
     - hypovolaemia
     - liver disease, transplantation
2. ***hyperkalaemia***
   - generally only with whole blood ∝ to the shelf-life of the unit
     ≤ 19-30 mmol/l after 21 days
   - rate of infusion important ≤ 1.5-2.0 ml/kg/min
   - again, $CaCl_2$ administration rarely required & should be based on biochemistry
   - ABP's better for ***neonates*** - check unit [$K^+$] for neonates
     - monitor by ECG at higher rates
3. ***hypothermia*** → L-shift of $HbO_2$ curve
   - all banked products stored at ~ 2-6°C and $T_X$ should be warmed 38-40°C
   - reduction of core temperature < 30°C ↑'s ***cardiac irritability*** and impairs coagulation
   - decreases of 0.5-1.0°C may induce postoperative ***shivering*** & ↑ $MRO_2$ ~ 400%
   - ≥ 42°C results in RBC destruction
   - warming with ***radiofrequency*** warmers is OK, microwaves result in rbc damage
4. ***acid-base*** * depends upon reason for $T_X$
   - pH of CPD ~ 5.5
   - freshly collected blood pH ~ 7.0-7.1, decreasing to pH ~ 6.9 after 21 days
   - most acid in WB is **$CO_2$ ~ 150 mmHg** → lungs
   - metabolic acidosis is still present when this is removed by adequate ventilation
   - however, metabolism of citrate generates $HCO_3^-$ and acidosis is rarely a problem providing ***hypovolaemia*** is avoided and liver function is adequate
   - $NaHCO_3$ may have be harmful → use according to AGA's only

## Transfusion Reactions

- ***Classification***

1. time of onset → immediate vs. delayed
   - as actual mechanisms are uncertain in many cases, the terms anaphylactic / anaphylactoid are not used → ***immediate generalised reaction***
2. aetiology → immune vs. non-immune

- ***Immune Reactions***

1. donor rbc serological incompatibility
   i. acute incompatible transfusion reaction / immediate generalised reaction
      → high titre anti-A or anti-B in recipient plasma
      ***acute haemolytic transfusion reactions***
   ii. delayed (X-match compatible) transfusion reaction
2. reactions against donor plasma protein antigens (eg. $F_{VIII}$ Ab's)
   i. anti-IgA antibodies in selective IgA deficiency
      - IgA deficiency **~ 1:900** / anti-IgA **~ 20-60%**
      - not all patients will have an IGR, but those who react will do so repeatedly
      - use autologous blood or IgA deficient donors
      - may also have subclass specific anti-IgA, with milder symptoms
   ii. anti-IgG antibodies
   iii. reactions to exogenous donor antigens - dietary, drugs
   iv. serum sickness
3. high titre alloantibody in donor plasma
   i. ABO incompatible donor plasma
   ii. high titre atypical rbc alloantibody in donor plasma
      - pregnancy or previous transfusion
      - usually Rhesus or Kell & results in lysis of recipient rbc's
      - interdonor incompatibility
        → screen all plasma for high anti-A/B, or atypical Ab's
        refrain from using ABO incompatible plasma unless unavoidable
   iii. delayed reactions to donor reaginic IgE Ab's (transfer of allergy)
   iv. leukoagglutinins → ***transfusion associated lung injury (TRALI)***
      - plasma from multiparous females, frequently use of FFP post-CPB
4. reactions due to contaminants
   i. plasma "activation" → complement and kininogen/kinin systems
   ii. histamine release in stored blood
   iii. generation of cytokines
   iv. chemical additives

- ***Non-Immune Reactions***

  i. incorrectly stored or out-of-date blood
  ii. inadvertently frozen blood
  iii. overheated blood
  iv. infected blood
  v. mechanical destruction (infusion under pressure)

- ***Acute Haemolytic Transfusion Reactions***

1. incidence ~ 1:4000-14,000
2. mortality ~ 1:100,000 (2.5-10%)
3. aetiology ~ 18% anti-A, 12% anti-D, 23% anti-Fy[a] (mainly IgM)
   * complement fixing with direct intravascular haemolysis
4. symptoms & signs
   - fever & chills
   - chest pain, dyspnoea, apprehension
   - nausea, flushing
   - bleeding diathesis[§]
   - hypotension[§] [§]may be the only signs ***under GA***
   - haemoglobinuria[§]
5. complications
   - anaemia
   - haemoglobinuria (? ***acid haematin*** precipitate → ***ARF***)
   - DIC, thrombocytopaenia
   - ARDS, MOSF
6. investigations
   i. CBP - Hb, platelets, helmet cells, ghosts
      - free Hb, haptoglobin, urine [Hb]
   ii. APTT, OSPT, FDP/XDP's
   iii. fibrinogen - not ↓'d with storage, \ ↓ = DIC
   iv. return used unit for recrossmatch
   v. sample to blood bank for Ab screen & direct antiglobulin test
   vi. $MBA_{20}$ - $K^+$, renal function
7. management
   i. cease $T_X$ immediately
   ii. ABC - increase $FiO_2$ ± IPPV as required
      - maintain BP, volume loading ± inotropes
   iii. maintain urine output ≥ 1.0 ml/kg/hr
      - IV fluids ± mannitol 12.5-50 g
        ± frusemide
   iv. alkalinise urine → pH > 8.0
      • $HCO_3^-$ ~ 0.5-1.0 mg/kg

- ***Delayed Haemolytic Transfusion Reaction***

| | | |
|---|---|---|
| 1. | incidence | ~ 1:6000<br>- F:M ~ 3:1 |
| 2. | aetiology | - anti-$Jk^a$, anti-E, anti-c<br>* non-complement fixing Ab, with removal in RES |
| 3. | symptoms & signs | - may be asymptomatic<br>- usually ~ 1 week<br>- may occur at 2-3 days, or after 1 month<br>- fever & chills<br>- jaundice<br>- haemoglobinuria |
| 4. | complications | - mortality rare<br>- may result in anaemia, ARF |
| 5. | investigations | - anaemia<br>- jaundice, hyperbilirubinaemia<br>- (+)'ve direct Coomb's test |
| 6. | management | - usually no active management required<br>- rare severe reactions managed as above<br>- determine rare or low titre Ab's for future |

- ***Nonhaemolytic Transfusion Reactions***

| | | |
|---|---|---|
| 1. | incidence | ~ 2-3% of all units and up to 8% of patients |
| 2. | aetiology | - Ab's against donor wbc's (HLA or "leukoagglutinins")<br>~ 2.5 x $10^9$ wbc's / unit of blood<br>- Ab's against other plasma protein components |
| 3. | symptoms & signs | - fever, chills, myalgias, nausea, non-productive cough<br>- resembles early onset of haemolytic reaction |
| 4. | investigations | - as for haemolytic reaction<br>- return remaining blood to check matching<br>- rule out occurrence of ***haemolysis*** |
| 5. | prophylaxis | - washed rbc's (7-10 days old)<br>- microfiltration<br>- frozen / thawed cells<br>- dextran sedimentation<br>- antihistaminics ($H_1$ & $H_2$), antipyretics, steroids |

- ***Post-Transfusion Jaundice***

1. ***haemolysis*** - free Hb → ***unconjugated***
   - stored rbc's
   - immunological
2. haematoma reabsorption / associated injuries
3. ***liver disease*** - hypoxia, hypotension → ***conjugated***
   - drugs
   - sepsis
   - post-transfusion hepatitis
   - pre-existing liver disease (Gilbert's ~ 7-10%)
4. ***post-hepatic obstruction***

## Infective Complications

***NB:*** donor blood tested for → HBV, HCV
HIV, HIV-2
syphilis (only room temperature storage)
malaria excluded by ***donor history***

- ***Human Immunodeficiency Virus***

- except for triple-washed red cells, the transmission rate from an infected component is **100%**
- 123 cases of transfusion-acquired HIV prior to testing in May 1985
- **78%** of a cohort of severe haemophilia A patients tested HIV positive in NSW

1. declaration form & private interview - late 1984
2. heat treatment of $F_{VIII}$ by CSL - late 1984
3. ELISA screening of all donors - ***May 1985***

***NB:*** ***no documented*** case of transfusion-acquired HIV since then in Australia

- first 5 years, 1985-90 → 46 positive donors
  overall incidence ~ 1:120,000
  NSW incidence ~ 1:70,000

***NB:*** USA estimated risk from ***screened products*** ~ 1:40,000

- theoretical risk of donation within the ***"window"*** period remains
- transmission also reported from ***organ donation*** from seronegative donors
- theoretically, seronegative transmission may be detected by antigen (**p24**) testing
- however, large studies have not supported the cost-effectiveness of this method
- presently used in Thailand in an attempt to curb the spread in that country

## ***Hepatitis Viruses***

***NB:*** ***most common*** post-transfusion infection,
likely to remain so despite introduction of hepatitis C testing

1. ***hepatitis A***
   - is potentially transmissible by transfusion and cases have been reported
   - there is no carrier state and the window of infectivity is small
   - the only effective means of prevention is screening ***history*** from donors

2. ***hepatitis B***
   - HBsAg testing introduced in 1970, making Australia the first country to test all donors
   - prior to HCV screening, still accounted for **~ 5-10%** of post-transfusion hepatitis, despite sensitive screening test
   - reduction of non-A non-B hepatitis with HCV screening will increase percentage of HBV cases
   - infective donors are missed due to,
     i. low titre HBsAg
     ii. donation during the "window" period,
     where donor has lost detectable HBsAg but remains clinically infective
   - testing for HBcAb has been advocated, but low specificity and controversial
   - currently in NSW **~ 3:10,000** donations are HBsAg positive
   - incidence increasing with immigration from S-E Asia

3. ***hepatitis C***
   - non-A non-B hepatitis commonest post-transfusion infection for the past 20 years
   - NSW mid-80's → ~ 1.7% of CABG's transfused got biochemical hepatitis
   - incidence fell by ~ 50% with introduction of ***donor declaration form***
   - HCV identified in 1989, thought to be responsible for ~ 90% of non-A non-B hepatitis
   - 2nd generation ELISA tests → ~ 0.3% of donations positive (NSW)
     ~ 0.1% confirmed by RIBA test

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***NB:*** risk is now ***unknown***, but "likely to be so low that it will be difficult to carry out a large enough study for it to be established" AIC 1993

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4. ***delta hepatitis***
   - defective RNA virus, dependent upon HBV for replication
   - may occur concurrently with HBV, ***coinfection***, or ***superinfection*** in a carrier
   - management is through prevention of HBV

5. *hepatitis E*
   - endemic form of non-A non-B hepatitis
   - mode of spread similar to HAV, ie. fecal-oral
   - theoretically transmissible through blood but no reported cases

## ***Cytomegalovirus***

- member of the herpes virus family
- geographical prevalence varies from ~ 40-100%
- primary infection usually unnoticed, unless the host is ***immunocompromised***
- most frequent cause of ***death*** in bone marrow transplantation → ***pneumonia***
- may contribute to disease progression and/or activation in ***HIV***
- at risk patients include,
    i. low birth weight & premature neonates
    ii. congenital immunodeficiency syndromes
    iii. splenectomised patients
    iv. those on immunosuppressive chemotherapy
    v. transplant recipients

- managed by transfusion with CMV negative blood, but limited supply due to high prevalence
- ***leukocyte filters*** have been shown to be effective in neonates but are expensive

## ***HTLV-1***

- retrovirus related to HIV → T-cell leukaemia ~ 1% of infections
  tropical spastic paraparesis

- endemic within some Aboriginal groups within Australia, and in areas of the Western Pacific
- screening is carried out for donors having been to high risk areas
- pilot study in the NT screening all donors
- no proven transmission in Australia, but 4 donors (+)'ve in the NT and 1 of 212 haemophiliacs found to have evidence of infection
- problems as ELISA screens also get HTLV-II, the pathogenicity of which is unknown

## ***Syphilis***

- *Treponema pallidum* is more likely to be present in the serum during the ***seronegative phase***
- routine screening therefore offers limited protection, however it does act as an aditional surrogate test for HIV infectivity
- the organism is destroyed by storage at 4°C, thus ***platelets*** are the likely medium
- there has been no recorded transmission in Australia in the past 20 years

## ***Malaria***

- Australian donors are excluded for ***12 months*** following overseas travel
- this is increased to ***24 months*** if chemoprophylaxis was taken
- a recent case of *P. falciparum* malaria in Victoria is believed to be the first case in 20 years
- in transfusion transmitted disease, the ***exoerythrocytic phase*** in the liver is bypassed
    → therefore relapses ***do not*** occur
- frozen red cells and cell-free blood components have been associated with infection

- ***Other Transmissible Diseases***

1. Chagas' disease - *Trypanosomiasis cruzi*
2. Lyme disease - *Borrelia burgdorferi* (spirochaete)
3. Jakob-Creutzfeldt
4. toxoplasmosis
5. brucellosis
6. filariasis
7. salmonellosis, typhus, measles

- ***Methods to Reduce Infection Transmission***

1. exclude donors from high risk groups
   - donor declaration form & interview
2. screen all donors for HIV, HBV, HCV & CMV Ab's, VDRL
3. avoid homologous transfusion & transfuse minimal unit requirement
4. avoid multiple donor components unless absolutely required
5. use autologous blood where possible

## Leukocyte Transfusion Effects

- ***Beneficial Effects***

1. longer renal graft survival
   - inactivation of alloreactive clones by high-dose immunosupressive therapy
   - induction of suppressor cells
   - induction of anti-idiotypic antibodies
   - improved by donors sharing one HLA-DR Ag
   - largely abandoned following the advent of ***cyclosporin*** therapy
2. graft versus leukaemia effect
   - increase in bone marrow transplant remission rates
   - 1 study only, not supported by subsequent study

- ***Adverse Effects***

1. HLA alloimmunisation
   i. non-haemolytic febrile transfusion reactions
      - most common effect ~ 1% of all transfusions
        ≤ 50% in multi-transfused patients
   ii. refractoriness to random donor platelets transfusions
      - occurs in 30-70% of multiple donor recipients
      - refractoriness may be nonimmunologic → consumption
      - HLA-Ab's present in ~ 50% of multiple donor recipients
      - ***critical immunogenic leukocyte load (CILL)*** for alloimmunisation
2. graft versus host disease in immunosuppressed
3. transmission or reactivation of CMV
4. transmission of HTLV-1
5. generalised immunosupression *suggestive evidence
   i. ↑ postoperative infection rate - including 1 prospective study
   ii. ↑ tumour recurrence - all retrospective studies
   - 5 studies ↑ incidence, 3 equivocal
   - 3 studies no relationship

***NB:*** studies pending assessing effects of leukodepleted blood products

- ***Methods of Leukocyte Depletion***

1. prestorage leukodepletion → centrifugation, washing, freezing & thawing
2. bedside filtration → clinically equally effective to date

- ***Recommendations for Leukodepleted Blood Products***

1. to prevent recurrent NHFTR $< 5 \times 10^8$
2. prevent/delay alloimmunisation to HLA-Ag's $< 5 \times 10^6$
3. those presently under investigation
   i. prevention of refractoriness to platelets
   ii. recurrence of febrile reactions to platelets
   iii. CMV infection
4. those where leukodepleted products are ***not recommended***,
   i. GVHD
   ii. acute lung injury due to donor anti-leukocyte Ab's
   iii. reactions or alloimmunisation in patients with limited transfusion exposure
   iv. reactions or alloimmunisation in patients receiving acellular components

# COMPONENT THERAPY

## ▪ ***Platelets***

1. ***random donor platelets*** - pooled from 6-8 donors
   - each bag contains ~ 40-50 ml → 5-6 x $10^{10}$ platelets
   - stored at room temperature and are viable for ***~ 3-5 days***
   - filters with pore sizes < 170 µm remove significant numbers
2. ***single donor platelets*** - collected by plateletpheresis
   - requires HLA matched donor to minimise antigenic differences

• causes for a reduction in platelet numbers,

a. ***reduced production*** - marrow failure (aplastic), marrow infiltration
   - deficient substrate ($B_{12}$, folate)

b. ***sequestration*** - splenomegaly

c. ***dilution*** - massive transfusion (≥ 1 BV)

d. ***accelerated destruction***
   i. consumptive - coagulopathy (DIC, PIH)
   ii. autoimmune - SLE, lymphoma, HIV, ITP
   iii. drug induced - aspirin, heparin (HITS I&II)

***NB:*** → 2 groups, gradual vs. rapid reduction in platelet numbers

• requirement for platelets depends upon ***cause*** and ***rate*** of development
• effects of transfusion variable, depending upon cause & preceding transfusion, $t_{½\beta}$ ~ 10 days,

a. 1 unit of platelets ~ 7,000-11,000 / $mm^3$ / $m^2$ SA increase
b. 0.1-0.3 units/kg ~ 20,000-70,000 / $mm^3$ (standard dose)

• indications,

1. platelet count < 10,000 x $10^9$/l * varies between institutions
2. platelet count < 50,000 x $10^9$/l + spontaneous bleeding or surgery
3. platelet dysfunction, ***irrespective*** of count + spontaneous bleeding or surgery

• important points,

a. antibody production is ∝ to units transfused

   → limited effectiveness of future transfusions

b. not all hospitals have platelets readily available
c. they should be administered immediately preoperatively
d. they should ***not*** be run through a micropore filter

## ■ ***Fresh Frozen Plasma***

• 200 ml standard volume contains ***all factors***, including,

1. VIII:C ~ $200^{U}$ - may be harvested prior to freezing
   - noted on unit label
2. IX ~ $200^{U}$
3. fibrinogen ~ 400 mg

• prepared within ***6 hrs***, after which the ***labile factors*** (V/VIII) begin to diminish, stored **-30°C**
• for same reason should be used ASAP upon thawing
• contains proportionally more ***citrate*** than whole blood
• administered as ABO compatible transfusion, volume ~ 200 ml/unit
• ***indications*** for use,

1. isolated factor deficiencies - laboratory proven
2. massive blood transfusion - rarely, when V/VIII activity < 25%
   + OSPT > 1.8 / fibrinogen > 0.8 g/l
3. reversal of warfarin effect
4. antithrombin III deficiency - thrombotic state
5. immunodeficiency states - source of globulins
6. thrombotic thrombocytopenic purpura
7. haemophilia A - rarely, as require 10-15 U/kg for an acute bleed
   ~ 4-5 units of FFP / 70 kg
8. von Willebrand's disease

## ■ ***Cryoprecipitate***

• fresh plasma frozen & thawed at 4-8°C → ~ 3% fails to redissolve, the cryoprecipitate
• then warmed to room temperature with **20-50 ml** of supernatant plasma
• ***single donor*** preparation, stored for up to 6 months at **-30°C**
• contains,

i. **VIII:C** ~ 20-85% of the original levels
   ~ 80-120 units / 10-15 ml of plasma, or
   ~ ½ VIII:C activity of FFP in $1/10^{th}$ the volume
   → ~ 120 ml for $R_X$ acute bleed in haemophilia A

ii. **fibrinogen** ~ 3-10x original plasma / ml
   ~ 250 mg / 10-15 ml of plasma, cf. 200 ml of FFP
   - may result in ***hyperfibrinogenaemia*** in haemophiliacs
   → paradoxical bleeding

iii. VIII:vWF ~ 40-70% original plasma

iv. F-XIII ~ 3-10x original plasma / ml

v. fibronectin

• indications,

1. ***haemophilia A***
   - factor VIII:C deficiency → principal use
   - not indicated for haemophilia B, as minimal content of factor IX
2. ***fibrinogen deficiency***
   - preferrable to commercial fibrinogen preparations, which are pooled from 500-5000 donations and carry a high infection risk
   - massive transfusion → plasma fibrinogen < 0.8 g/l
   - ***10 units*** increase plasma levels ~ 1 g/l in an adult (N:1.5-4.0 g/l)

■ ***Haemophilia B***

• patients with haemophilia B (IX deficiency) are managed with commercial concentrates which contain F-VII, IX and X
• concentrates are from pooled donor sources and have a greater risk of ***transmissible disease***
• this has now been reduced by heat treating, or ***monoclonal*** production

■ ***Prothrombinex***

• contains factors **II, IX** and **X** → ~ $250^{U}$ / 10 ml for each factor
• has low levels of VII
• prepared from human donor plasma
• presented as a freeze dried powder, requiring reconstitution with water
• screened for HBV, HBC and heat treated for HIV
• average dose ~ 1 ml/kg for acute haemorrhage, then 0.5 ml/kg each 24 hours

## Von Willebrands Disease

• heterogeneous disorder of factor **VIII:vWF** function, three types

1. type I - decreased VIII:vWF ***concentration***
2. type II - decreased VIII:vWF ***function***
3. type III - rare, combined disorder with severe clinical symptoms

***NB:*** all are ***autosomal dominant*** except for type III, ***incidence*** **~ 1:800-1,000**

• coagulation studies vary with time and may be ***normal*** when tested,

1. increased skin bleeding time
2. normal platelet count
3. may have a small increase in APTT

# PLASMA & COLLOIDS

## ***Haemaccel***

- synthetic polypeptide plasma volume expander
- **3.5%** ***gelatin*** solution, with the mean MW ~ 35,000-45,000
- gelatin prepared from hydrolysis of ***animal collagen***, cross linked by ***urea bridges***
- plasma expansion by **~ 70%** of infused volume
- renal excretion by GFR complete by 48 hours
- useful as a synthetic plasma substitute & as an insulin carrier

| | | |
|---|---|---|
| • gelatin | ~ 35 | g |
| • $Na^+$ | ~ 145 | mmol/l |
| • $Cl^-$ | ~ 145 | mmol/l |
| • $K^+$ | ~ **5.1** | mmol/l |
| • $Ca^{++}$ | ~ **6.25** | mmol/l |
| • $HSO_4/HPO_4$ | ~ small amounts | |
| • pH | ~ 7.3 | |
| • osmolality | ~ 300-306 | mosm/l |

- advantages,
  a. cheap, safe, reliable synthetic colloid
  b. low incidence of adverse reactions
  c. renal excretion
  d. long shelf half-life ~ 8 yrs at 15°C
     ~ 3 yrs at 30°C
- disadvantages,
  a. allergic reactions ~ 0.146% **~ 1:650**
     - skin rashes, pyrexia
     - anaphylactoid reaction ? due to ***hexamethylene diisocyanate***
     - renal failure rare
  b. short $t_{½\beta}$ ~ 1.5-6 hrs (x' ~ 3-4 hrs)
  c. renal excretion
  d. $Ca^{++}$ related complications

## ■ ***Dextrans***

- polysaccharides produced by fermentation of sucrose by *Leuconostoc mesenteroides* bacteria
- these are then hydrolysed and fractionated into different molecular weights
- advantages,
    a. stable, cheap, non-toxic
    b. non-pyrogenic plasma substitutes & expanders

## ■ ***Dextran 40 Rheomacrodex***

- 10% (100g/l) solution in normal saline or 5% dextrose
- average MW ~ 40,000, osmolality ~ 350-370 mosm/kg, ie. ***hypertonic***
- plasma $t_{½\beta}$ ~ 2-3 hrs with ~ 5% being metabolised (70 mg/kg/day)
    i. plasma volume expansion **~ 1.5-2x** infused volume
    ii. thromboembolic prophylaxis ~ 38% ↓ DVT
    iii. rheological microcirculatory benefit
    iv. CPB pump priming

- contraindications,
    i. thrombocytopaenia
    ii. coagulopathy
    iii. hypersensitivity

- problems,
    i. hypervolaemia, circulatory overload, CCF
    ii. anaphylactoid / anaphylactic reactions ~ 0.07% **~ 1:1500**
        - reduced by Promit (0.001%)
    iii. renal failure - renal tubular obstruction

- does ***not*** interfere with blood cross-matching or Coomb's testing, cf. high MW dextran
- maximum dose ~ 30 ml/kg/day

## ■ ***Dextran 70 Macrodex***

- 6% (60g/l) solution in normal saline or 5% dextrose
- average MW ~ 70,000, osmolality ~ 335 mosm/kg, ie. mildly ***hypertonic***
- plasma $t_{½\beta}$ ~ 6 hrs with ~ 5% being metabolised (70 mg/kg/day)
- problems are the same as for dextran 40, plus, interference with ***haemostasis*** with large volumes
    a. fibrinogen coating
    b. interferes with factor VIII
    c. decreased platelet adhesion and aggregation

    ***NB:*** ***does not*** interfere with normal X-match & indirect Coomb's, only enzyme assays

## ■ *SPPS NSA-5%*

- heat treated plasma protein solution, was mainly albumin, now marketed as NSA-5%
- prepared from fractionated plasma from pooled human donors
- ***pasteurised*** to kill HBV, HCV, HIV etc.
- shelf-life → **5 yrs** at 2-8°C
  → 1 yr at 25°C
- ***$Na^+$-octanoate*** is added to stabilise the short chain FFA and heat stabilise albumin
- acetate and citrate 1-2 mmol/l are added
- NaOH is added to bring the pH to 7.0

| | | |
|---|---|---|
| • human albumin | ~ 50 | g/l |
| • $Na^+$ | ~ 140 | mmol/l |
| • $Cl^-$ | ~ 125 | mmol/l |
| • octanoate | ~ 8 | mmol/l |
| • pH | ~ 7.0 | |
| • osmolality | ~ 300 | mosm/kg |

- main problem was ***anaphylactoid reactions*** (~ 0.02%), ? heat labile ***pre-kallikrein factor***
- other plasma substitutes include,

a. hydroxy ethyl starch - $t_{½\beta}$ ~ 24 hrs
   - reactions ~ 0.08%

b. fluosol DA

c. FFP

d. NSA-20% *cf. old HSA-conc. which was 25%

Common Intravenous Solutions [1]

| Solution | $Na^+$ | $Cl^-$ | $K^+$ | $Ca^{++}$ | Glu | Osm. | pH | Lact. | kJ/l |
|---|---|---|---|---|---|---|---|---|---|
| $D_5W$ | 0 | 0 | 0 | 0 | 278 | 253 | 5 | 0 | 840 |
| NaCl 0.9% | 150 | 150 | 0 | 0 | 0 | 300 | 5.7 | 0 | 0 |
| NaCl 3.0% | 513 | 513 | 0 | 0 | 0 | 855 | 5.7 | 0 | 0 |
| $D_4W$ / NaCl 0.18% | 30 | 30 | 0 | 0 | 222 | 282 | 3.5-5.5 | 0 | 672 |
| Hartmans | 129 | 109 | 5 | 0 | 0 | 274 | 6.7 | 28 | 37.8 |
| Plasmalyte | 140 | 98 | 5 | | | 294 | 5.5 | (27) | 84 |
| Haemaccel | 145 | 145 | 5.1 | 6.25 | 0 | 293 | 7.3 | 0 | 0 |
| NSA-5% | 140 | 125 | 0 | 0 | 0 | | 7 | 0 | ? |
| NSA-20% | | | | | | | | | ? |
| Mannitol 20% | 0 | 0 | 0 | 0 | 0 | 1,098 | 6.2 | 0 | 0 |
| Dextran 70 | 154 | 154 | 0 | 0 | 0 | 300 | 4-7 | 0 | 0 |

[1] values in mmol/l, irrespective of common presentation volume

# PLASMA EXCHANGE

- ***Rationale***

1. removal/reduction of circulating toxic factor
   i. antibodies - monoclonal
      - autoantibodies
      - alloantibodies
   ii. immune complexes
   iii. mediators of inflammation
   iv. chemicals
   v. drugs
2. replacement of deficient plasma factors
3. potentiation of drug action
4. enhanced RES function
5. altered immunoregulation
6. potentiation of other modes of therapy

- ***Acute Diseases***

1. ***immunoproliferative diseases*** with monoclonal Ab's
   i. hyperviscosity syndrome - Waldenstrom's macroglobulinaemia
   ii. cryoglobulinaemia
   iii. renal failure in multiple myeloma
2. ***autoimmune diseases***
   i. Goodpasture's syndrome
   ii. myasthenia gravis
   iii. GBS
   iv. SLE
   v. TTP
   vi. rapidly progressive GN
   vii. coagulation inhibitors
   viii. autoimmune haemolytic anaemia
   ix. pemphigus
3. plasma ***factor replacement*** → FFP replacement
   i. DIC
   ii. SIRS
   iii. immunodeficiency states

4. Reye's syndrome - mechanism unknown
5. ***toxin removal***
   i. paraquat poisoning
   ii. envenomation
6. rapid plasma removal & rbc replacement in severe anaemia with CCF/IHD

- ***Complications***

1. ***technical***
   i. vascular access - pneumothorax, arterial puncture
   ii. air embolism
   iii. acute hypo/hypervolaemia - unilateral pump failure
   - incorrect setting
   iv. heat loss - especially children
2. ***circulatory***
   i. hypo/hypervolaemia - need fluid balance chart, daily weight
   ii. vasovagal reactions
   iii. vasoactive reactions
   iv. immediate generalised response
3. ***haemostasis***
   i. require heparinisation unless existing coagulopathy
   ii. altered procoagulant / anticoagulant protein levels
   → variable effects, haemorrhagic & thrombotic
   iii. decreased antithrombin III & altered response to heparin
4. ***immunology***
   i. frequently pre-existing immunosuppression
   ii. reduction in immunoglobulin & complement levels with repeated exchange
   iii. bacteriacidal & opsonic properties impaired unless FFP used as replacement
   → use 2 units after large or frequent exchange
   iv. risk of post-transfusion infection - hepatitis
5. ***metabolic effects***
   i. disequilibrium syndrome - less than with haemodialysis
   ii. alterations of COP & oedema formation
   iii. altered transport & binding protein levels

# HAEMOSTATIC FAILURE

## Normal Coagulation

***NB:*** the "classical" division of coagulation into ***intrinsic & extrinsic systems*** is not applicable to humans *in vivo*,

1. no coagulopathy, nor disease state, is associated with deficiencies of several of the proteins of the ***intrinsic system***
2. ***thrombin*** generation is via
   i. tissue factor, factor VII, factors IX and X, plus
   ii. an absolute requirement for ***platelet phospholipid***, ***VIII:C*** and ***V*** as cofactors

- ***Critical Events***

1. the binding of ***von Willebrand Factor*** to the exposed ***subendothelium***
   - this may be deficient due to,
   i. diminished levels of vWF (vWD - type I)
   ii. structural abnormality of vWF, or (vWD - type IIa, IIb)
   iii. abnormality of collagen
2. subendothelial bound vWF exposes & binds multiple glycoprotein platelet receptors (**GPIb receptors**)
   - the **vWF-GPIb** interaction is probably central to many surgical coagulopathies
   - manipulation of this event is the likely 1° role of ***aprotinin***
   - this step fails when,
   i. too few platelets < 50,000 $\rightarrow$ critical impairment of surgical haemostasis
   ii. circulation failure - demargination is seen at PCV < 20%
   - functional dilution by blood flow
   iii. lack of GPIb - arises during CPB due to proteolytic degradation
   - absent from platelets stored > 3 days
   - ***Bernard-Soulier*** syndrome
   iv. GPIb dysfunctional - abnormal protein or already occupied
   - myeloma, ITP
   - dextran infusion

***NB:*** the next 2 steps of haemostasis, generation of the ***platelet plug***, and solidification of that plug by ***coagulation***, are completely dependent upon adhesion of platelets to the site of injury

Murphy *et al.* (BJA 1993) state that the ***bleeding time*** is the only practicable test of this axis, although it has poor predictive value as a ***screening test***, in the patient with clinically manifest coagulopathy it is a useful indicator (??)

## ***Platelet Plug Formation***

- activation of platelets occurs via ***thrombin***, ***ADP***, and possibly the GPIb-vWF complex
- release of procoagulants and ligands from alpha and dense granules results in further activation and platelet adhesion
- a satisfactory platelet plug will not be formed if,

1. there are too few platelets
2. they are functionally inert
   - storage > 3 days
   - CPB
   - aspirin, uraemia, alcohol
   - congenitally impaired

- subsequent activation of the coagulation cascade results in the formation of ***thrombin***, with the generation of ***fibrin*** from fibrinogen
- this self-polymerising species is then converted by X-linking of strands by ***factor*** $\mathbf{XIII_a}$
- abnormalities of this step may be due to,

1. congenital deficiencies - haemophilia A & B
2. acquired deficiencies
   i. anticoagulant therapy/overdose
   ii. vitamin K deficiency
   iii. liver disease, malnutrition
   iv. complex acquired coagulopathies
      - DIC
      - massive transfusion, dilution
      - CPB
      - liver transplantation

## ***Anticoagulant Mechanisms***

1. antithrombin pathways
   i. antithrombin III
   ii. proteins C & S
2. extrinsic pathway inhibition $\rightarrow$ $VII_a$-thromboplastin complex inhibitor
3. fibrinolytic system
   i. tPA released by endothelial cells & incorporated into fibrin clot
   ii. fibrinogen-bound plasminogen $\rightarrow$ ***plasmin***
   iii. plasmin cleaves several proteins
      - fibrinogen & fibrin
      - factor VIII:C and platelet GPIb

## Routine Tests of Coagulation

1. bleeding time
   - i. Simplate II - modified Ivy technique
     - torniquet @ 40 mmHg & standard template incision
     - normal range **< 9 *minutes***, operator dependent
   - ii. Duke or Ivy - less reproducible than Simplate II
2. platelet count ~ 150-400 x $10^9$/l
3. thrombin time - normal range 14-16s
   - tests final conversion of ***fibrinogen*** ® ***fibrin***
   - bypasses intrinsic & extrinsic systems, and is abnormal in,
   - i. afibrinogenaemia, hypofibrinogenaemia, dysfibrinogenaemia
   - ii. heparin therapy - corrects with protamine
   - iii. elevated FDP's - partially corrects with protamine
4. international normalised ratio / prothrombin time
   - tests the ***extrinsic pathway***, normal range ~ 13-17s
   - platelet poor citrated plasma is recalcified & brain thromboplastin added
   - time taken to clot is measured as a ratio of control reagent
   - standardised control reduces inter-laboratory variation
   - recommended Australasian Reference Thromboplastin, ART
   - i. VII deficiency
   - ii. liver disease, warfarin therapy, vitamin K deficiency
5. activated partial thromboplastin time
   - normal range ~ 25-35 s
   - screens for coagulation factor deficiency, except **VII & XIII**
   - recalcified, platelet poor citrated plasma, plus an activator & platelet substitute
   - varies with reagents used and laboratory
   - interpret with clinical findings and prothrombin time
   - i. factor deficiency → corrected by the addition of normal plasma
   - ii. factor inhibitor → not corrected by normal plasma
   - iii. heparin therapy → therapeutic range ~ 1.5-2.5 x baseline
6. fibrin/fibrinogen degradation products
   - blood collected into a tube containing thrombin & a fibrinolytic inhibitor
   - latex agglutination test against ***fibrinogen-related Ag*** in serum
   - standard FDP's don't differentiate between 1° and 2° fibrinolysis
   - XDP's measure ***D-dimer*** which indicates fibrinolysis after fibrin formation
   - i. ↑ FDP, XDP - local lysis of fibrin, DIC
     - malignancy, systemic infection, SIRS
   - ii. ↑ FDP - primary fibrinolysis
   - iii. normal XDP's helps exclude ***pulmonary thromboembolic disease***

7. fibrinogen - N: 1.5-4.0 g/l
   - test either based upon thrombin clotting time, heat precipitation or immunological methods
   - discrepancies between functional and immunological methods found in the presence of FDP's and dysfibrinogenaemia

   i. decreased production - hereditary a/hypo-fibrinogenaemia
   - liver disease
   - severe malnutrition syndromes

   ii. increased consumption - DIC
   - fibrinolysis

8. euglobulin lysis time
   - normal range > 90 minutes
   - ↓ time reflects the presence of activators of the ***fibrinolytic system***

9. thromboelastography
   - functional assessment of the entire coagulation cascade & fibrinolytic system
   - results may take up to several hours
   - requires multiple samples run sequentially throughout procedure
   - frequently require treatment prior to availability of results

| Common Coagulation Disorders | | |
|---|---|---|
| **APTT** - | **INR** - | • usually acquired<br>• liver disease, oral anticoagulants, DIC<br>• ¯ **II, V, X** |
| **APTT** - | **INR** « | • ↓ VIII:C, IX - haemophilias<br>• ↑ ATIII - heparin<br>• ↓ VIII:vWF |
| **APTT** « | **INR** - | • mild liver disease<br>• early in oral anticoagulant use<br>• ↓ VII - rare congenital deficiency |

## Acquired Coagulopathies in Surgical Patients

- ***Predisposing Factors***

1. sepsis
2. hypoxia
3. hypothermia
4. severe tissue damage
5. massive blood loss or prolonged hypotension
6. cardiopulmonary bypass CPB
7. pre-existing liver disease, liver transplantation
8. obstetric complications - AFE
   - abruption
9. pre-existing bleeding diathesis- vWD, thrombocytopaenia
   - anticoagulation, aspirin

- ***Hypovolaemic Shock / Massive Transfusion***

• diagnosis is based mainly upon ***clinical grounds***, with supporting laboratory data
• 2 underlying mechanisms,

1. dilution of platelets and coagulation factors
2. consumption 2° activation of tissue factor & tPA released from traumatised tissues

***NB:*** ***dilutional thrombocytopaenia*** is the most frequent cause, often becoming apparent at transfusions > 1 BV and platelets < 100,000 x $10^6$/$mm^3$
the platelet count ***does not*** determine the functional integrity of platelets

• prolongation of the OSPT and APTT in the absence of DIC is usually due to ***hypofibrinogenaemia***, the presence of DIC leads to loss of other factors (V & VIII:C)
• RDM states that fibrinogen not low in stored blood, \ ↓ fibrinogen = consumption / DIC
• this is supported by data from Red Cross BB, virtually no loss of fibrinogen with storage of whole blood, however if transfused large quantities of packed cells then this may become significant

***NB:*** all agree the use of prophylactic FFP or platelets in ***massive transfusion***, in the absence of clinical & laboratory evidence of coagulopathy, is ***not justified***

## ▪ ***Disseminated Intravascular Coagulation***

• non-localised activation of the coagulation and fibrinolytic systems
• trigger varies, but the universal pathology is circulating ***phospholipid*** → coagulation activation
• this may be manifest primarily as a,

| | | |
|---|---|---|
| i. | haemorrhagic disorder | - loss of platelets & soluble clotting factors<br>- especially ***fibrinogen***, V and VIII:C |
| ii. | thrombotic disorder | - distal gangrene & organ infarction |
| iii. | mixture of both | |

• ***heparin therapy*** is based on the premise that inhibition of ***thrombin*** will,

1. reduce the consumption of fibrinogen, other clotting factors and platelets
2. reduce both the thrombotic tendancy and the haemorrhagic disorder

***NB:*** there have been ***no trials*** which support this view
in several studies the heparin treated group have had a ***worse outcome***

• treatment is therefore aimed at,

1. correcting the underlying pathology, ie. removing circulating phospholipid, and
2. replacement component therapy

• there is no compelling evidence that administration of clotting factors & platelets increases the incidence of thrombotic complications with DIC
• other treatments which may become viable include antithrombin III and protein C

## ▪ ***Liver Transplantation***

| | | | |
|---|---|---|---|
| a. | complex coagulopathy from procedure itself | | |
| b. | preoperative ***liver dysfunction*** | → | ↓ II, V, VII, IX, X, XI and fibrinogen |
| | | → | ↓ plasminogen, $\alpha_1$-antiplasmin |
| | | → | ↓ proteins C & S, antithrombin III |
| c. | ***hypersplenism*** | - some patients | |
| d. | ***massive transfusion*** | - some patients | |

***NB:*** a low grade DIC or ***consumptive coagulopathy*** frequently exists,
due to decreased hepatic clearance of activated coagulation factors

• significant ***fibrinolysis*** may occur during the ***anhepatic phase*** due to,

1. increased release of tPA from hypoperfused distal tissues (?? why)
2. lack of hepatic $\alpha_1$-antiplasmin

• ***aprotinin*** is effective in preventing the coagulopathy with orthoptic liver transplantation
• earlier studies suggesting reduced blood-loss with antithrombin-III have not been supported

## ***Cardiopulmonary Bypass***

• recent studies have shown large doses of ***aprotinin*** reduce blood-loss associated with CPB
• originally studied in the 60's & 70's with no significant effect, but using much smaller (~ 50%) doses than present studies
• Royston 1987 reported a significant reduction in blood-loss associated with CPB for repeat valve replacement procedures
• the aim of this study was to assess the effects upon postoperative pulmonary function, the results on blood-loss were unexpected
• other studies have extended these findings to patients with,

i. septic endocarditis
ii. recent aspirin ingestion

• detrimental effects of CPB on haemostasis include,

1. platelets dysfunction / consumption
   i. loss of membrane structure & granule contents
   ii. generation of activation markers on the cell surface
2. activation of the fibrinolytic & contact systems
3. activation of granulocytes with degranulation

• the likely, not proven, site of action of aprotinin is platelet ***membrane GPIb***

a. loss of GPIb is one of the early events during CPB which is prevented by aprotinin
b. GPIb contains the binding site for thrombin-induced platelet activation
c. enzymatic hydrolysis of GPIb may result in platelet activation

• GPIb is a transmembrane hetrodimer, readily cleaved by plasmin, elastase and calpain
• all of these are direct ***platelet agonists*** and are inhibited by aprotinin,

1. ***plasmin*** - activity 2° tPA or contact system activation
2. ***elastase*** - generated from activated neutophils during CPB
   - inhibition requires greater concentrations cf. plasmin
3. ***calpain*** - cysteine protease present on thrombin stimulated platelets
   - ? also plasmin stimulated platelets

***NB:*** inhibtion of tPA-induced plasmin on the platelet surface could account for much or all of the observed effect

## ***Ruptured Aortic Aneurysms***

• ***mortality*** is strongly associated with coagulopathy and uncontrollable haemorrhage
• of those who reach hospital the mortality ~ 21-70%, mean ~ 50%
• postoperatively, haemorrhage and MOSF are the major causes of death
• coagulopathy *per se* is associated with other factors which increase mortality,

1. increased time for resuscitation
2. more extensive surgical procedures
3. larger transfusion requirement
4. renal failure

***NB:*** however, coagulopathy itself increases risk, being due to either,

i. DIC
ii. dilution of platelets and procoagulant factors
iii. a combination of both

• patients presenting appear to fall into 2 groups, one with a relatively good prognosis, the other with a mortality ~ 70-100%
• Bell *et al.* (Transfusion Med.1991) in a prospective study, took admission coagulation screens on 23 consecutive acute AAA's,

a. 6 of 13 patients with abnormal screens died
b. 0 of 10 with normal screens died

• these findings have been supported by other studies, with 4 of 4 and 11 of 15 dying
• it ***has not*** been demonstrated that early correction of the coagulation abnormality in these patients will improve survival
• previous attempts to avert the coagulopathy of massive transfusion with platelets & FFP have been unsuccessful

***NB:*** early & aggressive attempts to reverse ***tissue hypoxia*** probably offer the best chance of preventing the coagulopathy and improving survival in this patient group

## ***Fibrin Glue***

• prepared as a 2-part solution of ***fibrinogen*** and ***thrombin***
• direct application onto the bleeding site bypasses the physiological requirements for haemostasis
• may delay nerve and bone repair
• other complications, viral transmission, adhesion formation and unwanted thrombosis remain theoretical
• evidence of efficacy best demonstrated in the presence of congenital or acquired disorders
• recent large prospective trial comparing fibrin with conventional topical haemostasis showed 90% success cf. 12.4%

## METHODS OF HOMOLOGOUS TRANSFUSION REDUCTION

1. reduction of blood loss
   i. surgical techniques
      - diathermy & ligature
      - limb torniquets
      - local vasoconstrictor
   ii. ***anaesthetic techniques***
      - regional anaesthesia
      - controlled hypotension
      - pharmacotherapy
2. toleration of a lower haematocrit
3. autologous transfusion
   i. preoperative donation & autologous transfusion
   ii. acute venesection, isovolaemic haemodilution & autologous transfusion
   iii. intraoperative cell salvage
4. dedicated "homologous" transfusion

## Toleration of a Lower Haematocrit

- historically a Hct < 30% has been an indication for perioperative transfusion
- $O_2$ carrying capacity decreases ***linearly*** with Hct, however physiological $DO_2$ may be maximal at a Hct ~ 30%
- Fortune *et al.* (J.Trauma 1987) conducted a prospective study of trauma patients managed at either a Hct ~ 30 or a Hct ~ 40
   1. no improvement in cardiopulmonary function with a higher Hct
   2. increased ***shunt fraction*** in higher group due to greater number of transfusions

- animal data suggest a ***critical Hct* ~ 10%**, below which cardiovascular reserve is exhausted
- Tremper (ASA 1992),
   1. healthy patients with good CVS function tolerate **Hct ~ 20** and below if adequately volume resuscitated
   2. in patients with impaired myocardial function, Hct ~ 30% may be required
   3. signs of CVS decompensation require assessment of need for transfusion

## Controlled Hypotension

***Def'n:*** deliberate induction of a MABP ~ 50-65 mmHg

1. reduction of intraoperative ***blood loss***
   - first controlled study Eikenhoff & Rich 1966
   - most studies → **~ 50% *reduction***
   - variable response, some patients do not respond as expected
   - effects appear to be independent of changes in cardiac output
   - more effective than haemodilution in reducing transfusion requirement
2. improved ***visibility*** of the surgical field
   - may be better monitor than absolute pressure reduction

***NB:*** absolute pressure reduction may be less important than hypotension plus positioning & venous drainage

- ***Indications***

| | | |
|---|---|---|
| a. | neurosurgery | - aneurysm<br>- tumour resection |
| b. | orthopaedic | - joint replacement<br>- bone transplant<br>- extensive back surgery |
| c. | oncology | - large tumours & exenteration procedures |
| d. | plastic surgery | - large tumours<br>- head and neck procedures |
| e. | ENT | - middle ear surgery, rhinoplasty<br>- head and neck tumours |
| f. | patient refusal of transfusion & anticipated major blood-loss | |

- ***Monitoring***

| | | |
|---|---|---|
| 1. | routine | - $FiO_2$, $S_pO_2$, $ETCO_2$, NIBP, ECG, temperature, spirometry |
| 2. | IABP | * ***radial*** not dorsalis pedis<br>- inaccuracies at low MABP with vasodilatation |
| 3. | CVP / PAOP | ∝ estimated blood loss & presence of CVS disease |
| 4. | mixed venous $P_{vO2}$ where higher doses of SNP used | |
| 5. | investigational | |
| | i. | EEG, processed EEG, SSEP's |
| | ii. | gastric mucosal pH |

- ***Methods of Hypotension***

1. controlled haemorrhage
2. regional anaesthesia
3. inhalational anaesthetics
4. vasodilators
   - i. nitrovasodilators - SNP, GTN, hydrallazine
   - ii. ganglionic blocking agents - trimethaphan
   - iii. adrenergic blocking agents - $\alpha$, $\alpha/\beta$
   - iv. adenosine
   - v. $PGE_1$
   - vi. calcium channel blockers & $Mg^{++}$
5. central $\alpha_2$-agonists - clonidine, dexmedetomidine

- ***Organ System Effects***

***NB:*** end-organ effects depend upon,

i. the ***method*** of hypotension (hypovolaemia $\rightarrow \downarrow$ perfusion)
ii. the ***duration*** & ***magnitude*** of hypotension
iii. preexisting end-organ dysfunction

1. CNS
   - assessed by $^{133}Xe$ clearance, EEG changes, jugular venous $P_{vO2}$
     $\rightarrow$ no permanent changes in cerebral function
   - current rationale for lower limit for MABP ~ 50-65 mmHg based upon the lower limit of ***cerebral autoregulation***
   - curve shifted to the right in chronic hypertensive patients
   - possibly some advantage using SNP at lower levels of MABP
     $\rightarrow$ better preservation of CBF and BBB function
   - deep isoflurane anaesthesia results in better preservation of cellular $P_{O2}$ values
   - at MAP ~ 50 mmHg, $CMRO_2$ is favourably influenced
   - ***all*** agents may result in increased CBV & ICP, thus should not be used prior to opening of the cranium, unless ICP is monitored
2. Respiratory
   - i. $\uparrow$ dead space $\propto$ $\downarrow$ MAP, $\uparrow$ mean $P_{AW}$, $\uparrow$ head-up tilt
     - prevented by maintenance of CO with ***volume loading***
   - ii. $\uparrow$ shunt $\propto$ $\downarrow$ HPV
     - effects are greatest in ***normal*** subjects, cf. CAL patients $\rightarrow$ no change
     - SNP > GTN >> isoflurane
   - controlled ventilation preferred

3. CVS
   - deep halothane was associated with ↓↓ CO → SNP, GTN, trimethaphan
   - IV agents ***are not*** associated with regional ischaemia in the absence of ***severe stenosis*** → > 40% reduction in resting CBF
   - ***trimethaphan*** may offer some advantage in the presence of severe IHD
   - ***isolflurane*** → ↓ SVR & minimal change in CO
   - Reiz *et al.* 1983 → isoflurane induced coronary steal
   - retrospective & outcome studies show no significance of "steal" during CABG, but ? no direct data relating induced hypotension doses
   - further, episodes of clinical "steal" have usually been ascribed to concurrent hypotension, (Merin, Adv.Anesth.1989)
   - ***adenosine*** also appears effective & safe but requires further testing in the presence of IHD
4. Renal
   - RBF/GFR decrease but readily return following hypotension
   - no adverse effects & renal dysfunction is infrequently seen
5. Gastrointestinal
   - no portal venous autoregulation & minimal hepatic autoregulation
   - no changes in LFT's at MABP ~ 50-65 mmHg
   - severe changes and centrilobular necrosis seen at MABP < 25 mmHg
6. Eye
   - uveal and retinal arterial supplies
   - no precapillary sphincters in the uveal circulation, \ ***pressure passive*** flow
   - changes in MAP directly transmitted to IOP
   - transient visual impairment & rarely blindness may result

- ***Contraindications***

1. longstanding uncorrected hypertension
2. major end-organ dysfunction
   i. cerebrovascular disease
   ii. severe ischaemic heart disease
   iii. hepatic or renal disease
3. peripheral vascular disease
4. uncorrected hypovolaemia
5. severe anaemia

***NB:*** most of these are relative contraindications, depending upon severity, eg. hypotension via GTN is used in the $R_x$ of severe angina !

- ***Complications***

1. mortality ~ 2-10:10,000
   ~ 0.01-0.007% directly related to anaesthesia
   ~ same as for other general anaesthesia (USA figures)
2. CNS - dizziness, prolonged awakening
   - cerebral venous thrombosis
   - cerebral, cerebellar infarction
3. retinal thrombosis
4. renal dysfunction, ARF
5. postoperative bleeding into the operative site

## Pharmacological Reduction in Blood-Loss

1. synthetic inhibitors of fibrinolysis - epsilon aminocaproic acid
   - tranexamic acid (~ 7x as potent)
   - bind to the same site & inhibit ***plasminogen*** activity
   - demonstrated to reduce blood loss post-CABG ~ 10-20%
   - possible fatal ***thrombotic complications***, but none seen in CABG studies
   - contraindicated in suspected DIC or with thrombotic tendency
2. ***aprotinin***
   - naturally occurring ***protease inhibitor*** → plasmin, trypsin, kallikrein
   - high dose therapy may also have a platelet protective effect during bypass
   - exact doses / timing of therapy uncertain, but must be given pre-bypass
   - substantially increases the ACT, \ require ACT > 750s on bypass (N > 400)
   - one study showed reduction from ~ 1500 ml → 300 ml
3. ***DDAVP***
   - synthetic anologue **1-deamino-8-*d*-arginine vasopressin** (ADH)
   - increases VIII:vWF and VIII:C activity
   - nonspecific increase in platelet activity
   - early reports showed reduced blood loss post-CABG, later reports ***no change***
   - indicated for ***haemophilia A*** and ***type I von Willebrand's disease***
   - it is not effective in types II & III
   - dose 0.3-0.4 µg/kg - ampoules 4.0 µg/ml
4. ***epogen*** - recombinant DNA ***erythropoietin***
   i. renal failure and other chronic anaemia states
   ii. in combination with preoperative autologous donation programmes
   - efficacy in perioperative haemorrhage requires evaluation
   - significant elevation of reticulocyte count not evident for ~ 1 week
   - very expensive & major side effect is ***hypertension* ~ 50%**

## Autologous Transfusion

1. preoperative donation & storage
2. acute preoperative phlebotomy & haemodilution
3. perioperative salvage from the surgical site

### ▪ *Preoperative Donation & Storage*

1. minimisation of transfusion reactions - excluding ***clerical errors***
2. minimal disease transmission - bacteraemia is an absolute C/I
3. stimulation of ***erythropoiesis*** - hidden benefit
4. long-term frozen storage in patients with unusual antibodies

• requires ~ 72 hours to normalise ***plasma proteins***, therefore last donation should be at least 3 days prior to surgery
• all patients should receive ***iron supplements***
• "high risk" patients are not necessarily unable to donate

***NB:*** it is ***not recommended*** to use a unit of autologous blood unless transfusion actually indicated, due to small incidence of clerical error etc.

### ▪ *Acute Preoperative Phlebotomy & Haemodilution*

• fast, easy and inexpensive
• less planning than pre-donation
• limited number of units, with decreasing Hct in each
• not suitable for patients anaemic preoperatively
• will also dilute platelets and coagulation factors, therefore avoid with coagulopathy
• volume replacement either with crystalloid (3:1) or colloid
• the estimated ***withdrawal volume*** is given by the estimated blood volume and Hct,

$$V_W \sim EBV \times \frac{H_I - H_E}{H_{AV}}$$

where $H_I$ = initial Hct, $H_E$ = endpoint and $H_{AV}$ = the average

• blood is collected into standard anticoagulant bags, requiring thorough mixing
• may be kept safely,

a. at room temperature ~ 6 hrs
b. refrigerated ~ 24 hrs

- ***Intraoperative Blood Salvage***

1. semicontinuous flow centrifuge → washed cells with a Hct ~ 60-70%
2. cannister collection & dispossable liner
3. single use, self-contained revision

***NB:*** 2 & 3 → unwashed cells, little data re Hct

- none of these techniques will have functioning ***platelets*** or ***coagulation factors***
- all are relatively contraindicated in the presence of malignant cell or bacterial contamination

## Red Blood Cell Substitutes

1. stroma-free haemoglobin SFH
   - i. free Hb → $P_{50}$ ~ 12-14 mmHg
     - prepared by filtration of outdated, lysed rbc's
     - small size of free $\alpha/\beta$ chains results in ready ***glomerular filtration***
     - plasma half-life ~ 3-4 hours, ∴ limited use
   - ii. ***modified rDNA Hb***
     - 1 amino-acid change on $\alpha$-chains maintains tetrameric structure
     - longer plasma half-life
     - $P_{50}$ ~ 32 mmHg
     - a solution of 7 gm% has an oncotic pressure ~ 25 mmHg
2. perfluorochemical emulsions PFC
   - inert, immiscible liquids with an $O_2$ solubility ~ 20x normal plasma
   - emulsified forming suspensions ~ 0.1 µm, but problems with stability
   - content ***linear*** with $P_{aO2}$ therefore require high $FiO_2$
   - fluorocrits ~ 2% with a $P_{aO2}$ ~ 500 mmHg → $C_{aO2}$ ~ 1.5 ml%
   - "Fluosol DA 20%" trialed in Japan

***NB:*** both of these solutions are cleared by the reticuloendothelial system, and have effective plasma half-lives of ~ 24 hours

# THE ANAEMIAS

## Classification

1. abnormal ***iron metabolism***
   i. iron deficiency anaemia
   ii. anaemias with 2° iron loading - sideroblastic anaemias
   - transfusional haemochromatosis
2. ***megaloblastic*** anaemias
   i. cobalamin deficiency
   ii. folate deficiency
   iii. other causes
3. anaemia of ***chronic disease***
4. ***haemolytic*** anaemias
5. anaemias with ***abnormal haemoglobins***
6. primary ***marrow*** failure & the myeloproliferative disorders

- ***Iron Deficiency Anaemias***

1. increased utilisation - postnatal & adolescent growth spurts
2. physiological iron loss - menstruation & pregnancy
3. pathological iron loss
   i. GIT or GUS blood-loss
   ii. pulmonary haemosiderosis
   iii. intravascular haemolysis
4. decreased iron intake
   i. cereal-rich, meat-poor diets, food faddists
   ii. elderly & indigent persons
   iii. malabsorption syndromes, post-gastrectomy

- ***Sideroblastic Anaemias***

1. hereditary or congenital sideroblastic anaemia
2. acquired sideroblastic anaemia
   i. drugs / toxins - alcohol, lead, isoniazid, chloramphenacol
   ii. neoplasia & inflammatory disease
   iii. alkalating agent chemotherapy - cyclophosphamide

- ***Megaloblastic Anaemias***

1. ***cobalamin deficiency***
   - i. inadequate intake - vegetarians, rarely
   - ii. malabsorption
     - ↓ intrinsic factor - pernicious anaemia
       - post-gastrectomy
       - congenital absence or dysfunction (rare)
     - terminal ileal disease - tropical sprue, non-tropical sprue
       - regional enteritis
       - surgical resection
       - neoplasms & granulomatous disorders (rare)
       - selective $B_{12}$ malabsorption
     - competition for $B_{12}$ - tapeworm
       - bacteria, blind loop syndrome
     - drugs - PAS, cholchicine, neomycin
     - other - **$N_2O$**, transcobalamin II deficiency
2. ***folic acid deficiency***
   - i. inadequate intake - alcoholics, teenagers (fads), some infants
   - ii. increased requirements - infancy, pregnancy
     - malignancy
     - increased erythropoiesis (chronic haemolysis)
     - chronic exfoliative skin disorders
     - haemodialysis
   - iii. malabsorption
     - intestinal disease - tropical sprue, non-tropical sprue
     - drugs - phenytoin, ethanol, barbiturates
   - iv. impaired metabolism
     - ↓ dihydrofolate reductase - methotrexate
       - pyrimethamine, triamterene, pentamidine, etc.
     - alcohol
     - congenital enzyme abnormalities
3. ***other causes***
   - i. drugs which impair DNA metabolism
     - ***nitrous oxide*** - ↓ methionine synthase, ***10-formyl-THF***
     - purine antagonists - 6-mercaptopurine, azathioprine
     - pyrimidine antagonists - 5-FU, cytosine arabinoside
     - miscellaneous - acyclovir, zidovudine, hydroxyurea
   - ii. metabolic disorders - rare
   - iii. unknown aetiology
     - refractory megaloblastic anaemia
     - Di Guglielmo's syndrome (atypical acute non-lymphocytic leukaemia)
     - congenital dyserythropoietic anaemia

- ***Anaemia of Chronic Disease***

1. chronic inflammatory disorders
   i. infection
   ii. connective tissue disorders
   iii. malignancy
2. uraemia
3. endocrine failure - hypothyroidism, Addison's
   - hypogonadism, panhypopituitarism
4. hepatic failure

- ***Haemolytic Anaemias***

1. extrinsic abnormalities
   i. splenomegaly
   ii. red cell antibodies - ***immunohaemolytic anaemias*** (see below)
   iii. mechanical trauma
      - impact - march haematuria, CPB pump
      - turbulence - artificial valves, calcific stenoses
      - microangiopathic - HUS, pre-eclampsia, DIC, TTP
   iv. direct toxic effect - malaria, clostridial infection
2. membrane abnormalities
   i. spur cell anaemia
   ii. paroxysmal nocturnal haemoglobinuria
   iii. hereditary spherocytosis
   iv. rare causes - hereditary elliptocytosis, stomatcytosis
3. intrinsic red cell abnormalities
   i. enzyme deficiency
      - Embden-Meyerhof (glycolytic) - pyruvate kinase, hexokinase
      - hexose-monophosphate shunt - ***G6PD***
   ii. haemoglobinopathies
   iii. Thalassaemias

- ***Immunohaemolytic Anaemias***

1. ***warm antibody*** immunohaemolytic anaemia
   - i. idiopathic
   - ii. lymphomas - Hodgkin's, non-Hodgkin's lymphoma
     - chronic lymphocytic leukaemia
   - iii. SLE
   - iv. tumours - rarely
   - v. drugs
     - α-methyldopa type → warm Ab type
     - penicillin type → hapten mediated
     - quinidine type → "innocent bystander"
2. ***cold antibody*** immunohaemolytic anaemia
   - i. cold agglutinin disease
     - acute - mycoplasma infection
       - infectious mononucleosis
     - chronic - idiopathic
       - lymphoma
   - ii. paroxysmal cold haemoglobinuria

- ***Abnormal Haemoglobins***

1. sickle syndromes
   - i. sickle cell trait - AS
   - ii. sickle cell anaemia - SS
   - iii. double heterozygous states
     - sickle β-Thalassaemia
     - sickle C disease - SC
     - sickle D disease - SD
2. unstable Hb variants
   - congenital Heinz body haemolytic anaemia
3. variants with high $O_2$ affinity
   - familial erythrocytosis
4. M haemoglobins - familial cyanosis

## Myeloproliferative Disorders

1. ***chronic myeloid leukaemia***
   - massive splenomegaly & leukocytosis ~ 50,000 - 200,000
   - chronic, relatively indolent, phase & the blastic phase which is rapidly fatal
   - characteristic chromosomal abnormality, ***Philadelphia chromosome***
2. ***polycythaemia rubra vera***
   - increased rbc mass with ↑ wbc's and platelets ~ 50%
   - pruritis, plethoric facies, retinal vein engorgement, symptoms of impaired cerebral blood flow
   - accelerated atherosclerotic and thrombotic disease, or haemorrhagic disease
   - splenomegaly ~ 75%
3. ***myelofibrosis***
   - fibrosis of bone marrow and extramedullary erythropoiesis, mainly the liver and spleen → hepato-splenomegaly
   - thrombotic tendency, haemorrhage is uncommon
4. ***essential thrombocytosis thrombocythaemia***
   - excessive megakaryocyte proliferation, with platelets ≥ 800,000
   - symptoms resemble PRV, with haemorrhagic or thrombotic complications

# ANAPHYLAXIS

***Def'n:*** ***anaphylaxis:*** symptom complex following exposure of a ***sensitised*** individual to an antigen, produced by immediate hypersensitivity or a type I hypersensitivity reaction, associated with IgE mediated mast cell degranulation

***anaphylactoid reactions:*** are indistinguishable from true anaphylaxis, however the immune nature of the reaction is either unknown, or not due to a type I hypersensitivity reaction

\ ***immediate generalised reaction*** may be a better term

## ▪ ***Aetiology***

1. ***anaphylaxis***
   - i. prior sensitisation to an antigen, either alone or in combination with a hapten
   - ii. synthesis of antigen specific **IgE**, which attaches to mast cells & basophils
   - iii. subsequent exposure →
     - mast cell & basophil degranulation
     - release of ***histamine*** + SRS-A (LT - $C_4$, **$D_4$**, $E_4$)
       ECF-A, NCF
       PAF, heparin
2. ***anaphylactoid reactions***
   - i. exposure & combination of antigen with **IgG, IgM** ± a hapten
   - ii. activation of ***complement*** via the classical pathway ($C_{1q}$, $C_4$, $C_2$)
   - iii. formation of ***anaphylatoxins*** - $C_{3a}$, $C_{5a}$
     - mast cell & basophil degranulation → ***histamine***, SRSA, etc.
3. direct release of histamine

## ▪ ***Common Antigens***

1. blood & blood products
2. XRay contrast media
3. antibiotics
4. STP, muscle relaxants
5. sulphonamides

- ***Presentation***

***NB:*** variable latent period, but usually within ***30 minutes*** of exposure

1. respiratory
   - dyspnoea, chest tightness
   - stridor, laryngeal obstruction
   - ***bronchospasm*** (*$LTD_4$)
   - raised peak $P_{AW}$, ↑ slope of alveolar plateau, ↓ $ETCO_2$
   - pulmonary oedema
2. cardiovascular
   - ***hypotension***, tachycardia ± arrhythmias
   - most common and may be sole finding
   - cardiovascular "collapse"
   - pulmonary oedema is a common finding at autopsy
   - ? existence of "myocardial depressant factors"
3. cutaneous
   - erythematous blush, generalised urticaria
   - ***angioedema***
   - conjunctival ingection & chemosis
   - pallor & cyanosis
4. gastrointestinal
   - nausea, vomiting, abdominal cramps & diarrhoea

- ***Management***

***NB:*** multiple actions simultaneously / conclude surgery / call for experienced help

1. cease administration of the likely antigen
2. maintain oxygenation
   i. maximal $O_2$ via face mask
   ii. IPPV via bag/mask
   iii. intubate & 100% $O_2$ ASAP *cease anaesthetic agents
3. support circulation
   i. CPR if no output
   ii. ***adrenaline***
      - inhibits mast cell degranulation, ↑ SVR, venous return, ↓ bronchospasm
      - hypotension: 10-50 µg boluses prn or infusion if available
      - collapse: 0.5-1.0 mg stat, then infusion
   iii. volume expansion*"whatever is available"
      - Haemaccel, NSA-5%, CSL, N.saline
      - CVP monitoring once situation under adequate control

4. manage ***bronchospasm***
   - i. maximise $FiO_2$
   - ii. slow RR, high E:I ratio ventilation
   - iii. adrenaline ~ 0.5 mg IM if no access
     - IV dependent upon MAP & ECG monitoring
   - iv. aerosol bronchodilators
   - v. aminophylline - additive effects with adrenaline
     ~ 5-6 mg/kg loading dose over 30-60
   - vi. suction ETT
   - vii. volatile agents - if isolated bronchospasm with maintenance of MAP
5. monitoring
   - i. ECG, NIBP, IABP when possible
   - ii. $S_pO_2$, $ETCO_2$, AGA's
   - iii. CUD, CVP ± PAOP
   - iv. transfer to ICU
6. other therapy
   - i. antihistamines - no benefit in acute episode
     - $H_2$ blockers contraindicated acutely
     - may be useful for ongoing angioedema
     - require both $H_1$ & $H_2$ for prophylaxis
   - ii. sedation - if intubated & resuscitation successful
   - iii. steroids - marginal benefit in acute episode
     - may be useful for ongoing bronchospasm & angioedema
     - required in addition to antihistamines for prophylaxis
7. followup
   - i. blood specimen
     - ***tryptase*** level - released from mast-cells/basophils, stable in plasma
     - complement - levels decreased with anaphylactoid responses
     - re-type screen & cross-match if due to blood reaction
   - ii. return unused blood products to the blood bank
   - iii. intradermal ***skin testing***
     - histamine releasing agents ~ 1:10,000
     - non-histamine releasing agents ~ 1:1,000
     - graded reponses of limited value, use ***absolute*** result
   - iv. medic-alert bracelet & accompanying letter(s)

| Mechanisms of Immunological Injury | | |
|---|---|---|
| Mechanism | Pathophysiology | Disease types |
| Type I<br>• immediate hypersensitivity<br>• IgE mediated | • basophil & mast cell degranulation<br>• histamine, SRSA, ECFA, NCF<br>• immediated wheal & flare | • anaphylaxis<br>• atopy |
| Type II<br>• cell cytotoxicity<br>• IgG, IgM mediated | • direct phagocytosis or cell lysis<br>• activation of complement, classical<br>• tissue deposition of complement | • blood transfusions<br>• Goodpasteur's syndrome<br>• autoimmune cytopaenias |
| Type III<br>• immune complex<br>• IgG, IgM, IgA mediated | • tissue deposition of Ag-Ab complexes<br>• accumulation of PMN's, macrophages & complement | • SLE<br>• serum sickness<br>• necrotising vasculitis |
| Type IV<br>• delayed hypersensitivity<br>• T-cell mediated | • T-cell induced mononuclear cell accumulation<br>• release of lymphokines & monokines<br>• often with granuloma formation | • TB, sarcoid<br>• Wegener's granulomatosis<br>• granulomatous vasculitis |