輸血(Blood transfusion)

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學習大綱(Outline)

- 血液成份和血品製造
- 各種血品的介紹和使用的適應症
- 輸血的併發症：急性 vs 長期併發症
- 紅血球抗原和抗體的介紹
- 輸血其它相關議題

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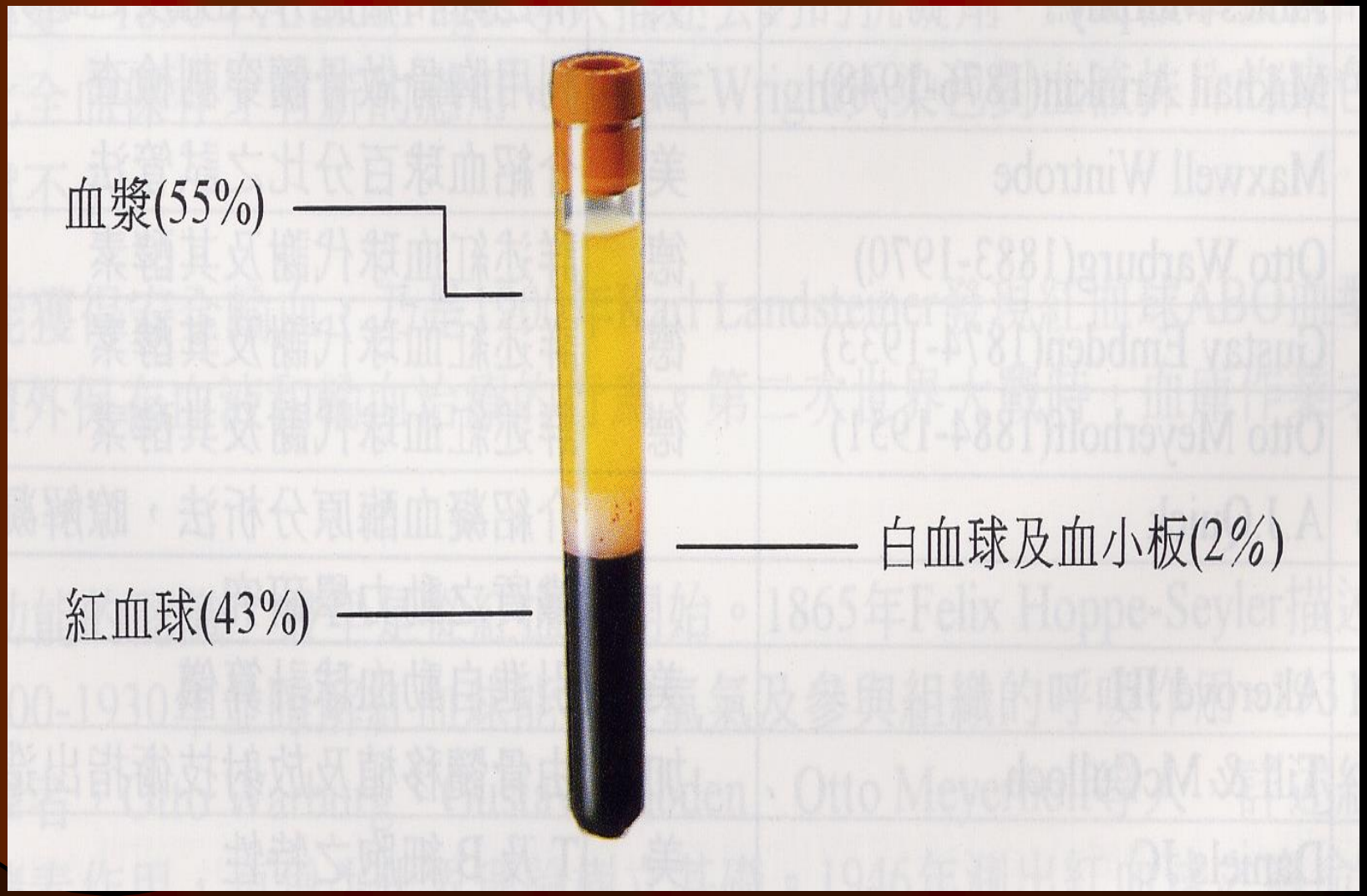
血液組成

- 血液是由血球和血漿所組成
- 血球包括紅血球、白血球和血小板，其中白血球又分為中性球、嗜酸性球、嗜鹼性球、單核球、淋巴球五種
- 血漿中含有各種凝血因子、酵素、白蛋白、免疫抗體及各種化學物質

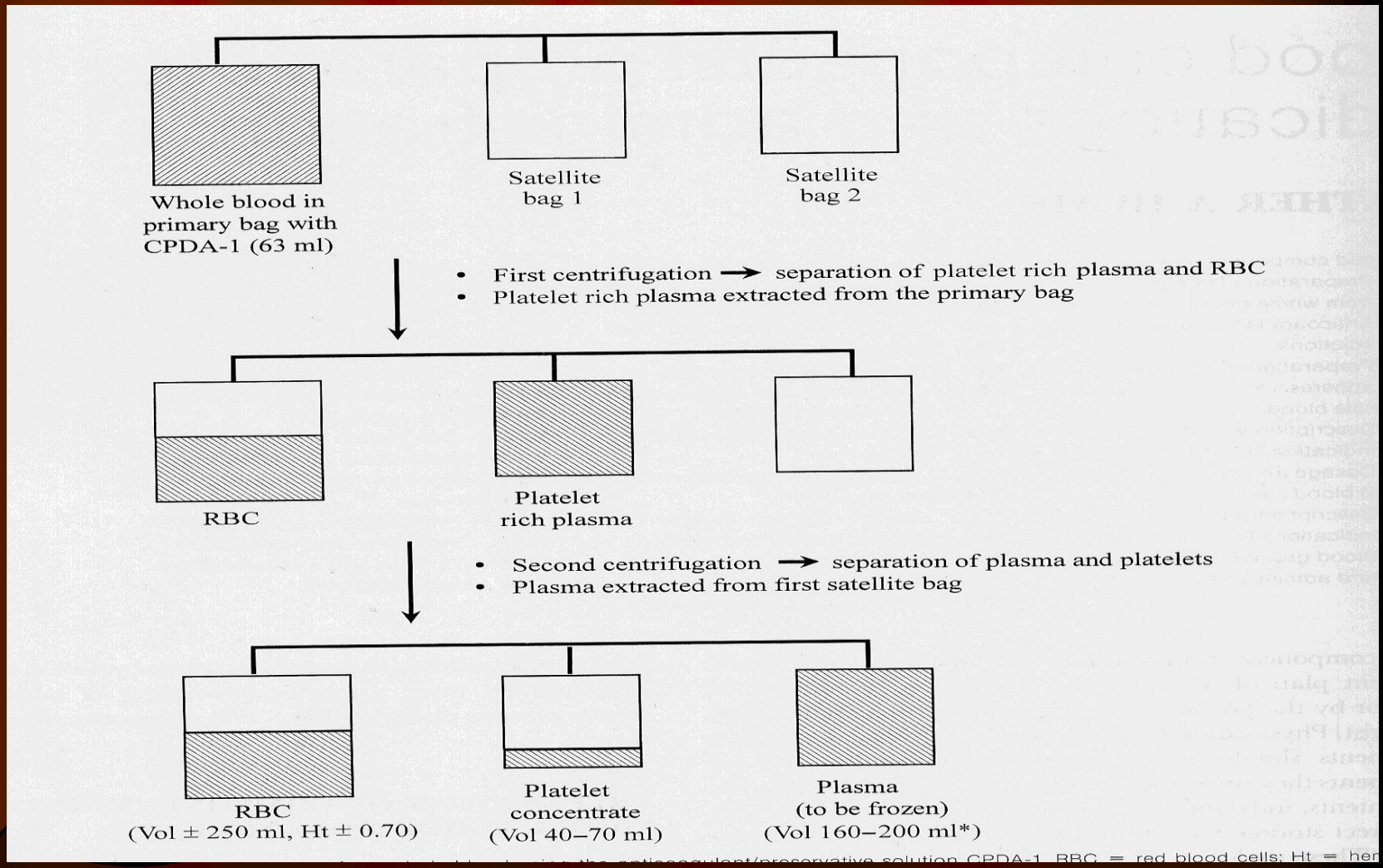
Blood component preparation

- Blood components are prepared from blood collected by whole blood or apheresis donation.
- WB is collected into sterile blood bags that contain a premeasured amount of anticoagulant/preservative (AP) solution
- The AP solution in common use is CPDA-1 (citrate-phosphate-dextrose-adenine)
- Automated apheresis procedures are sued to separate and collect platelets, granulocytes and plasma.

全血主要成份



Preparation of blood components from whole blood



anticoagulant/preservative solution CPDA-1, RBC = red blood cells; Ht = her

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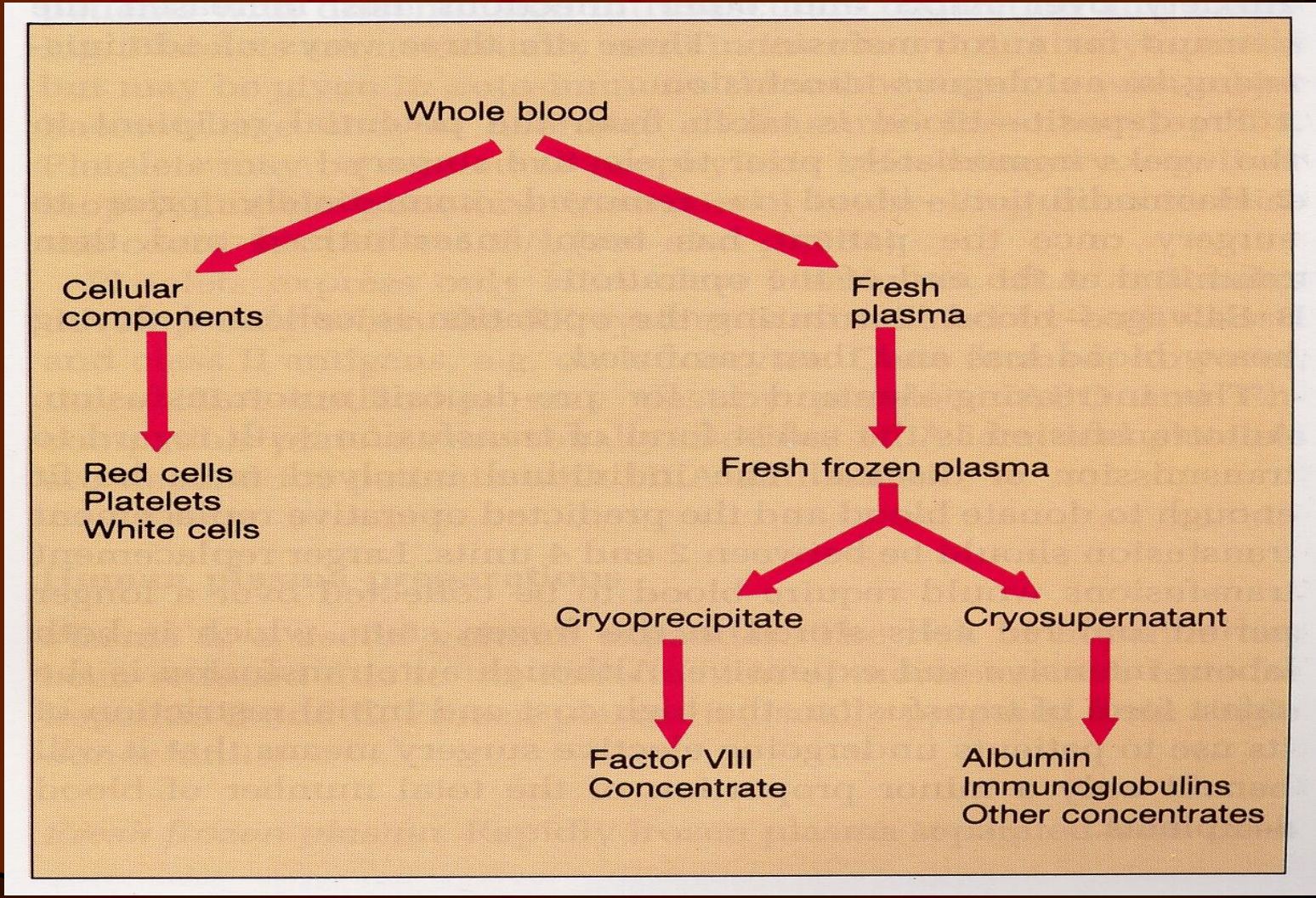

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Whole Blood (WB)

- Storage: 1-6^{o}C, 21-42 days
- Indication (emergent need RBC+plasma):
  1. rapid, massive blood loss, which require the simultaneous restoration of oxygen-carrying capacity and blood volume
  2. coagulation factor and platelet are rarely sufficient to correct the corresponding deficiencies
  3. massive transfusion

Massive Transfusion

- Definition

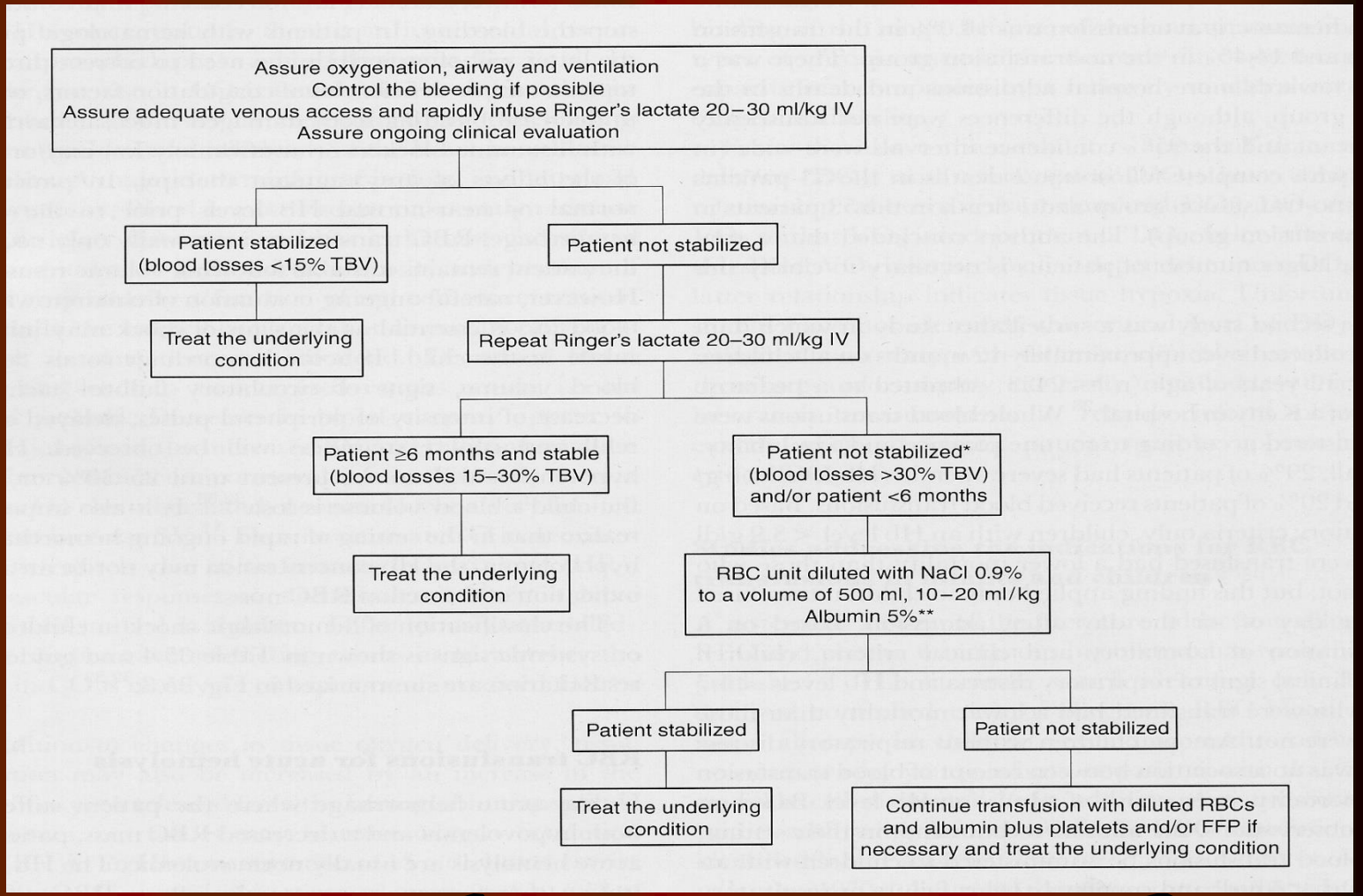
  Replacement of a patient's total blood volume with stored blood in <24 hours
- Use whole blood/FFP/platelet
- Other consideration:

  metabolic, bleeding (thrombocytopenia), coagulation problems (coagulation factor).

Red Blood Cells

- Storage: 1-6^{o}C, PRBC:35-42 days
- Indication:
  1. acute blood loss (eg, hemorrhagic shock)
  2. acute hemolysis
  3. chronic anemia
  4. thalassemia major

Treatment to hemorrhagic shock



Red Blood Cells

- Blood group choice
- Dosage and administration

  Dosage: 10cc/kg (usual entire unit), raise Hb:3g/dl

  Rate (usually): 2-4 hours
- If the anemia has developed slowly and the Hb< 5g/dl, it may be necessary to administer RBC transfusion more slowly and/or in smaller quantities to avoid precipitating cardiac failure from circulatory overload.

Choice of ABO blood groups for RBC, plasma and platelet transfusion

Recipient blood group	Acceptable ABO group of blood component to be transfused		
	RBCs*	Plasma	Platelets**
O	O	O	O
		A, B, AB	A, B, AB
A	A	A	A
	O	AB	AB
B	B	B	B
	O	AB	AB
AB	AB	AB	AB
	A, B, O		A

Red Blood Cells

- Packed RBCs
- Washed RBCs
- Frozen deglycerolizes RBCs
- Leukocyte-poor RBCs (RLPR: Remove Leukocyte Packed RBCs)

Washed RBC

- Preparation: RBCs washed then resuspended with normal saline (90% of WBC are reduced)
- Storage: 1-6^{o}C, 24 hours
- Indication
  1. history of repeated febrile and/or allergic reactions
  2. Prevent of severe allergic reaction due to anti-IgA (IgA deficiency)
  3. paroxysmal nocturnal hemoglobinuria

Leukocyte-Poor RBC

- RLPR: Remove Leukocyte Packed RBCs
- Preparation: RBCs leukodepleted by filtration
- Indication:
  1. history of repeated febrile and/or allergic reactions
  2. prevention of HLA alloimmunization
  3. prevention of CMV transmission
  4. patients with transfusion dependent

Platelets (PLT)

- Storage: 5 days at 20-24^{o}C, 1 unit:30-40cc
- Fresh random donor (pooled) PLT vs Single donor PLT
- PPH (platelet pheresis) 1 bag: platelets from a single donor containing 12 units of PLT, about 200cc
- If ABO matched PLTs are not available, units with plasma compatible with the recipient's RBCs should be chosen
- ABO-incompatible PLT is associated with poorer post transfusion response and platelet refractoriness
- 0.1u/kg PLT, raise PLT 25,000/uL

Indications for PLT transfusion

- Decreased PLT production (aplastic anemia, bone marrow infiltration with leukemic or other malignant cells, chemotherapy):

  1. prophylactic PLT transfusion:

     # stable patients: below 10,000/uL

     # in BMT patient, keep PLT>20,000/uL

     # invasive procedure: PLT>50000/uL

  2. therapeutic PLT transfusion

Prophylactic platelet transfusions in patients with thrombocytopenia due to decreased platelet production

Platelet count $<10 \times 10^9$/l
Platelet count $<20 \times 10^9$/l and bone marrow infiltration, severe mucositis, DIC, anticoagulation therapy, a platelet count likely to fall below 10×10^9/l prior to next possible evaluation, or risk of bleeding due to local tumor invasion
Platelet count $<30–40 \times 10^9$/l and DIC (e.g. during induction therapy for promyelocytic leukemia), extreme hyperleukocytosis, or prior to lumbar puncture or central venous line insertion
Platelet count $<50–60 \times 10^9$/l and major surgical intervention

Indications for PLT transfusion

Increased PLT destruction:

- ITP: Thrombocytopenia due to ITP should only be treated with PLT transfusions in the presence of CNS or other life-threatening bleeding
- Conditions other than ITP (eg, septicemia, trauma, DIC) may result in PLT consumption that is sufficiently severe to require PLT transfusion.
- PLT increment and survival are usually decreased and a larger number of units administered at more frequent intervals my be necessary.

Platelet Refractoriness

- Def: consistently inadequate response to PLT transfusion

  Failure to achieve a CCI>7500/uL at 1 hour following an adequate dose (in the non-bleeding patient 1 unit/10 kg, maximum 6 units) of pooled donor platelets on >2 occasions
- Causes:
  * Immune: (HLA or platelet-specific alloantibodies)
  * Non-immune: amphotericin B, vancomycin, ciprofloxacin, fever, infection, splenomegaly, DIC, BMT

Platelet Refractoriness

Corrected platelet count increment (CCI):

(Posttransfusion-pretransfusion) x body surface (m^2)/ Number of platelets transfused ($x10^{11}$)

- Platelet transfusion is successful when

  CCI>7500/uL within 10-60 minutes and

  CCI>4500/uL, 18-24 hours after transfusion

Platelet Refractoriness

Management

1. Remove of the underlying causes
2. ABO-identical PLT
3. Fresh as opposed to stored platelets
4. HLA-matched PLT for HLA alloimmunization
5. Platelets lacking the corresponding antigen for PLT-specific alloantibodies
6. IVIG?

Granulocytes

- Storage: 20-24^{o}C, <24 hours
- Indication:

  profound neutropenia not expected to recover within a week, severe bacterial infection has been documented and clinically deteriorating despite optimal antimicrobial therapy
- Disadvantages:

  time-limited, febrile transfusion reaction, CMV infection, pulmonary reaction, GVHD, frequently (short half-life in granulocytes), large doses, effect is not definite
- G-CSF replace granulocytes

Plasma and plasma derivatives

- Fresh-Frozen Plasma (FFP)
- Cryoprecipitate
- Plasma-derived FVIII and V-W Factor (vs recombinant)
- Plasma-derived FIX (vs recombinant)
- Albumin
- Immunoglobulins

Plasma

- Proteins that maintain osmotic pressure and immunity
- Components of the coagulant, anti-coagulant, and fibrinolytic systems
- Other protein which have diverse activities
- Fats, carbohydrates, and minerals in concentrations similar to those in the circulation
- Blood-born disease

Fresh Frozen Plasma

- Storage: -18°C for 12 months, thawed at 30-37°C, transfusion in 6 hrs
- Dosage and administration
  * ABO compatible with the recipient's RBCs
  * dose of FFP depends on the clinical situation and the underlying disease process
  * dose:10-20ml/kg
  * post-transfusion monitoring of the patient's coagulation status (eg PT/aPTT) is important for optimal treatment

Indication for FFP

- Reversal of warfarin effect
- Severe liver disease:
  invasive procedures or surgery in patients with liver disease and PT>1.5-fold normal or and INR>2.2
- DIC
  generally not recommended in the absence of bleeding or chronic DIC
- Massive transfusion
- Congenital deficiencies of hemostatic or anticoagulant proteins
- Hemolytic uremic syndrome/Thrombotic thrombocytopenia purpura

Cryoprecipitate

- Cryoprecipitate is the precipitate formed when FFP is thawed at 4^{o}C
- Storage: -18^{o}C,12 months;
  thawed 30-37^{o}C, transfusion in 6 hrs
- Content: fibrinogen, Factor VIII, V-W factor, Factor XIII, fibronectin
- Indication: hemophilia A, V-W disease, fibrinogen deficiency, Factor XIII deficiency, bleeding due to acquired fibrinogen deficiency, e.g. severe liver disease, DIC

Immunoglobulins

- Intramuscular vs intravenous (IVIG)
- Specific human immune globulin: high titers to an infectious agent (e.g. hepatitis, zoster) or RhD antigen
- 5S vs 7S (intact immunoglobulin)
- Indication: immunodeficiency, Kawasaki disease, ITP, other autoimmune disorders, severe sepsis (?)
- Dose: 2gm/kgw
- Adverse effect: hypersensitivity reactions (fever, rigors, headache, nausea, myalgia, rash), anaphylactic reactions, aseptic meningitis

Blood transfusion should be **individualized**, taking into account the **clinical situation**

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Hazards of Transfusion: acute transfusion reaction

- Acute hemolytic transfusion reaction (AHTR)
- Transfusion-related acute lung injury
- Allergic reaction
- Febrile non-hemolytic transfusion reaction
- Massive transfusion
- Storage lesions: hyperkalemia, poor platelet function with increased storage time, low 2,3 DPG
- Anticoagulant/preservative solution
- Cold storage conditions
- Coagulopathy
- Bacterial contamination

Acute hemolytic transfusion reaction

- **Intravascular hemolysis (IgM mediated, ABO antibodies)**
- **Clinical features: fever, chills, back and chest pain, nausea, SOB, hypotension, DIC, acute renal failure**
- **Management**

1. stop immediately

2. the donor blood and post-transfusion samples of patient's blood should be sent to blood bank

3. aggressive intravenous hydration and alkalization

4. steroid, antihistamine, adrenaline

5. manage DIC, renal injury, shock

Acute hemolytic transfusion reaction

Most ABO hemolytic transfusion reactions are a result of **misidentifying** the intended recipient of a unit of blood and are therefore **avoidable**

Allergic reaction and Febrile reaction

Allergic reaction:

- allergy to soluble plasma proteins
- itching, urticaria, bronchospasm, anaphylasix
- management: antihistamine, washing RBC

Febrile non-hemolytic transfusion reaction

- causes: WBC, bioreactive substances:IL-1ß, IL-6, IL-8, TNF
- management: pre-storage leukoreduction

Anticoagulant/Preservative solution

- Cause: citrated blood components
- Risk factors: massive transfusion, plasma exchange, peripheral stem cell collection, poor hepatic function
- Manifestation: hypocalcemic, alkalotic, hypokalemic

Adverse reaction with delayed occurrence

- Transfusion-associated alloimmunization
- Post-transfusion purpura
- Transfusion-associated graft versus host disease
- Transfusion-associated immune modulation
- Transfusion transmitted infection
- Iron overload

Transfusion transmitted infection

- Hepatitis: HAV, HBV, HCV, HDV, HGV
- Human immunodeficiency virus 1: HIV 1
- Human immunodeficiency virus 2: HIV 2
- Human T-cell lymphotropic virus: HTLV
- Cytomegalovirus: CMV
- Malaria, syphilis, etc

輸血問題

- 台灣的血液做B肝、C肝及愛滋的篩檢，但是因為有空窗期，所以還是會有感染的危險
- 每次輸血得B肝的機率只有6萬3千分之一；得愛滋的機率是百萬分之一；得C肝的機率為10萬3千分之一
- 輸血感染的機會微乎其微，父母不必過度擔心
- 用親人的血並不好，因為較容易產生各種副作用及排斥

Transfusion-Associated Graft-Versus Host Disease (TA-GVHD)

- Engraftment donor T lymphocytes attack recipient who is unable to reject them
- All cellular blood components are implicated
- Acute syndrome, occurring within 4-30 days. dysfunction of skin, liver, GI tract, bone marrow
- Major risk factors: congenital or acquired deficiency of cell-mediated immunity
- Treatment of TA-GVHD is always ineffective

Indications for irradiated blood

Infants/fetus <4 months of age

- Fetus received *in utero* transfusion
- Premature infants and those of low birth weight (<1200 g)
- Known or suspected congenital cellular immunodeficiency
- Congenital leukemia, malignancy undergoing chemotherapy
- Infant undergoing exchange transfusion for Rh hemolytic disease with/without history of intrauterine transfusion
- Recipient of familial blood or HLA-matched cellular products

Children >4 months of age

- Known or suspected congenital cellular immunodeficiency
- Malignancy (hematologic/solid tumor) undergoing chemotherapy/radiotherapy
- Recipient of solid organ or stem cell transplantation
- Recipient of familial blood or HLA-matched cellular products

Patients for whom risk is not well established to support irradiation

- Infants >1200 g in NICU setting but without history as described above
- All children undergoing open-heart procedures, including ECMO
- Any child with a conal-truncal heart defect until congenital T-cell immunodeficiency is ruled out
- HIV infection

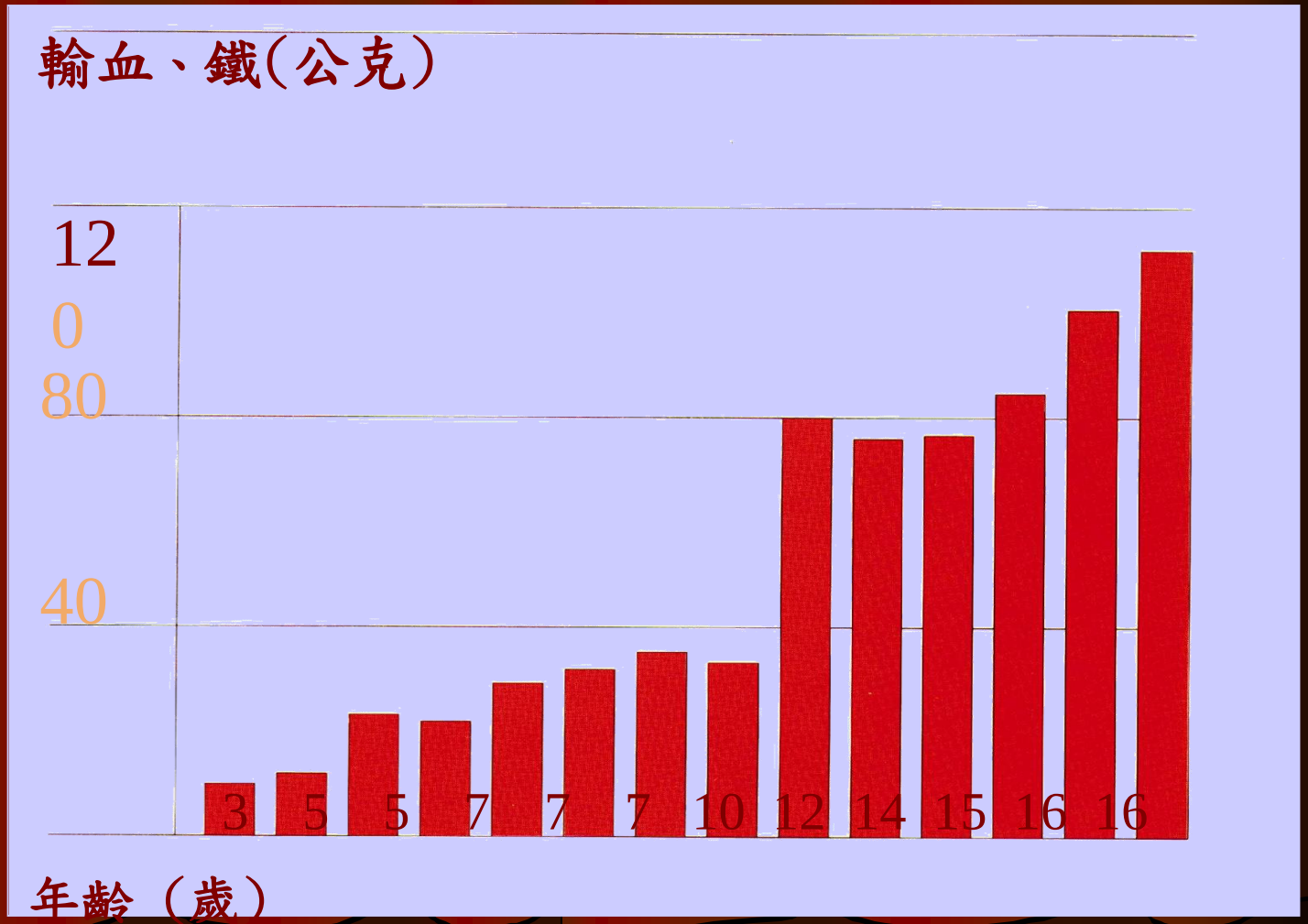
為什麼會鐵質過度沉積?

1.長期反覆輸血

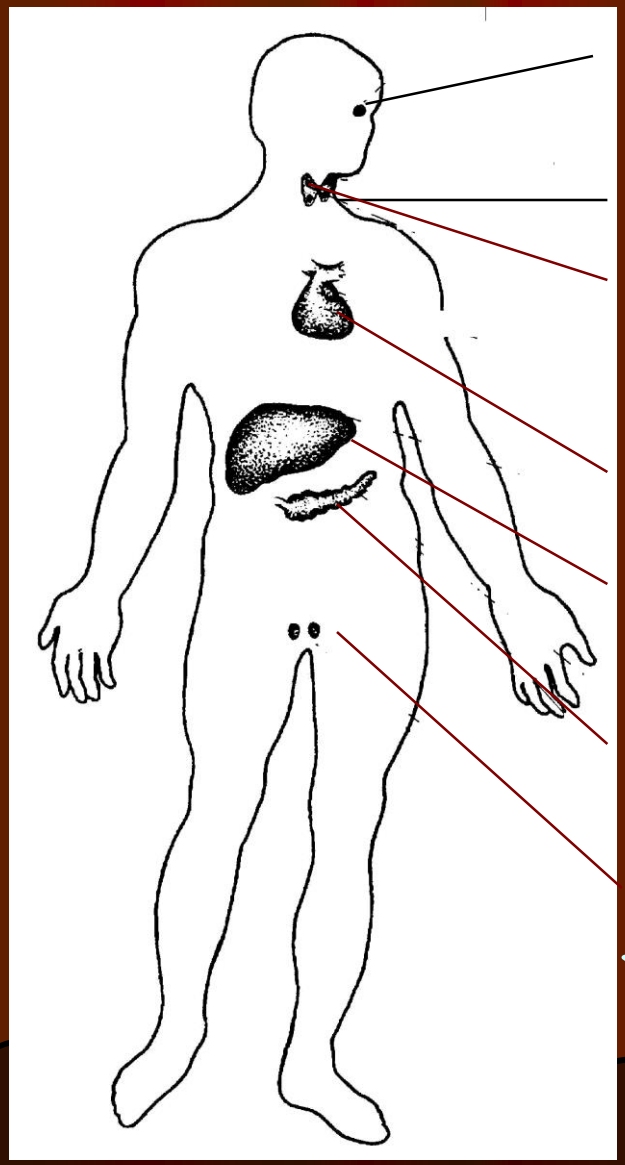
2.腸道對鐵質的吸收大量增加鐵質過度沉積,

造成各種併發症,所以需使用排鐵劑

重型海洋性貧血鐵沉積



重度海洋性貧血鐵沉積所造成的傷害



腦垂體

甲狀腺

副甲狀腺

心臟

肝臟

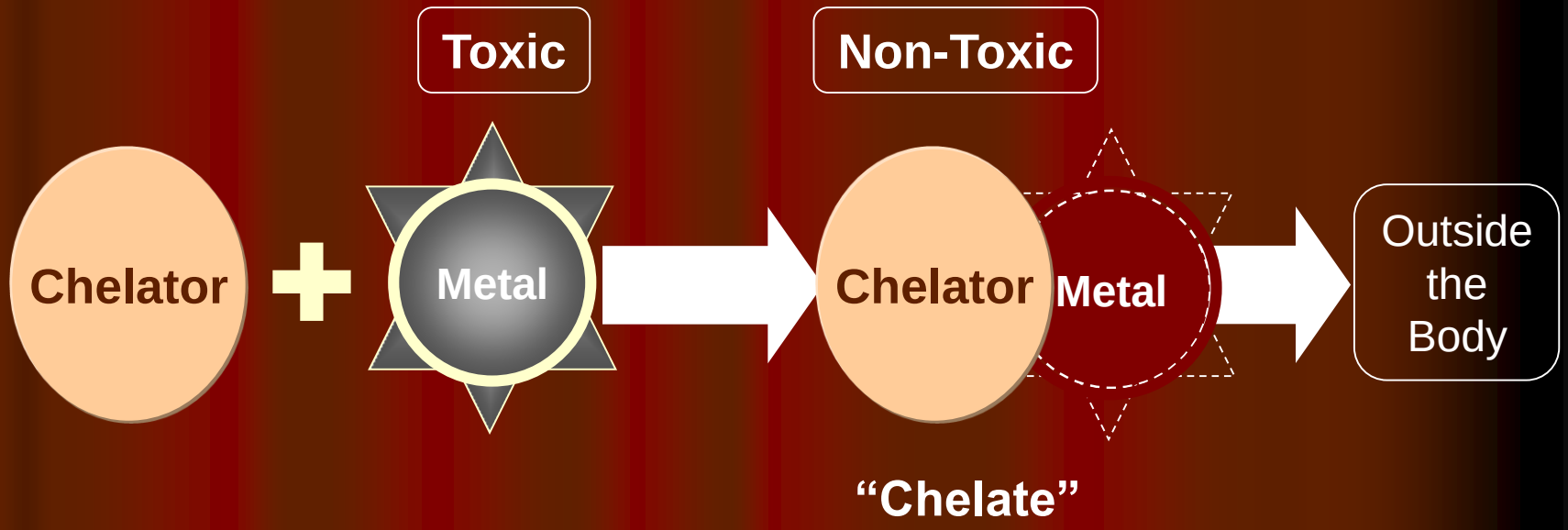
胰臟

生殖器

重度海洋性貧血會有那些身體上的問題?

1.心臟(主要死因): 鐵過度沉積
2.肝臟: 鐵沉積、肝炎
3.脾臟: 脾腫大
4.骨骼: 臉部骨變型、易骨折
5.皮膚: 膚色變深
6.內分泌: 甲狀腺，副甲狀腺,糖尿病
7.生長發育、青春期的問題
8.聽力、視力的問題

What is Chelation Therapy?



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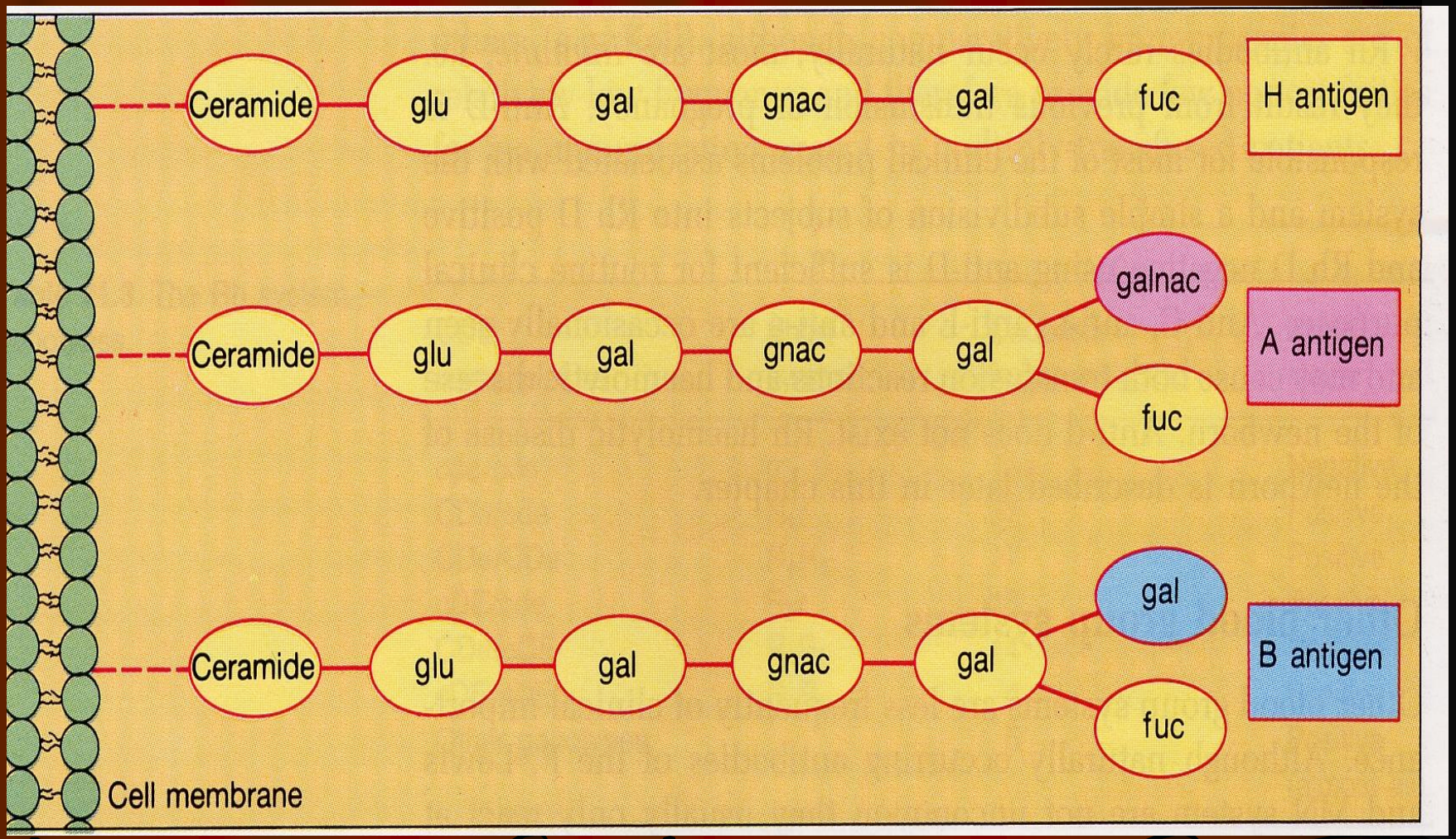
Red cell antigens/antibodies

- Red cell antigens (blood groups): ABO, Rh, other blood group systems.
- Blood group antibodies: naturally occurring, immune antibodies (by transfusion or tansplacental)
- Direct/indirect antiglobulin (Coombs) test

Structure of ABO blood group antigens



Clinically important blood group systems

Systems	Frequency of antibodies	Cause of haemolytic transfusion reaction	Cause of haemolytic disease of newborn
ABO	Very common	Yes (common)	Yes
Rh	Common	Yes (common)	Yes
Kell	Occasional	Yes (occasional)	Yes
Duffy	Occasional	Yes (occasional)	Yes
Kidd	Occasional	Yes (occasional)	Yes
Lutheran	Rare	Yes (rare)	No
Lewis	Occasional	Yes (rare)	No
P	Occasional	Yes (rare)	Yes (rare)
MN	Rare	Yes (rare)	Yes (rare)
Ii	Rare	Unlikely	No

Pretransfusion tests

1. determine patient's blood group (ABO and Rh)
2. antibody-screen test: screen patient's serum for atypical antibodies
3. cross-matching: red cells from donor tested against patient's serum

Blood Transfusion

- Immune hemolytic anemia: alloimmune vs autoimmune hemolytic anemia
- Hemolytic disease of the newborn (HDN)

- Special considerations for newborns
- Directed donation
- Hematopoietic growth factors: G-CSF, GM-CSF, Erythropietin (Epo), Tpo

Transfusion Medicine, 2003, **13**, 311–314

ORIGINAL ARTICLE

Haemolytic disease of the newborn due to maternal irregular antibodies in the Chinese population in Taiwan

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Received 1 April 2003; accepted for publication 13 June 2003

SUMMARY. From 1991 to 2000, amongst 23 886 full-term healthy Chinese babies delivered at our hospital, 2615 babies developed neonatal hyperbilirubinaemia. After excluding other causes of hyperbilirubinaemia and identifying the irregular antibodies, 15 cases of haemolytic disease of the newborn (HDN) due to maternal irregular antibodies were diagnosed; three cases were born in our hospital and 12 cases were referred. Amongst these 15 babies, six cases had HDN due to anti-E, three cases due to anti-E + c, three cases due to anti-D, one case due to anti-c and two cases due to 'Mi' antibodies reacting with MiIII phenotype cells (anti-Hil and anti-Mur). Although there were four cases of hydrops fetalis, only one of the patients expired.

The prevalence of HDN caused by maternal irregular antibodies has been estimated to be 0·01%. Therefore, routine prenatal screening for irregular antibodies was not rational in the Chinese population in Taiwan. Anti-E and anti-E + c were the important irregular antibodies resulting in HDN. Although few cases of HDN due to anti-'Mi' have been reported, Anti-'Mi' is significant in regions with a high prevalence of the MiIII phenotype.

Key words: Chinese, haemolytic diseases of the newborn, irregular antibodies.

Table I. Data of the patients with haemolytic disease of the newborn due to maternal irregular antibodies

Irregular antibodies	Gravida para	Transfusion history	Initial haemoglobin ($g\,dL^{-1}$)	Peak bilirubin level ($mmol\,L^{-1}$)	Treatment	Others
Anti-E	G3P3	No	16·4	300	Phototherapy	
Anti-E	G3P3	No	12·1	350	Phototherapy	
Anti-E	G4P2	Yes	5·1	320	EBT	Hydrops
Anti-E	G3P1	No	12·7	267	Phototherapy	
Anti-E	G3P2	No	15·2	322	Phototherapy	
Anti-E	G3P3	No	13·5	317	Phototherapy	
Anti-E + c	G2P2	Yes	11·2	417	EBT	
Anti-E + c	G3P2	No	13·0	402	EBT	
Anti-E + c	G2P2	No	15·1	283	Phototherapy	
Anti-D	G5P3	No	12·2	412	EBT	
Anti-D	G3P1	No	4·1	300	EBT	Hydrops, expired
Anti-D	G2P2	Yes	3·6	265	EBT	Hydrops
Anti-c	G2P2	No	10·8	417	EBT	
Anti-Hil	G2P2	No	11·2	300	Phototherapy	MiIII gene
Anti-Mur	G1P1	No	4·4	101	Phototherapy	Hydrops IT, MiIII gene

EBT, exchange blood transfusion; IT, intrauterine transfusion; Mi, Miltenberger.

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Blood Transfusion

Autologous transfusion

1. preoperative autologous blood donation
2. acute normovolemic hemodilution
3. intraoperative cell salvage and retransfusion

Blood transfusion and Hematopoietic stem cell transplantation (HSCT)

- Peripheral blood stem cell harvest
- HSC component processing (plasma removal, RBC removal) and cryopreservation
- Blood component transfusion

Hemapheresis

Component apheresis

- Platelet, plasma, granulocyte
- Peripheral blood stem cell (auto vs allo)

Therapeutic apheresis

- Therapeutic leukapheresis
- Therapeutic thrombocytapheresis
- Therapeutic plasma exchange (Guillain-Barre, TTP, etc)

總 結

- 了解各種血品使用適應症:

  特別是RBC和PLT

- 知道如何避免輸血的併發症和如何處理:

  特別是輸血反應要如何處理