IMMUNOHEMATOLOGY

Kenneth Alonso, MD, FACP

Immune hemolytic anemia

- Red cell survival shortened due to deposition of immunoglobulin and/or complement on the cell surface
- Extrinsic hemolytic anemia with extravascular or intravascular hemolysis
- Autoimmune
- Most common type
- More common in women
- 70% are IgG antibodies (warm)
- Systemic lupus erythematosus most common
- 30% IgM antibodies (cold)
- Atypical pneumonia (anti-I antibodies)
- Mycoplasma pneumonia (anti-I antibodies)

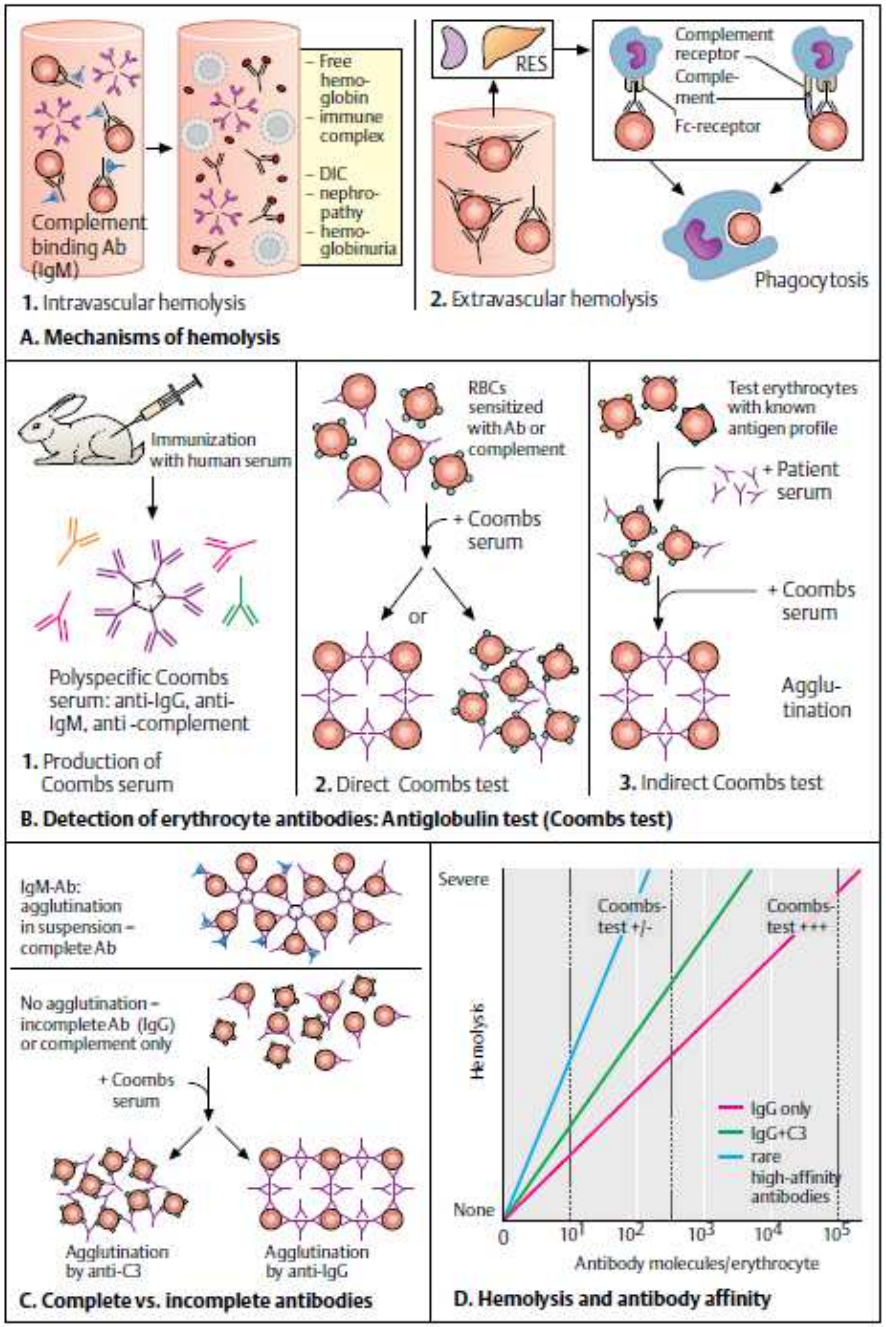
Immune hemolytic anemia

- Drug induced
- IgG antibody directed against drug attached to red cell membrane
- Penicillin
- Drug-IgM immunocomplex deposits on the red cell
- Quininidine
- Autoantibody induction by altering antigens on red cells
- α-Methyldopa alters Rh antigens on red cell
- autoantibody against altered antigen

Immune hemolytic anemia

- Alloimmune
- Production of an antibody against a foreign antigen not on the individual's red cells
- ABO hemolytic disease of the newborn (Anti-A or B)
- Rh hemolytic disease of the newborn (anti-D)
- Hemolytic transfusion reaction (atypical antibody)
- Indirect Coombs' detects (free) antibodies in serum

Immune mediated hemolysis



Burmester, GR, Pezzutto, A, Color Atlas of Immunology. 2003. Thieme. Stuttgart. p119 Accessed 12/10/2019

Pathogenesis

- IgG-mediated hemolysis
- Red cells coated by IgG phagocytized by splenic macrophages
- Spherocytes produced if only a small amount of the membrane is removed
- IgM-mediated hemolysis
- Red cells agglutinate
- Extravascular or intravascular hemolysis dependent upon degree of complement activation
- Usually intravascular hemolysis
- Direct antihuman globulin test (Direct Coombs') detects cells sensitized with IgG and/orC3b

Pathogenesis

- Complement-mediated hemolysis
- Red cells coated by C3b alone are phagocytized by liver macrophages
- Extravascular hemolysis
- Red cells coated by both IgG and C3b are phagocytized by hepatic and splenic macrophages
- Extravascular hemolysis
- Red cells coated by C5-C9 (membrane attack complex, MAC)
- Intravascular hemolysis

Warm antibodies

- IgG but may fix complement (C3b)
- High binding affinity at 37C (core temperature)
- IgG coated red cells bind to Fc receptor on macrophages (spleen)
- Portion of cell membrane removed
- Spherocytes
- C3b coated red cells removed by macrophages (liver)
- C3b is an opsonin
- IgG and C3b coated red cells are phagocytized by macrophages (spleen, liver)
- Extravascular hemolysis
- Haptoglobin levels decreased

Cold antibodies

- IgM
- High affinity binding at 4C
- Fixes complement
- When coated red cell circulates to warmer tissues (core), IgM dissociates, leaving MAC on the red cell
- Coated red cells phagocytized by macrophages (spleen, liver, bone marrow)
- Intravascular hemolysis
- May see schistocytes
- Haptoglobin levels decreased
- Microangiopathic hemolytic anemia is not autoimmune, but due to mechanical factors.

Blood group

- i antigen is the I antigen precursor
- I antigen is the ABH precursor.
- H antigen is a fucose attached to glycolipid in the cell membrane.
- If N-acetylgalactosamine is added to the H antigen, A antigen is produced (group A)
- If galactose, B antigen (group B).
- If no addition is made to H antigen, it is a group O (Ø or 0).
- O_h (Bombay) is a result of suppression of gene expression of normal A/B and secretor genes

ABO antigen structure

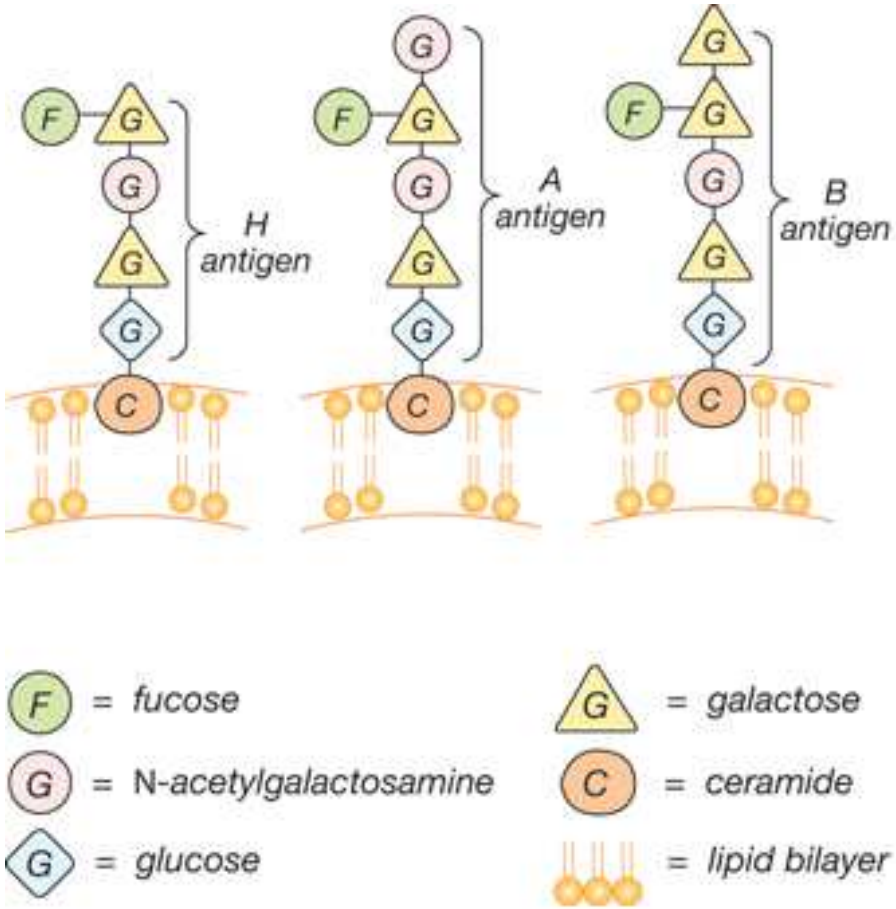


Fig. 32-10 Accessed 02/02/2010

Source: Barrett KE, Barman SM, Boitano S, Brooks H: *Ganong's Review of Medical Physiology, 23rd Edition*: http://www.accessmedicine.com

Blood group inheritance

- Genes are co-dominant (chromosome 9p).

		A	B	O	Father's phenotype
Mother's phenotype	A	AA	AB	AO	
	B	AB	BB	BO	
	O	AO	BO	OO	

- The child's phenotype is A (AA or AO genes)
- The child's phenotype is B (BB or BO genes)
- The child's phenotype is AB (AB genes)
- The child's phenotype is O (HH genes)

Blood group

- Isohemagglutinins are naturally occurring antibodies in the serum
- Synthesized in Peyer's patches
- Epitopes resembling A and B antigens from plants, bacteria, food are trapped by M cells that overlie Peyer's patches
- M cells transport antigens to proximate B cells in the epithelium
- Natural antibodies develop
- IgM
- Newborns do not have isohemagglutinins

Blood group

- Those with blood group A have anti-B antbodies
- Those with group B have anti-A antibodies
- Those with group O have both anti-A and anti-B antibodies.
- Those with group AB do not have anti-A or anti-B antibodies.

How blood group is determined

	Front Type		Back Type	
Blood Group	Anti-A	Anti-B	A cells	B cells
O	-	-	+	+
A	+	-	-	+
B	-	+	+	-
AB	+	+	-	-

1. Patient cells are treated in separate test tubes with Anti-A and Anti-B IgM antibodies.
2. Patient serum is added to separate test tubes containing A cells and B cells.

A positive reaction refers to agglutination of the cells with exposure to the appropriate antibody.

Blood group distribution

TYPES	DISTRIBUTION	RATIOS
O +	1 person in 3	38.4%
O -	1 person in 15	7.7%
A +	1 person in 3	32.3%
A -	1 person in 16	6.5%
B +	1 person in 12	9.4%
B -	1 person in 67	1.7%
AB +	1 person in 29	3.2%
AB -	1 person in 167	0.7%

Chimpanzees mostly have blood group A, almost no blood group O, but never blood group B.
The Gorilla has blood group B, almost no blood group O, but never Blood type A.
Man has groups A, B, and AB. The majority of humans of whatever ethnic or racial group have blood group O.
This reflects mating habits and tribal range.

http://www.bloodbook.com/world-abo.html
Accessed 12/10/2019

Blood group distribution by tribe or race

http://www.bloodbook.com/world-abo.html

Accessed 12/10/2019

PEOPLE GROUP	O	A	B	AB
Aborigines	61	39	0	0
Abyssinians	43	27	25	5
Ainu (Japan)	17	32	32	18
Albanians	38	43	13	6
Grand Andamanese	9	60	23	9
Arabs	34	31	29	6
Armenians	31	50	13	6
Asian (in USA - General)	40	28	27	5
Austrians	36	44	13	6
Bantus	46	30	19	5
Basques	51	44	4	1
Belgians	47	42	8	3
Blackfoot (N. Am. Indian)	17	82	0	1
Bororo (Brazil)	100	0	0	0
Brazilians	47	41	9	3
Bulgarians	32	44	15	8
Burmese	36	24	33	7
Buryats (Siberia)	33	21	38	8
Bushmen	56	34	9	2
Chinese-Canton	46	23	25	6
Chinese-Peking	29	27	32	13
Chuvash	30	29	33	7
Czechs	30	44	18	9
Danes	41	44	11	4
Dutch	45	43	9	3
Egyptians	33	36	24	8
English	47	42	9	3

Blood group distribution by tribe or race

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Eskimos (Alaska)	38	44	13	5
Eskimos (Greenland)	54	36	23	8
Estonians	34	36	23	8
Fijians	44	34	17	6
Finns	34	41	18	7
French	43	47	7	3
Georgians	46	37	12	4
Germans	41	43	11	5
Greeks	40	42	14	5
Gypsies (Hungary)	29	27	35	10
Hawaiians	37	61	2	1
Hindus (Bombay)	32	29	28	11
Hungarians	36	43	16	5
Icelanders	56	32	10	3
Indians (India - General)	37	22	33	7
Indians (USA - General)	79	16	4	1
Irish	52	35	10	3
Italians (Milan)	46	41	11	3
Japanese	30	38	22	10
Jews (Germany)	42	41	12	5
Jews (Poland)	33	41	18	8
Kalmuks	26	23	41	11
Kikuyu (Kenya)	60	19	20	1
Koreans	28	32	31	10
Lapps	29	63	4	4
Latvians	32	37	24	7
Lithuanians	40	34	20	6
Malasians	62	18	20	0
Maoris	46	54	1	0
Mayas	98	1	1	1
Moros	64	16	20	0

Blood group distribution by tribe or race

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Accessed 12/10/2019

Navajo (N. Am. Indian)	73	27	0	0
Nicobarese (Nicobars)	74	9	15	1
Norwegians	39	50	8	4
Papuas (New Guinea)	41	27	23	9
Persians	38	33	22	7
Peru (Indians)	100	0	0	0
Philippinos	45	22	27	6
Poles	33	39	20	9
Portuguese	35	53	8	4
Rumanians	34	41	19	6
Russians	33	36	23	8
Sardinians	50	26	19	5
Scotts	51	34	12	3
Serbians	38	42	16	5
Shompen (Nicobars)	100	0	0	0
Slovaks	42	37	16	5
South Africans	45	40	11	4
Spanish	38	47	10	5
Sudanese	62	16	21	0
Swedes	38	47	10	5
Swiss	40	50	7	3
Tartars	28	30	29	13
Thais	37	22	33	8
Turks	43	34	18	6
Ukrainians	37	40	18	6
United Kingdom (GB)	47	42	8	3
USA (US blacks)	49	27	20	4
USA (US whites)	45	40	11	4
USA Blood Types (US all)	44	42	10	4
Vietnamese	42	22	30	5
Welsh	?	?	?	?

Blood type

- Rh antigens are found only on the red cell membrane.
- D antigen is present on fetal membranes by day 38.
- Genes are C/c, D/-, E/e.
- Co-dominant (chromosome 1)
- CC, Cc, and cc possible genotypes
- EE, Ee, and ee possible genotypes
- D/D, D/-, -/- possible genotypes.
- The absence of D antigen is signified by the use of d
- Thus, DD, Dd, and dd as genotypes
- Weakly expressed D antigen has also been called D^u.

Blood type

- The presence of the D antigen defines Rh positive status.
- The absence of D antigen (-/-) defines Rh negative status
- Rh_{null} lacks RHAG gene (Rh core complex)
- D,c,e potent allo-antigens
- Rh positive blood should not be administered to Rh negative patients.

Rh complex in red cell membrane

RhD+		RhD-	
Gene complex	Short notation	Gene complex	Short notation
CDe	R^1	cde	r
cDE	R^2	Cde	r'
cDe	R^o	cdE	r"
CDE	R^z	CdE	r^y

Pourazar, A, "Red cell antigens: Structure and function" Asian Journal of Transfusion Science. 2007 1:24-32 Table 1 doi: 10.4103/0973-6247.28069
Accessed 21/10/2019

Other important blood groups

- Lewis
- Le a/b genes produce soluble antigens which may be adsorbed onto the red cell surface.
- Inherited separately from but influenced by ABH secretor genes
- Secretor: Le^{a-b+}
- Non-secretor (se/se): Le^{a+b-}
- Not generally expressed in newborns although 50% are Le^{a+}
- Phenotypic expression may change during pregnancy.

Other important blood groups

- Group O Le^{a+} cells contain more Le^{a+} than do group A or B cells
- May induce alloimmune hemolytic anemia if transfused to someone with potent anti-Le^{a} antibody
- Anti-Le antibodies are predominantly IgM
- <u>These are the only blood group antigens not associated with hemolytic disease of the newborn</u>

- Le^{a} gene product binds Bordatella pertussis and Staph. aureus toxins (secretor)
- Le^{b} gene product binds H. pylori (non-secretor)

Other important blood groups

- Luther
- Lu a/b genes are related to the genes responsible for the secretion of ABH substances.
- The gene product is a laminin ligand

Other important blood groups

- Anti-P_1 is a naturally occuring IgM antibody.
- Present in 75% of English population
- P_1 is the antigen for Parvovirus B19R
- Heterogeneous distribution on red cells
- Anti-P1 in high titer may reflect
- Echinococcus infection
- Exposure to pigeon eggs or droppings
- As they contain antigens similar to P

Other important blood groups

- An immune IgG-anti-P_1 antibody is found in paroxysmal cold hemoglobinuria
- This is a cold hemolysin that adsorbs to red cells at temperatures <20C
- Leads to complement lysis at core body temperatures
- Clinically, following cold exposure, there is a system complaint of pain associated with the development of hemoglobinuria

Other important blood groups

- Kell
- K (Kell)/k (Cellano) at 7q33
- Kp (Penny)a/b and Js a/b are SNPs.
- The gene products are Zn-metalloproteinases
- The Kell null phenotype (Kx) is associated with chronic granulomatous disease.
- Acanthocytosis of red cells and neural cells
- Late onset muscular dystrophy
- Form antibody to K when exposed
- Third most common cause of hemolytic disease of newborn

Rare blood groups

- African American Blacks - **U-** and **Duffy-**
- American Indians and Alaskan Native peoples - **RzRz**
- Pacific Island peoples and Asians - **Jk (a- b-)**
- Hispanics - **Di (b-)**
- Russian Jews - **Dr (a-)**
- Whites - **Kp (b-)** and **Vel**

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Accessed 12/10/2019

Blood group and type

- MNSs antigens.
- The genes involved are M/N and S/s.
- Naturally occuring IgM antibodies to these antigens are found
- The gene products function as receptors for Plasmodium falciparum and for viruses
- Anti-S and anti-s IgG (immune) antibodies may be found after sensitization in pregnancy or by transfusion.

Other important blood groups

- Duffy
- Fy a/b genes
- More common in blacks
- Related to Rh system
- Receptor protein for Plasmodium vivax
- Erythrocyte chemokine receptor
- Associated with prostate cancer and kidney transplant rejection

Other important blood groups

- Kidd
- Jk a/b genes
- Gene product functions in urea transport in vasa recta and in medulla
- Null phenotype in Polynesians
- 10^3 fold diminished transport

Other important blood groups

- Anti-I is a naturally occuring IgM antibody.
- It does not react with umbilical cord cells (i antigen).
- By 18 months of age, i antigen is no longer detectable on umbilical cord cells
- Ii antigens antithetical
- Genes coding for i associated with congenital cataracts in a Japanese population
- Autosomal recessive
- Elevated titers may be found in Mycoplasma pneumoniae infections.
- Auto-anti-I (or IH) is an IgG antibody found in cold agglutinin disease.

Function of blood group antigens

Antigen	Gene	Gene product	Function	BG discovery
P	P	Globoside	Parvovirus B19R	Landsteiner and Levine 1927
MNSs	Mm	Glycophorin A and B	*P. falciparum* and virus R	Landsteiner and Levine 1927
LW	LW	IgSF protein (ICAM-4)	Ligand for integrins (CD11/CD18)	Levine and Stetson 1939
Rh	RH	Transport protein structure	Transported matter unknown integrity of cell metabolism and shape expression of surface Ags	Landsteiner and Wiener 1940
Lutheran	LU	IgSF protein (B-CAM)	Laminin ligand	Callender *et al* 1946
Kell	KEL	Glycoproteins	? Zn-metalloproteinases ? role in erythropoiesis	Coombs *et al* 1946
Duffy	FY	Receptor protein for	*P. vivax* and Chemokines	Cutbush *et al* 1950
Lewis	LE	Glycoconjugates	*B. pertussis* and *S. aureus* R	Grubb *et al* 1951
P, P^K, P_1	P_p, P^K	Globoside	Entral bacteria R	Levine *et al* 1951
Kidd	JK	Transporter protein	Urea transport	Allen *et al* 1951
Diego	DI	Band 3	Anion exchanger (O_2/cO_2 gas exchange)	Layrisse *et al* 1955
Cartwright	YT	GPI-linked protein in RBC integral protein in cells of the nervous system	Function unknown (Acetulcholinestrase neurotransmission)	Eaton *et al* 1956
Gerbich	GE	GlycophorinsC/D	Red cell shape and integrity	Rosenfield *et al* 1960
Colton	CO	Aquaporin-1	Water transport	Heisto *et al* 1967
In^aAnWJ	IN	CD44 protein	Haemophilus influenza RHyaluronic acid ligand	Badakere *et al* 1974 Telen *et al* 1993
Kx	XK	Transport protein	Neurotransporter, expression of Kell Ags, red cell membrane and muscle cell integrity	Marsh *et al* 1975
Cromer	CROM	DAF (complement)	Complement regulation. *E. coli*, Enterovirus R	Denials *et al* 1989
Knops	KN	CR1 (CD35) protein	Binding and transport of C3B/C4b coated immunocomplexes, aspecific binding of IgG	Moulds *et al* 1992
OK^a	OK	IgSF protein (CD147)	? growth factor R ? induction of extracellular metalloproteinases	

Pourazar, A, “Red cell antigens: Structure and function” Asian Journal of Transfusion Science. 2007 1:24-32 Table 2 doi: 10.4103/0973-6247.28069 Accessed 21/10/2019

Antibody detection in a cross-match

- Blood group and type are first determined on both donors and recipients
- The autoantibody screen in a cross-match is employed to detect clinically important antibodies that may precipitate a hemolytic reaction.
- The first step may be an immediate spin in saline.
- IgM antibodies are detected in the cross-match during the immediate spin in saline.
- They react optimally at 4°C.
- Bind complement.
- Cold antibodies
- This step is often referred to as a minor crossmatch

Antibody detection in a cross-match

- The obligatory second step is incubation at 37°C in a low ionic strength solution (LISS) or albumin (lowers ζ-potential)
- IgG antibodies are detected in the cross-match, often following incubation at 37°C in albumin
- Warm antibodies
- Followed in the obligatory third step by the addition of anti-globulin (Direct Coomb's test).
- Antibodies to Duffy, Kell, Kidd, MNSs, and Rh antigens are the ones more commonly detected
- Delayed hemolytic reactions are associated with a positive Direct Coombs test.
- Major crossmatch

Red cell transfusion criteria

- Heart rate increases linearly in response to the acute isovolemic anemia:

  Heart rate (beats/min) = 116 - 4.0 x Hb

- Delivery of O_2 = Cardiac output x ((1.39 x (Hb) x SaO_2) + (PaO_2 x 0.0031))

  DO_2 <12ml/kg indicative of poor tissue perfusion.

Red cell transfusion criteria

- For hospitalized adult patients who are hemodynamically stable, transfuse if hemoglobin
- <7.5 g/dL for patients undergoing cardiac surgery
- <8 g/dL for those undergoing orthopedic surgery or those with preexisting cardiovascular disease
- For hospitalized adult patients with hematologic or oncologic disorders, transfuse if hemoglobin <7 g/dL
- For for critically ill children and those at risk of critical illness who are hemodynamically stable and without a hemoglobinopathy, cyanotic cardiac condition, or severe hypoxemia, transfuse if hemoglobin <7 g.dL

Red cell transfusion criteria

- For for hemodynamically stable children with congenital heart disease, the transfusion threshold is based on the cardiac abnormality and stage of surgical repair:
- 7 g/dL (biventricular repair)
- 9 g/dL (single-ventricle palliation)
- 7 to 9 g/dL (uncorrected congenital heart disease)

Red cell transfusion

- Transfuse only packed red cells.
- 75% of transfused cells are circulating at 24 hours.
- Leukocyte filters are effective in removing white cells and platelet fragments that accompany red cells in unit to be transfused.
- White cells may be associated with acute lung injury immediately following transfusion.
- Minimize by using units from men.
- Best to use blood stored <14 days.

Red cell transfusion

- 2,3 DPG levels may fall to 10% of normal in blood stored for 42 days
- Levels return to normal with 24 hours of transfusion.
- Nitric oxide levels remain low.
- Unit may have been stored up to 42 days.
- Potassium in stored plasma may reach 8.5 mEq/L
- Ammonia in stored plasma may reach 900 ug/dL
- May wash with saline prior to infusion to reduce levels

Red cell transfusion

- Group O cells may be given to anyone
- Universal donor
- Must remove plasma as it contains antibodies
- Group AB may receive group A or B or O blood in the absence of AB.
- Universal recipient
- Group A blood is associated with fewer reactions in AB patients, however
- Optimally, donor cells are grouped, typed, and have been screened for antigens that may react with antibodies in the recipient's serum

Red cell transfusion

- Frozen red cells
- Washed to remove glycerol preservative.
- Best choice for IgA deficient patients.
- Leukocyte reduced blood
- Best to avoid graft versus host disease (GVHD)
- Transplant patients
- Irradiated blood
- Best to avoid CMV transmission.

Allergic transfusion reaction

- Fever, uriticaria, wheezing common
- Potential for anaphylaxis
- Most common transfusion reaction
- Type I IgE mediated hypersensitivity reaction to proteins in donor blood
- Stop the transfusion to determine that this is not a hemolytic reaction.
- May control symptoms with antihistamines
- IgA deficient recipients with anti-IgA antibodies from previous exposure must receive blood products that lack IgA to prevent anaphylaxis

Febrile transfusion reaction

- Fever and flushing
- Not life threatening.
- Related to the level of IL-1 in the plasma of the stored unit of blood.
- Type II hypersensitivity reaction to HLA antigens of donor leukocytes
- Stop the transfusion to determine that this is not a hemolytic reaction.
- If not, it may be controlled with adjusting the rate of transfusion, the administration of antihistamines and acetaminophen.

Acute hemolytic transfusion reaction

- Life threatening
- Presents with severe back pain and a sense of doom
- Associated with hematuria
- The plasma will be tinted red as well.
- STOP the transfusion.
- Begin saline diuresis
- Prevent acute renal failure from hemoglobin precipitation in tubules
- Urine alkalinization may not be of use
- Heparinize the patient if DIC has begun.
- Pressors may be required to maintain blood pressure.

Acute hemolytic transfusion reaction

- Type II hypersensitivity reaction
- Pre-existing high affinity “natural” IgM antibodies, usually against polysaccharide blood group antigens A or B, bind to red cells and rapidly induce complement mediated lysis, intravascular hemolysis, and hemoglobinuria.
- Usually ABO incompatibility
- Intravascular hemolysis
- May occur with atypical antibody to rare antigen not detected in major crossmatch (until after upregulation by exposure)

Acute hemolytic transfusion reaction

- Acute symptoms a result of complement activation
- The donor unit and patient blood are taken for extensive screening against multiple cell panels
- Not only for diagnosis
- But patient likely to require red cell replacement because of extensive hemolysis
- A delayed reaction typically caused by IgG antibodies from previous exposure
- Haptoglobin diminished

ABO hemolytic disease of the newborn

- Transplacental passage of maternal IgG antibodies resulting in extravascular hemolysis in the fetus
- Anti-A and anti-B antibodies from group O mothers to fetuses whose fathers are not group O
- 25% of all pregnancies
- Usually in first-born
- May recur in later pregancies if ABO incompatibility

ABO hemolytic disease of the newborn

- Unconjugated bilirubin produced in fetus is metabolized by the maternal liver
- Neonatal jaundice in first 24 hours as the infant's liver is immature and cannot handle the bilirubin load
- Little risk for kernicterus
- Positive Direct Coombs'
- Mild, if any, normocytic anemia
- Spherocytes on blood smear

Rh hemolytic disease of the newborn

- Mother is Rh negative and fetus is Rh positive
- Thus, father is Rh positive
- As cytotrophoblast is absent during last trimester, increased risk for fetomaternal bleed
- Mother exposed to fetal Rh positive blood
- Mother develops IgG anti-D antibody
- Does not affect first pregnancy (as antibody produced is IgM and does not cross placenta)
- But will affect subsequent Rh incompatible pregnancies (IgG produced)
- Anti-D antibodies cross placenta and coat fetal red cells

Rh hemolytic disease of the newborn

- Extravascular hemolytic anemia in fetus
- Fetus may develop high output cardiac failure
- May lead to left and right heart failure with ascites and peripheral edema
- Extramedullary hematopoiesis in liver and spleen
- Unconjugated bilirubin metabolized in mother's liver
- Following delivery, there is neonatal jaundice
- Unconjugated bilirubin exceeds albumin carrying capacity and circulates
- Positive Direct Coombs'
- No spherocytes

Rh hemolytic disease of the newborn

- In hemolytic disease, bilirubin levels may rise rapidly
- The unconjugated form (indirect bilirubin) is less water soluble and crosses the blood-brain barrier
- The saturation point of albumin binding is 20mg/dl.

- Deposition in lipid laden tissues begins to occur at those levels.
- Acute bilirubin encephalopathy
- Kernicterus refers to chronic and permanent sequelae of deposition of unconjugated bilirubin in basal ganglia.

Rh hemolytic disease of the newborn

- Erythroblastosis fetalis is an older name
- Bilirubin has a special affinity for the globus pallidus, the hippocampus, and the subthalamic nucleus.
- In the hippocampus, kernicterus involves the CA2-CA3 sectors of the pyramidal layer
- Hypoxic-ischemic encephalopathy involves the CA-1 sector

Rh hemolytic disease of the newborn

- Bilirubin binds to cell membranes and is toxic to neurons and oligodendroglia.
- Damages mitochondria
- Inhibits oxidative phosphorylation
- Causes calcium release promoting apoptosis
- Stunts axonal and dendritic growth.
- The acute toxic injury is aggravated by inflammatory reactions of microglia and astrocytes.

Rh hemolytic disease of the newborn

- In severe kernicterus, affected structures have a bright yellow color
- Kernicterus means nuclear jaundice
- Microscopically, they show neuronal necrosis with eosinophilic (“red”) neurons.
- In burned-out cases, neuronal loss, gliosis and atrophy are seen

Bilirubin encephalopathy

- Neonates present with
- Jaundice
- Lethargy
- Poor sucking
- Hypotonia or hypertonia (disappears after first week)
- Have a high pitched cry
- Opisthotonus (arching of trunk)
- Retrocollis (backward arching of neck)
- Seizures
- Opisthotonus and retrocollis associated with evolution to chronic encephalopathy

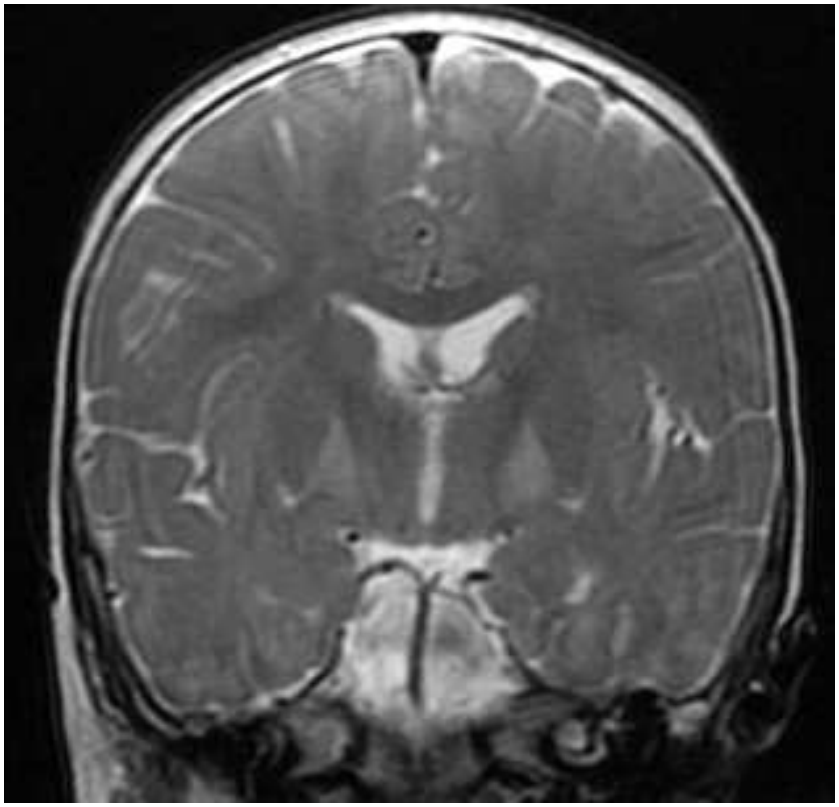
Bilirubin encephalopathy

- Acute terminal phase
- Muscle rigidity
- Paralysis of upward gaze
- Periodic oculogyric crises
- Mortality 4%
- Exchange transfusion required
- 2% mortality
- 12% complications

Bilirubin encephalopathy

- Permanent neurologic symptoms
- Less severe injury may only have hearing loss as a sequel of damage tocochlear nuclei
- Severe loss manifest as well with
- Choreoathetosis (after the first year)
- Spasticity
- Ataxia
- Limitation of upward gaze
- Mental retardation

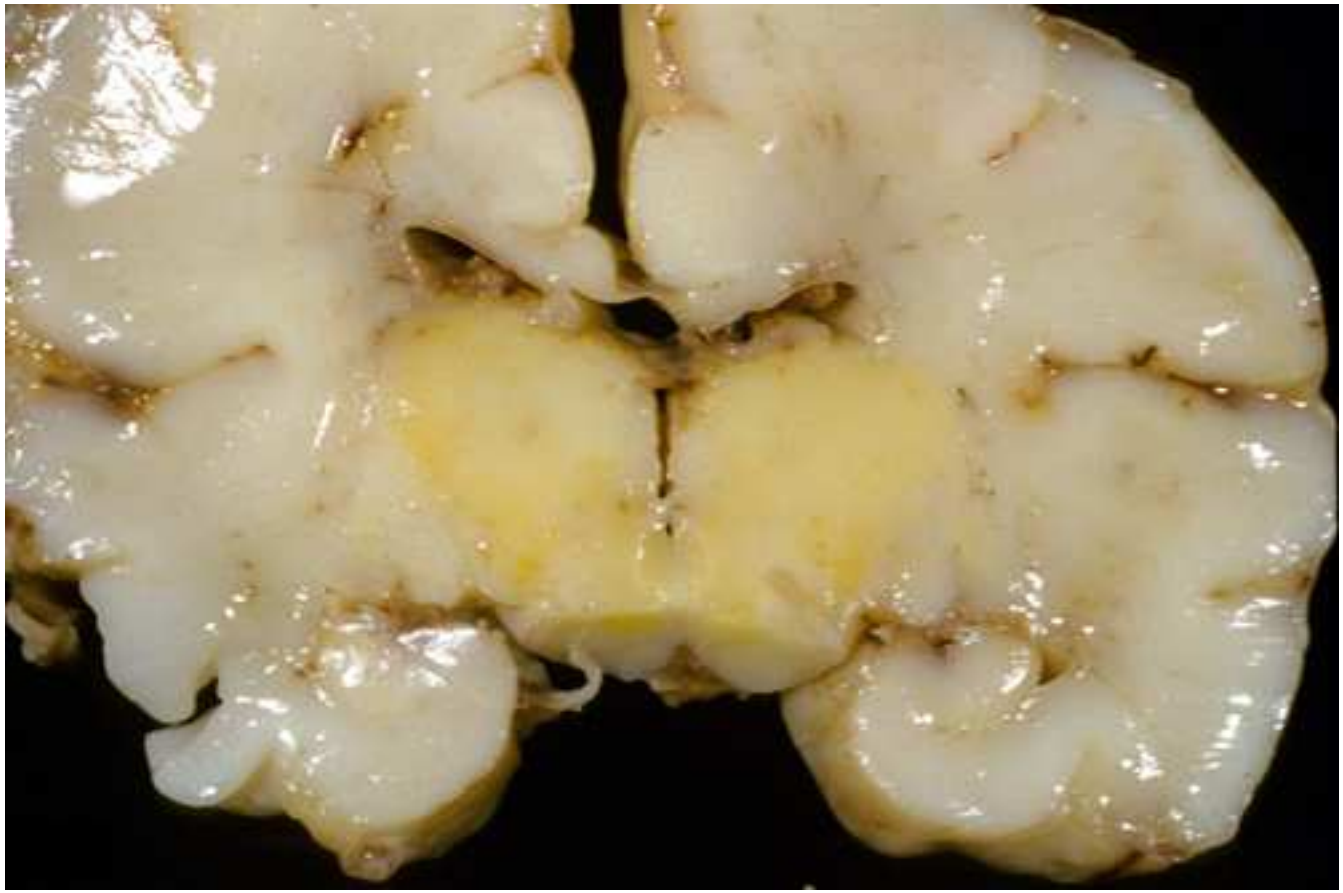
Kernicterus



The MRI shows high T2 signal in the globus pallidus.

http://neuropathology-web.org/chapter3/chapter3eBilirubinencephalopathy.html
Accessed 12/10/2019

Kernicterus



http://neuropathology-web.org/chapter3/chapter3eBilirubinencephalopathy.html
Accessed 12/10/2019

Decision points

Serum Bilirubin and Kernicterus

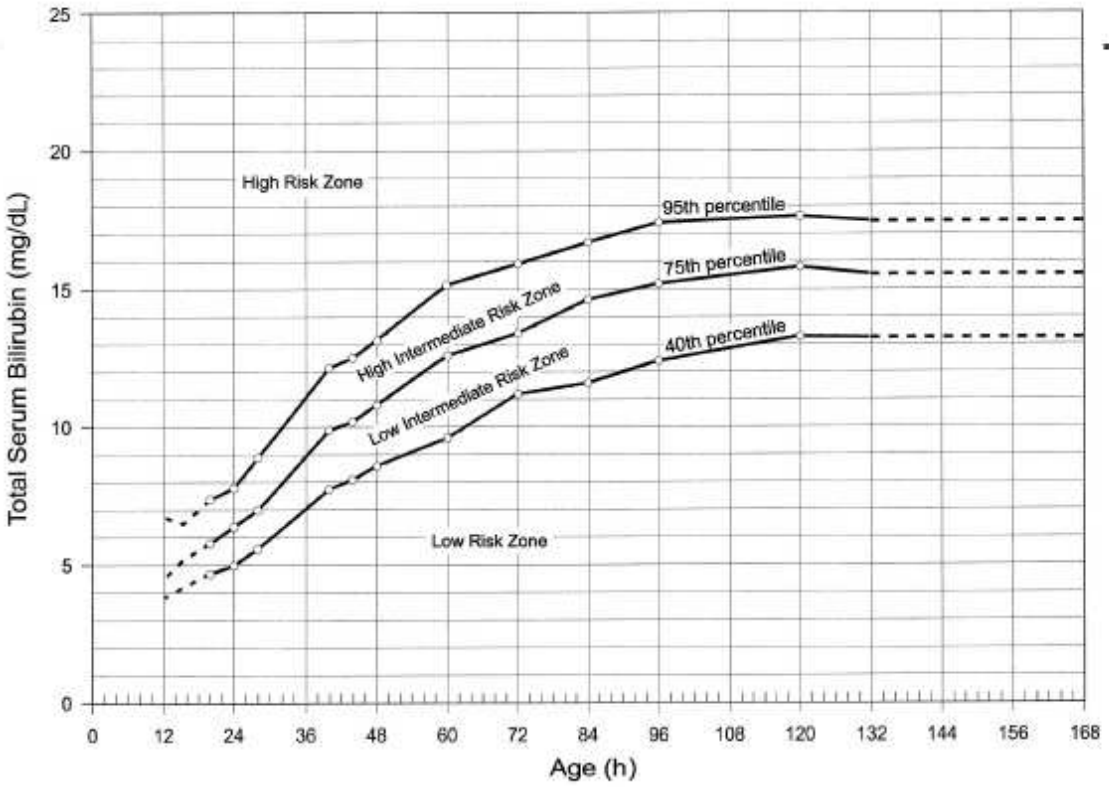
Kernicterus in Rh-isoimmunization:

Serum level	Incidence
10-18 mg/dL	0 %
19-24 mg/dL	8 %
25-29 mg/dL	33 %
30-40 mg/dL	73 %

Volpe JJ: Neurology of the Newborn. 3rd Ed. pp 490-514, 1995

Decision points

Early identification: Nomograms



Bhutani et al. Pediatrics 103:6, 1999

Treatment

- **Early treatment critical**
- Check bilirubin level within 24 hours after birth if not obviously jaundiced
- Transcutaneous determination is not accurate in darker skinned babies
- Phototherapy (>30 uW/cm^2/nm)
- Blue-while fluorescent bulbs
- High intensity LED (blue, blue-green) gallium nitride lamps
- Photoisomer of bilirubin is water-soluble and is excreted
- Exchange transfusion if phototherapy not successful in stemming rise in bilirubin

Rh sensitization

- In the case of Rh positive blood administration to an Rh negative patient, the transfusion should be stopped.
- Exchange transfusion possible but associated with significant morbidity.
- Anti-D immunoglobulin is preferred.
- Anti-D immune globulin prevents allo-immunization of the Rh negative patient.
- If an Rh-negative patient has received Rh-positive blood, administer anti-D immune globulin

Anti-D immunoglobulin

- 300ug dose is administered first at 28 weeks for Rh negative mothers
- Unless the father of the child is also Rh negative
- A second dose is recommended postpartum as 15-20% of patients will have a low titer at term.
- Smaller dose (50ug) administered if abortion or ectopic pregnancy before 12 weeks gestation.
- Smaller dose administered if molar pregnancy.
- Smaller dose administered following platelet transfusion.

Anti-D immunoglobulin

- Blocks the afferent limb of antibody generation
- Mechanisms
- Rapid macrophage mediated clearance of anti-D coated red blood cells in the spleen
- And/or down-regulation of antigen-specific B cells before an immune response occurs.
- Not all maternal red cell binding sites are coated with anti-D administered passively
- Epitope masking is not the mechanism that prevents allo-immunization.

Anti-D immunoglobulin

- Large volume fetal-maternal blood transfer is noted after
- Abdominal trauma
- Fetal death
- Antepartum hemorrhage in the third trimester
- A rosette test is sensitive to fetal-maternal blood transfer.
- Estimate of the volume of fetal blood cells in the maternal circulation may be determined by a Kleihauer-Betke or fetal red cell stain.
- The dose of anti-D immunoglobulin is adjusted accordingly (15ml generally calls for a second 300ug dose).

Fresh frozen plasma

- While Group AB Rh-negative plasma can be given to anyone, grouped and typed specific plasma is preferred
- **Fresh frozen plasma**
- Used to correct bleeding problems due to:
- vitamin K deficiency
- liver failure
- Factor XI deficiency
- Replacement of coagulation factors lost following massive transfusion (ratio of plasma:RBC >3)
- But in non-trauma situation, increases risk of lung injury

Coagulation factors

- Do not use fresh frozen plasma to reverse warfarin anticoagulation in the absence of intracranial bleeding; use vitamin K
- **Cryoprecipitate**
- Used in the treatment of deficiency of
- von Willebrand factor
- Factor XIII
- Fibrinogen.
- **Recombinant factor VIII or IX**
- Preferred for treatment of hemophilia.

Platelet transfusions

- **Platelets** are administered to maintain counts >50,000/ul if invasive surgery is planned.
- Spontaneous bleeding unusual if counts >10,000/ul.
- Platelets are chosen based on group and type.
- Improved survival may result from platelets chosen by aggregation studies.

Transfusion related acute lung injury

- TRALI is a severe, frequently fatal complication in which factors in a transfused blood product trigger the activation of neutrophils in the lung microvasculature
- Sudden onset of respiratory failure
- Bilateral pulmonary infiltrates
- Most common antibodies associated with TRALI are those that bind MHC class I antigens.
- Often found in multiparous women
- Fresh frozen plasma as well as platelet transfusions usual causes
- Mortality rates as high as 67%