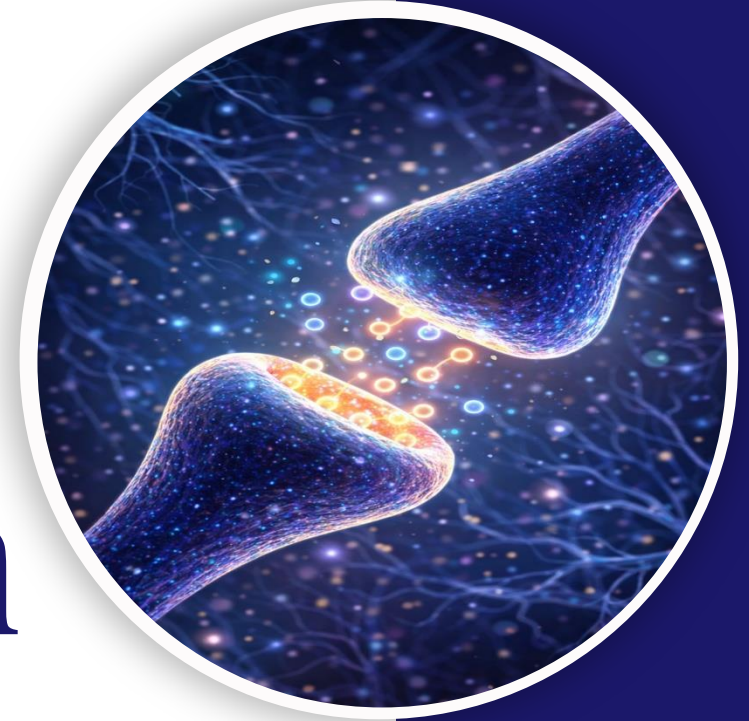


بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ
(وَفَوْقَ كُلِّ ذِي عِلْمٍ عَلِيمٌ)



HLS Physiology | MID 9

Blood Groups & Transfusion



Written by : **Muhannad Al-Rqibat**
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بسم الله الرحمن الرحيم،

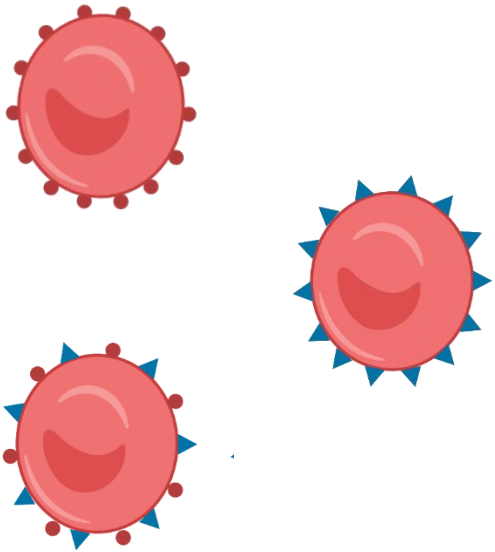
نرجو منكم الدعاء لزميلنا في الدفعة
عون العدوان، الذي وافته المنية.

اللهم ارحمه واغفر له، وأسكنه فسيح جناتك، وأنر قبره وأنس وحشته، واجعل قبره روضةً من رياض
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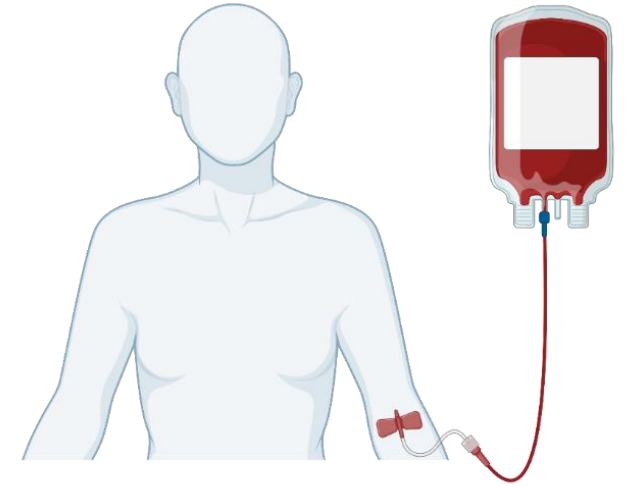
اللهم اجبر قلوب أهله وذويه، وارزقهم الصبر والسلوان، وألهمهم جميل الصبر وحسن العزاء.

رحمه الله رحمةً واسعةً وأسكنه الفردوس الأعلى من الجنة...

Blood Groups



Blood Groups and Transfusion Reaction



PowerPoint Notes are in Red

Multiplicity of Antigens in the Blood Cells

- RBCs carry many antigens belonging to different blood-group systems. ABO and RhD are especially important in transfusion practice.

Introduction to Red Cell Antigens

Red cells perform similar functions in all of us, but the antigens on their surfaces differ. These differences can determine whether transfused cells survive or become targets of an immune reaction. We will start with A, B, O, and Rh blood groups, then use them to understand transfusion reactions and hemolytic disease of the fetus and newborn. Throughout the lecture, keep asking: where is the antigen, where is the antibody, and what happens when they meet?

The red cell membrane carries many different antigens. These are inherited structures that the immune system can recognize. We normally tolerate the antigens on our own cells; however, transfused red cells may carry antigens that the recipient does not have. ABO and RhD are especially important, but they are not the only blood group systems. For example, two people can both be A positive and still differ in other red cell antigens. Therefore, matching ABO and RhD is essential, but additional compatibility testing may still be needed.

Blood Groups

ABO System

- The ABO blood group is based on two **carbohydrate antigens carried on glycolipids and glycoproteins**, called A and B.
- Six possible combinations: OO, OA, OB, AA, BB, and AB.
- A and B are codominant; O is recessive.

Look at the example: one parent is AO and the other is BO. The possible combinations are AB, AO, BO, and OO. Therefore, this particular couple can have children with any of the four ABO groups. Each pregnancy is a new event. Having one child with a particular group does not determine the next child's group.

Father's Blood Type:

	A	O
Mother's Blood Type:		
B	AB	OB
O	AO	OO

Each square represents a 25% probability of having a child with that combination of alleles.

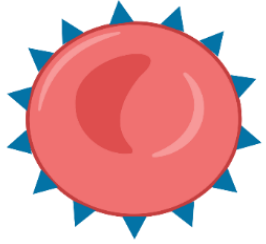
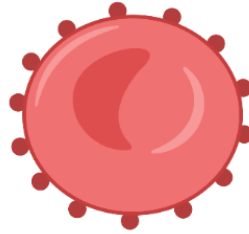
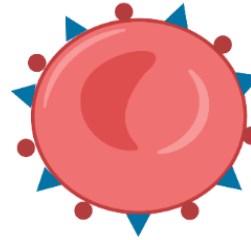
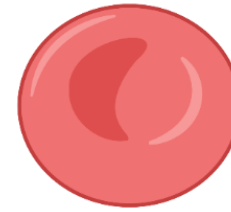
The ABO system is based mainly on two antigens: A and B. These are carbohydrate structures carried on molecules in the red cell membrane. A person may have A, B, both, or neither.

Each person inherits one ABO allele from each parent. There are three main alleles: A, B, and O, but each person is only two. A and B are codominant, meaning both are expressed when present together. O is recessive to A and B.

O-A-B Blood Types

Let us connect the inherited genotype to the red cell surface. A and AO both produce A antigen, so both give blood group A. BB and BO both produce B antigen, giving blood group B. AB expresses both antigens. OO expresses neither A nor B.

Notice that six genotypes produce four blood groups. This means that knowing someone's blood group does not always tell us their exact genotype. Also, when we say that group O has no antigens, we mean no A or B antigens. Group O red cells still carry other antigens.



Genotype

OA/AA

OB/BB

AB

OO

Antigen

A

B

AB

Neither A nor B

Blood group

A

B

AB

O

Blood Groups

Agglutination

Agglutination: antibodies cross-link RBCs, producing clumps.

Antigen (Agglutinogen)

Antibody (Agglutinin)

An agglutinogen is an antigen on the red cell surface. An agglutinin is an antibody that can bind that antigen and contribute to clumping.

For example, anti-A binds A antigen.

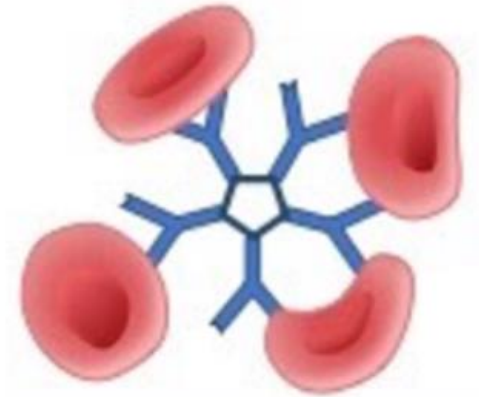
Antibodies have multiple antigen-binding sites. IgG has two, while pentameric IgM has up to ten. This allows an antibody to connect antigens on different cells, producing a network of red cells.

We call this clumping agglutination. IgM is particularly effective at producing it.

Because the agglutinins have **two binding sites (IgG type) or ten binding sites (IgM type)**, a single agglutinin can attach to **two or more RBCs** at the same time, thereby causing the **cells to be bound together** by the agglutinin.

This binding causes the cells **to clump**, which is the process of agglutination.

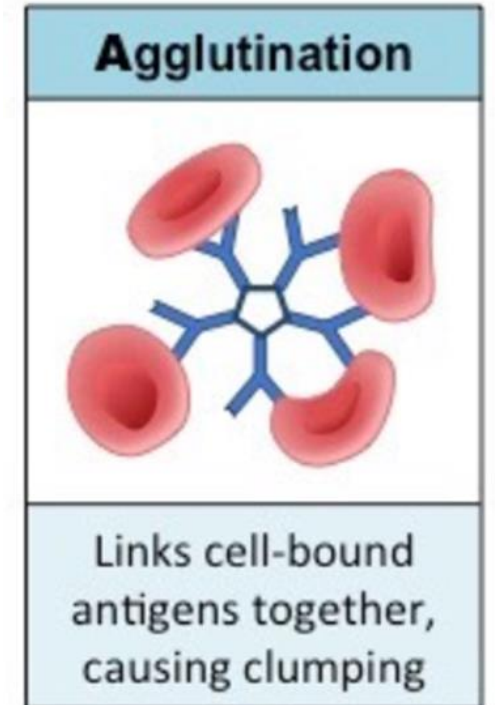
Agglutination



Links cell-bound antigens together, causing clumping

Agglutinins (antibodies)

- ABO antibodies are mainly IgM; IgG antibodies also occur, especially in group O.
- When type A agglutinogen is not present in a person's RBCs, antibodies known as anti-A agglutinins develop in the plasma.



Where are the antibodies? They are in the plasma.

In the usual adult ABO pattern, a person develops antibodies against the ABO antigen that their own cells lack.

If A antigen is absent, anti-A develops. If B antigen is absent, anti-B develops.

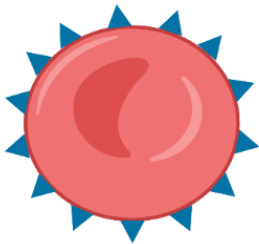
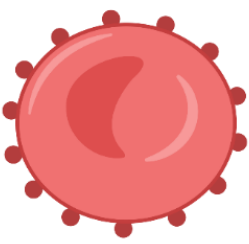
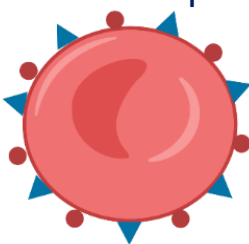
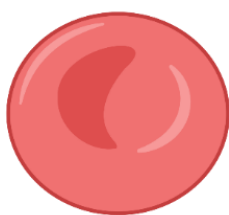
These antibodies are immunoglobulins produced by plasma cells derived from B lymphocytes.

Most ABO antibodies are IgM, although IgG also occurs, particularly in group O.

The antibody class matters because it influences what happens after binding. IgM is effective at activating complement, while IgG can cross the placenta.

O-A-B Blood Types

Now let us put the antigens and antibodies together.
Group A has A antigen on the cells and anti-B in the plasma.
Group B has B antigen and anti-A.
Group AB has both antigens and normally neither anti-A nor anti-B.
Group O has neither antigen and both antibodies. If group B reds enter a group A recipient, which antibody recognizes them?
The recipient's anti-B recognizes B antigen on the donor cells.
This interaction is the starting point of an ABO incompatible red cell transfusion reaction



Genotype

OA/AA

OB/BB

AB

OO

Antigen

A

B

AB

Neither A nor B

Blood group

A

B

AB

O

**Antibody
(Agglutinins)**

anti-B

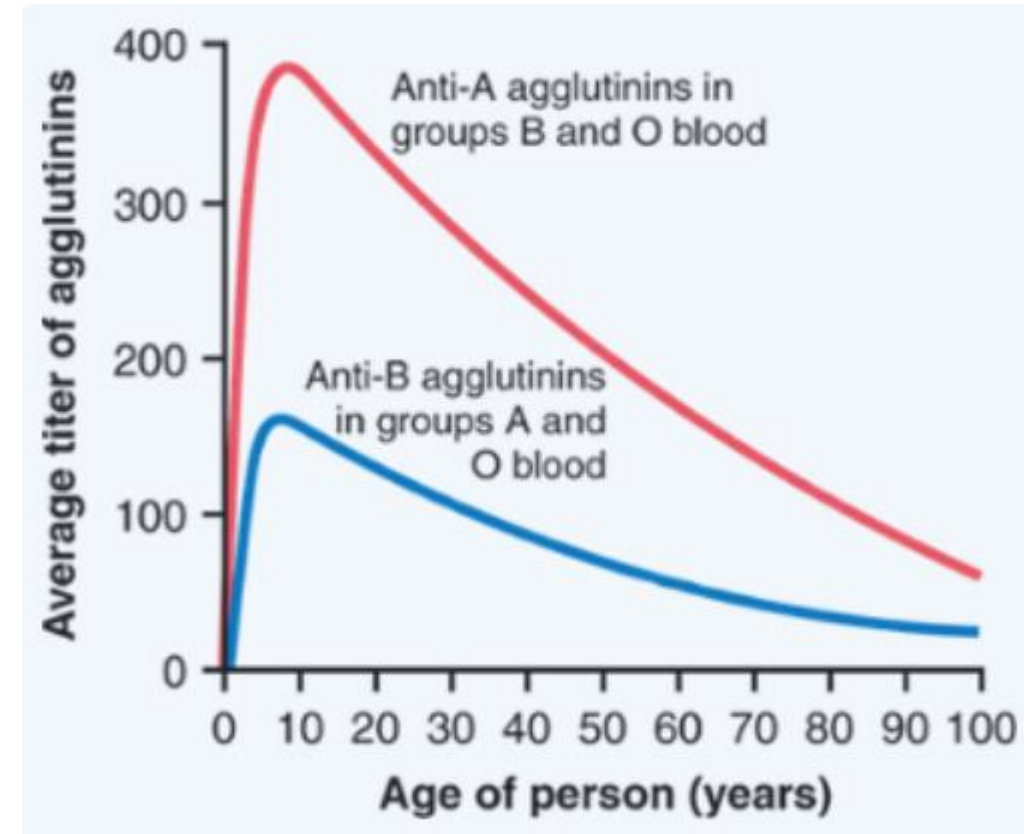
anti-A

**Neither Anti-A
Nor anti-B**

**Anti-A
& anti-B**

Agglutinins (antibodies)

- Immediately after **birth**, the quantity of agglutinins in the plasma is almost **zero**.
- **Two to 8 months** after birth, an infant **begins** to produce agglutinins.
- A **maximum** titer is usually reached at **8 to 10 years** of age, and this gradually declines throughout the remaining years of life.



****Also, the neonate has few, if any, agglutinins, showing that agglutinin formation occurs almost **entirely after birth**.**

**** The infant's own ABO antibody production is low at birth and develops during infancy.**

- This graph shows how ABO antibody levels change with age.
- The infant's own production is very low at birth, antibodies production beginning during approximately the first two to eight months, rising through childhood, reaching a peak around eight to ten years, and then gradually declining.
- The term titer describes antibody activity using dilution testing. A higher titer means that a reaction can still be detected after greater dilution.
- Do not focus too much on memorizing every point on the graph. The main message is that these antibodies develop after birth.
- Also low antibody production by the newborn does not mean that all antibodies are absent. Maternal IgG may already have crossed the placenta.

Here is an important question: why would someone develop A antibody if they have never received group A blood?

An explanation could be that we encounter environmental substances, including structures associated with bacteria and food, that resemble A and B antigens. The immune response to these substances can antibodies that also recognize the corresponding blood group antigen.

This is why ABO antibodies are often called naturally occurring. They can develop without a previous transfusion.

Therefore, an ABO incompatible reaction can happen during the first incompatible transfusion. The recipient may already have the antibody before any donor cells enter the circulation.

Agglutinins (antibodies)

- But **why** are these **agglutinins** produced in people who do not have the **respective agglutinogens** in their RBCs?
- Exposure to environmental antigens, including microbial antigens that resemble A and B structures, stimulates antibodies against the ABO antigens the individual lacks

Blood Groups

Rh System

- There are **six common types of Rh antigens**, each of which is called an *Rh factor*. These types are designated C, D, E, c, d, and e.
- The type **D antigen** is widely **prevalent** in the population and considerably more antigenic than the other Rh antigens
- Anyone who has the **D antigen** is said to be Rh positive, whereas a person who does **not have type D antigen** is said to be **Rh negative**.

However, it must be noted that even in Rh-negative people, some of the other Rh antigens can still cause transfusion reactions, although the reactions are usually much milder.

- The Rh system behaves differently. For our purposes, the most important antigen in Rh system is D antigen. A person whose cells carry D is called Rh positive, while a person whose cells lack D is called Rh negative. Being Rh negative also does not mean that the cells lack every other Rh antigen. D is highly immunogenic.
- If a D-negative person encounters D-positive red cells, they may develop anti-D. Unlike the usual ABO antibodies, anti-D generally develops following red cell exposure, such as transfusion or pregnancy.

ABO versus RhD

Feature	ABO	RhD
Antibody development	Develop after birth following exposure to environmental A/B-like antigens	Anti-D develops after exposure to D-positive RBCs through pregnancy or transfusion
Predominant antibody	Mainly IgM IgG also occurs, especially in group O	Immune anti-D is mainly IgG
Placental transfer	IgM does not cross IgG anti-A/anti-B can cross	IgG anti-D crosses

Let us compare the two systems. ABO antibodies commonly develop after birth following environmental exposure. Anti-D usually requires exposure to D-positive red cells. ABO antibodies are mainly IgM, although IgG also occurs. Immune anti-D is predominantly IgG; IgM does not cross the placenta, while IgG can. That explains why anti-D is important in pregnancy. It also explains why some IgG ABO antibodies can affect the fetus or newborn. Now ask yourself: does every D-negative person have anti-D? Remember D-negative describes what is missing from the red cell surface. It does not tell us whether sensitization has occurred

Blood Groups

Blood Typing

Anti-A	Anti-B	Anti-Rh	
			A-
			B+
			AB+
			O-

In blood typing, we use antibodies of known specificity to identify antigens on the patient's red cells. We test separate portions of the cells with anti-A, anti-B, and anti-D. If the cells agglutinate with anti-A, A antigen is present. If they agglutinate with anti-B, B antigen is present. A reaction to anti-D indicates D-positive cells.

Let us read the rows. The first reacts with anti-A only, so it is A negative. The second reacts with anti-B and anti-D, so it is B positive. The third reacts with all three, so it is a AB positive. The last reacts with none, so it is O negative. We are using the reaction to detect cell surface antigens.

Blood Groups

Blood matching

- **Blood typing** puorg doolb rojam eht seifitnedi
- **Blood matching** detceles eht rehtehw sessessa .tneipicer eht htiw elbitapmoc era sllec ronod

- Before giving a transfusion to a person, it is necessary to determine the **blood type** of the **recipient** and **donor** blood so that the bloods can be appropriately matched.
- In a cross-match, the possible **donor RBCs** are **mixed** with the **recipient's serum**. If **agglutination does not occur**, the recipient does not have antibodies that will attack the donor RBCs.
- Alternatively, the **recipient's serum** can be **screened** against a test panel of RBCs having **antigens** known to cause blood transfusion reactions to detect any antibodies that may be present.

Except in extreme emergencies, it is safest to individually cross-match blood before a transfusion is undertaken even though the ABO and Rh typing is already known, because there are approximately 23 other minor human erythrocyte antigen systems, with hundreds of subtypes.

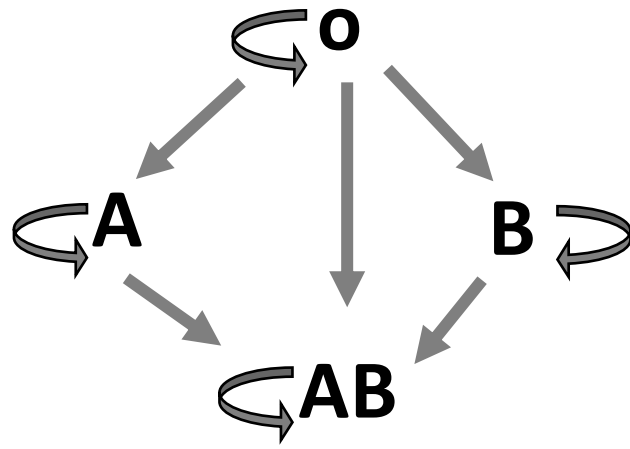
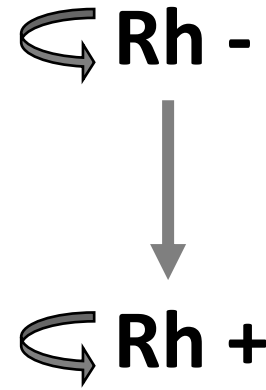
- **In a serological crossmatch, we test the donor's red cells against the recipient's plasma** wonk ot tnaw ew esuaceB ?noitanibmoc siht yhW .
.sllec ronod esoht kcatta dluoc taht seidobitna sah tneipicer eht rehtew

- **Antibody Screen and Compatibility Test:**

An antibody screen uses reagent red cells with known antigens to look for clinically significant antibodies in the recipient's plasma. Screening and crossmatching therefore provide related information. They are not simply interchangeable alternatives. The textbook introduces compatibility through the presence or absence of agglutination. In practice, laboratories use validated methods capable of detecting important antibodies that may not produce obvious clumping in a simple mixture. Done, done, done.

Blood Groups

Red-cell transfusion compatibility



Read these arrows from the red cell donor to the recipient:

ABO & Rh Red Blood Cell Transfusion Compatibility:

- **ABO System Dynamics:**

Group O (Universal Donor): Can safely donate to all blood groups because its red blood cells lack both A and B antigens.

Group AB (Universal Recipient): Can receive blood from all groups. However, because it possesses both A and B antigens, it can only donate to other AB recipients.

Groups A and B: Can donate to their own respective blood groups and to AB recipients.

- **Rh (D) Factor Considerations:**

Rh- (D-) Recipients: Must strictly receive Rh- blood. This prevents sensitization, where the immune system would mistakenly build antibodies against foreign D antigens.

Rh+ (D+) Recipients: Can safely receive both Rh+ and Rh- blood.

Why? Because their own red blood cells already naturally possess the D antigen. Their immune system recognizes it as "self," meaning it will not lead to an attack against the donor blood, regardless of whether that blood has the D antigen or lacks it.

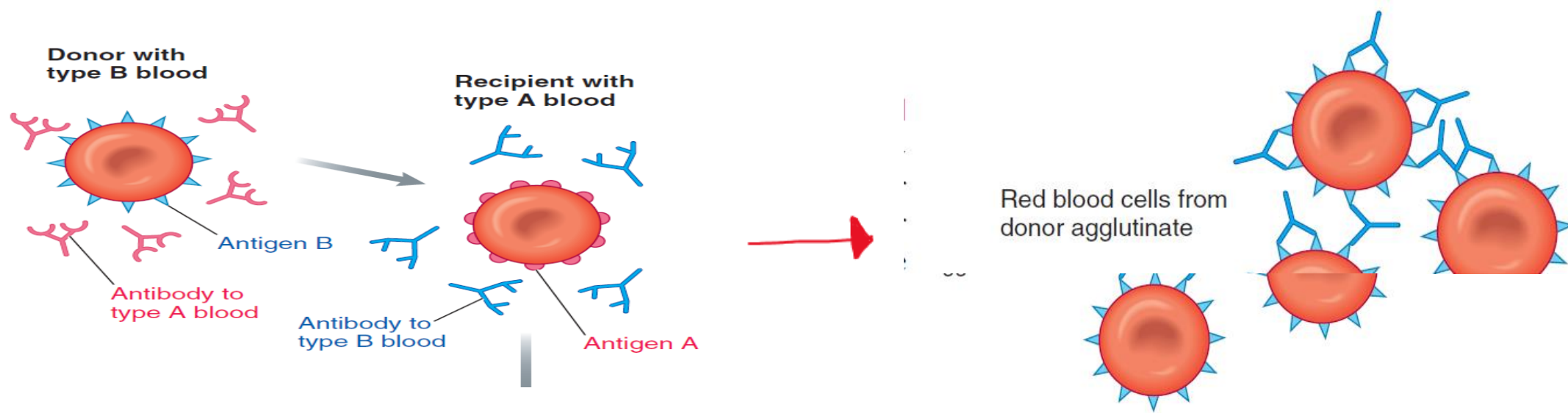
Which blood component does the patient need?

- **RBCs** restore oxygen-carrying capacity.
 - **Platelets** support primary hemostasis.
 - **Plasma** supplies coagulation factors.
 - **Cryoprecipitate** supplies fibrinogen.
-
- **With RBC transfusion, consider recipient antibodies against donor RBCs.**
 - **With plasma, consider donor antibodies against recipient RBCs. (Important)**

****The plasma portion of the donor blood immediately becomes diluted by all the plasma of the recipient (decreasing the titer of the infused agglutinins). The small amount of infused blood does not significantly dilute the agglutinins in the recipient's plasma**

Blood Groups

Transfusion reaction



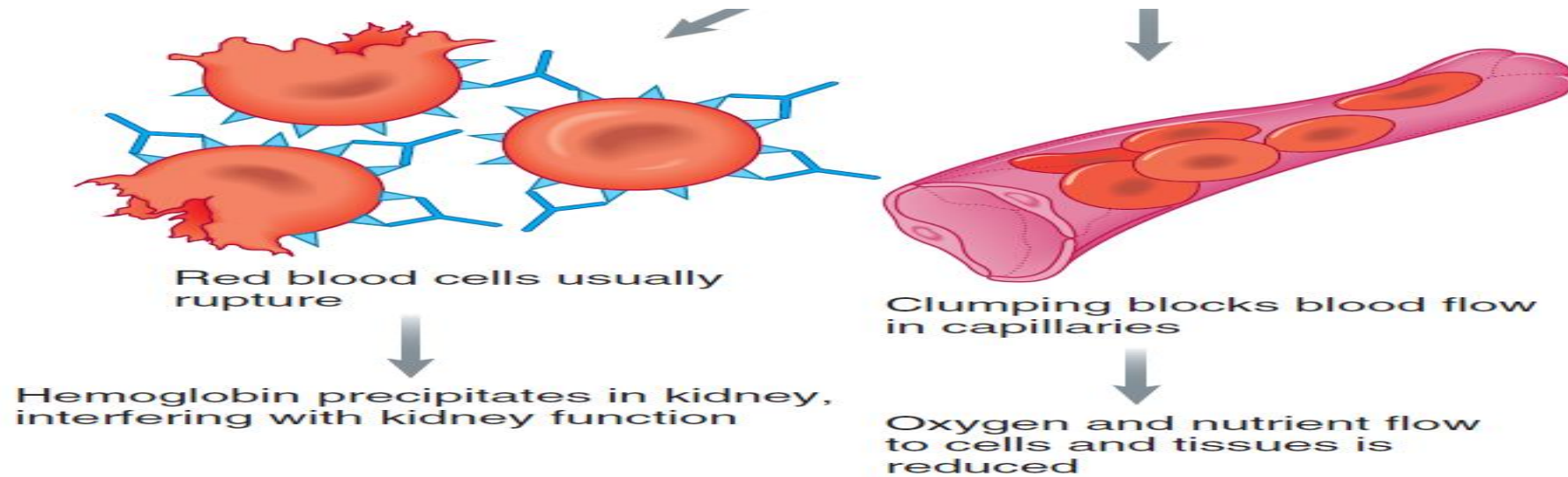
The Mechanism of an Incompatible Transfusion:

(Example: Group B Donor to Group A Recipient):

- **The Mismatch:** The donor's red blood cells carry **B antigens**, but the recipient's plasma naturally contains **Anti-B antibodies**.
- **The Immune Reaction:** The recipient's antibodies immediately recognize the donor cells as a threat. They bind to the donor's B antigens, causing the red blood cells to link together and clump (agglutination).
- **The Clinical Consequence:** The primary goal of a transfusion is to improve oxygen transport. However, in an incompatible match, the recipient's immune system quickly destroys and removes the donor cells, making the transfusion both ineffective and highly dangerous.

Blood Groups

Transfusion reaction



How Transfusion Reactions Cause Kidney Damage?

Kidney injury during a severe transfusion reaction is a dangerous combination of immune responses, circulatory failure, and rbc's destruction (hemolysis). This damage occurs through three main mechanisms:

- **Decreased Renal Blood Flow:** The release of immune reaction mediators directly constricts blood vessels, reducing blood flow to the kidneys.
- **Circulatory Shock:** A severe systemic reaction causes a massive drop in arterial blood pressure. This severely starves the kidneys of perfusion and leads to a noticeable decline in urine output.
- **Hemoglobin Toxicity:** Intravascular hemolysis releases large amounts of free hemoglobin into the bloodstream. Once the body's haptoglobin is fully saturated, the excess hemoglobin filters directly into the renal tubules, causing severe tubular injury and harmful pigment formation

How antibodies destroy incompatible RBCs

Both begin when recipient antibodies bind to donor RBC antigens.

	Extravascular hemolysis	Intravascular hemolysis
Mechanism	Macrophages remove antibody-coated RBCs	Complement activated by antibodies, leading to the formation of membrane attack complex (form membrane pores and ruptures RBCs (lysis)
Site of destruction	Mainly spleen and liver	Within blood vessels
Hemoglobin fate	Breakdown mainly inside macrophages	Release directly into plasma
Typical example	IgG anti-D-mediated RBC destruction	ABO-incompatible transfusion (often involving IgM) (faster reaction)

**** Both pathways begin when recipient antibodies recognize antigens on incompatible donor red cells...**

In extravascular hemolysis, macrophages recognize coated cells and remove them, mainly in the spleen and liver. Hemoglobin breakdown occurs primarily within macrophages.

In intravascular immune hemolysis, complement activation can proceed to the membrane attack complex, causing RBC rupture and release of hemoglobin into plasma. Anti-D is an example of predominantly IgG-mediated extravascular destruction. ABO-incompatible RBC transfusion is a classic example of potentially severe complement-mediated intravascular hemolysis. These are typical associations, not exclusive rules: some IgG antibodies activate complement, and complement coating can also promote extravascular removal.

The two mechanisms may coexist: **Agglutination** means antibody-mediated cross-linking and **clumping**; it is distinct from destruction, and visible clumping is not a prerequisite.

Characteristics of Rh Transfusion Reactions:

- Likely cause **no immediate reaction**.
- **Anti-Rh antibodies** can develop in sufficient quantities during the next **2 to 4 weeks** to cause **agglutination** of those **transfused cells** that are still circulating in the blood.
- These cells are then hemolyzed by the tissue macrophage system. Thus, a **delayed transfusion reaction** occurs, although it is usually **mild**.

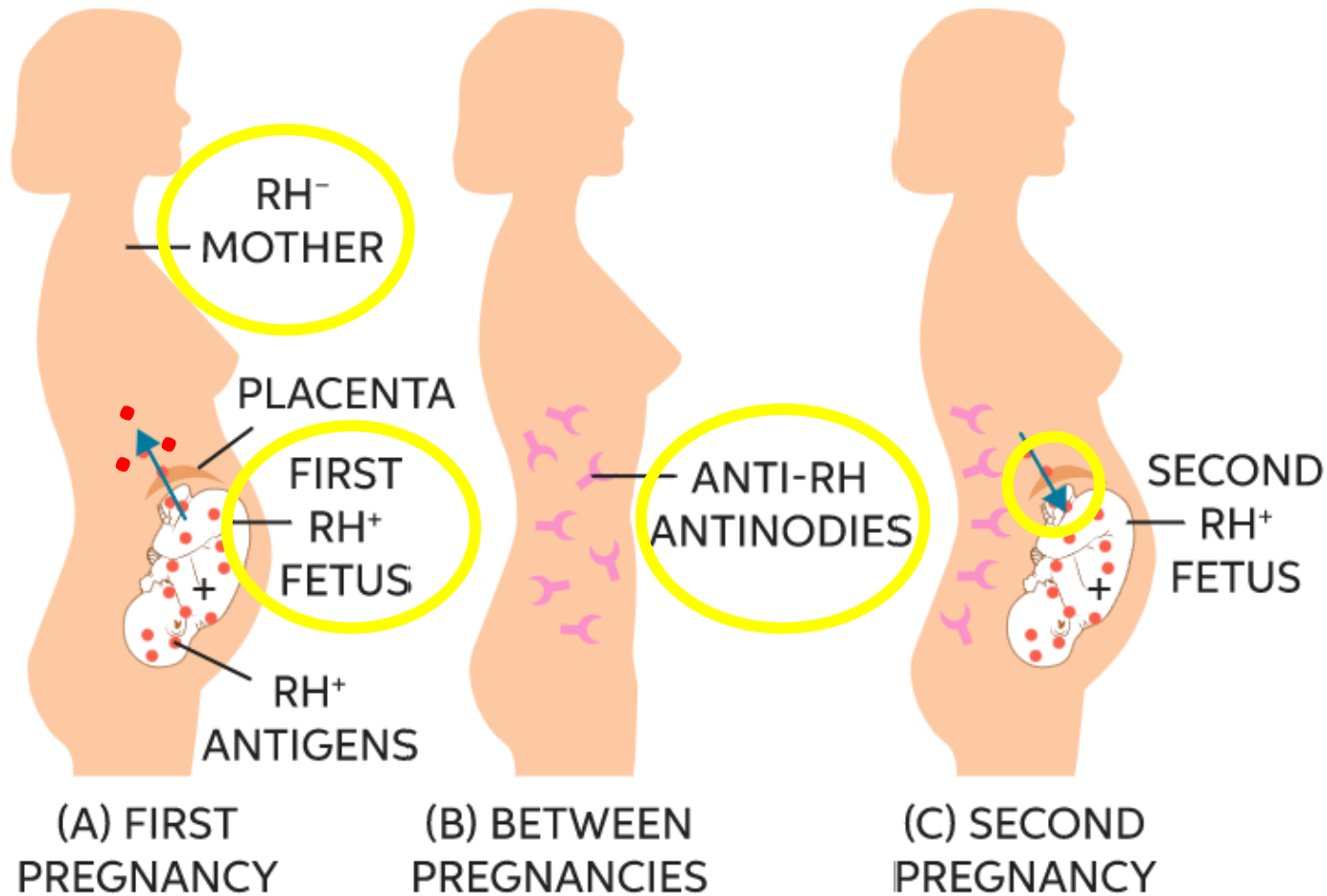
First Exposure to Rh+ Blood (in an Rh- Recipient):

- **No Immediate Reaction:** Unlike the ABO system, an Rh- person does not naturally possess Anti-D antibodies. Because of this, an initial transfusion of Rh+ blood will not trigger an immediate, acute immune response.
- **Sensitization & Delayed Cell Destruction:** The exposure stimulates the immune system to start producing Anti-D antibodies. Over the following weeks, as antibody levels rise, macrophages will gradually target and remove the remaining donor red blood cells (extravascular hemolysis). The speed of this clearance varies from person to person.
- **Long-Term Consequences:** This first exposure permanently "sensitizes" the patient's immune system. Even though the first reaction was delayed and mild, the body is now primed to launch a severe, immediate attack upon any future exposure to Rh+ blood—posing a critical danger for future transfusions or during pregnancy with an Rh+ fetus.

Characteristics of Rh Transfusion Reactions:

- On **subsequent transfusion** of Rh-positive blood into the same person (**sensitized**), who is now already immunized against the Rh factor, the transfusion reaction is **greatly enhanced** and can be **immediate** and as **severe** as a transfusion reaction caused by mismatched type A or B blood.
- **In the second exposure**, if a sensitized Rh- patient receives Rh+ blood, any circulating Anti-D antibodies will instantly bind to and attack the newly transfused cells. Even if the patient's antibody levels have naturally dropped over time, their immune system retains a permanent memory of the D antigen. This re-exposure triggers a **powerful secondary immune response**, causing the body to rapidly produce a massive surge of new antibodies. Because of this immune memory, the secondary reaction is much faster, stronger, and more dangerous than the patient's first exposure, leading to the rapid destruction of the donor red blood cells

Hemolytic Disease of the Newborn Erythroblastosis Fetalis:



See Next Slide:

Hemolytic Disease of the Newborn Erythroblastosis Fetalis:

- **Pregnancy** can expose an Rh- mother to the D antigen if her fetus inherits an Rh+ blood type from the father. Although maternal and fetal circulations are completely separate, small amounts of fetal blood can enter the mother's bloodstream, particularly during delivery. **This exposure sensitizes the mother, causing her immune system to produce Anti-D antibodies.**
- **If she becomes pregnant again with another Rh-positive baby**, these newly formed antibodies can cross the placenta and bind to the fetus's red blood cells, leading to their destruction (**hemolysis**) by macrophages. Because the mother's own red blood cells lack the D antigen, she is not targeted by these antibodies and remains completely unaffected by the immune reaction.
- Fetal hemolysis causes severe anemia, prompting the fetal liver and spleen to enlarge as they rapidly produce new red blood cells to compensate. This **releases immature cells (erythroblasts) into the bloodstream**, giving the condition its name: **Erythroblastosis Fetalis**. The severe anemia overworks the heart, potentially causing **heart failure and fluid accumulation (hydrops)**. Additionally, the rapid destruction of red blood cells produces large amounts of bilirubin. Before birth, the placenta safely clears this bilirubin into the mother's bloodstream. After birth, this clearance route is lost. If the newborn's liver cannot process the sudden bilirubin overload, severe **jaundice develops**. This excess unconjugated bilirubin can then cross into the brain, causing permanent neurological damage known as **kernicterus**.

Hemolytic Disease of the Newborn

Erythroblastosis Fetalis

- Hemolytic anemia (fetal)
- Jaundice.
- The liver and spleen become greatly enlarged.
- Presence of nucleated blastoid red blood cells.
- Permanent mental impairment or damage to motor areas of the brain.

Although the severe anemia of erythroblastosis fetalis is usually the cause of death, many children who barely survive the anemia exhibit permanent mental impairment or damage to motor areas of the brain because of precipitation of bilirubin in the neuronal cells, causing the destruction of many of these cells, a condition called **kernicterus**.

Treatment of the Erythroblastotic Neonate:

Treatment for hemolytic disease depends on its severity:

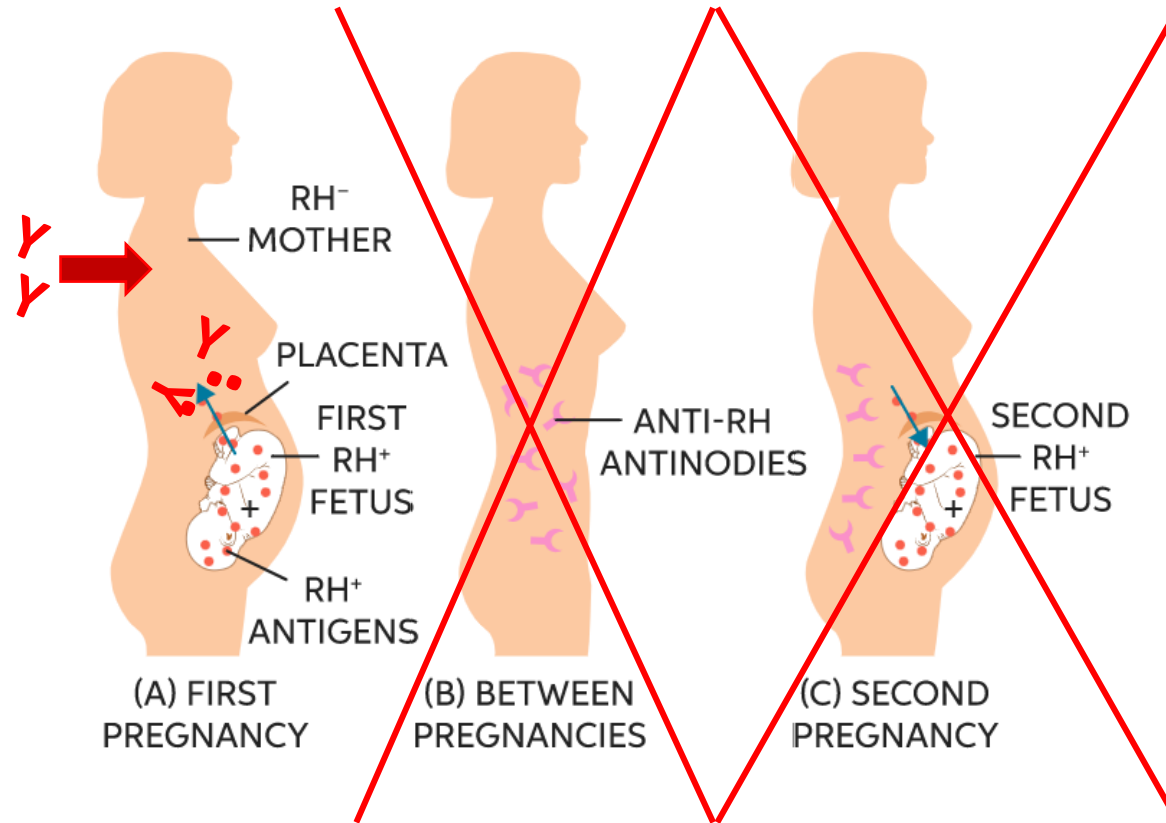
- **Mild to moderate cases** use phototherapy to eliminate bilirubin and simple red blood cell transfusions to correct anemia.
- **In severe cases**, an exchange transfusion is performed, where portions of the infant's blood are gradually removed and replaced with compatible donor blood. This crucial procedure rapidly lowers bilirubin levels, washes out circulating maternal antibodies, and provides functional red cells.
- **For Anti-D mediated disease**, the transfused donor cells must be Rh-negative so the remaining maternal antibodies cannot target or destroy them. Because maternal antibodies can persist in the infant's bloodstream for weeks after birth, close medical monitoring must continue even after the baby initially improves.

Treatment of the Erythroblastotic Neonate

- One treatment is to **replace the neonate's blood with Rh-negative blood.**
- This procedure may be repeated several times during the first few weeks of life
- Anti-Rh agglutinins from the mother usually circulate in the infant's blood for another 1 to 2 months after birth, destroying more and more red blood cells.
- This keeps the bilirubin level low and thereby prevent complications.

****By the time these transfused Rh-negative cells are replaced with the infant's own Rh-positive cells, a process that requires 6 or more weeks, the anti-Rh agglutinins that had come from the mother will have been destroyed.**

Prevention of the Erythroblastotic Neonate



See next Slide:

Prevention of the Erythroblastotic Neonate:

- The primary goal of prevention is to stop an Rh-negative mother from developing her own permanent antibodies against an Rh-positive fetus. **This is achieved by administering Anti-D immunoglobulin before sensitization can occur.** Standard protocol requires giving this injection during weeks 28 to 30 of pregnancy, and again within 72 hours after delivery **if the baby is confirmed to be Rh-positive.** Additional doses are also given after any medical event where fetal red cells might cross into the mother's circulation.
- It may sound contradictory to give Anti-D antibodies to prevent the mother from forming Anti-D. The explanation is that this treatment provides a **temporary supply of antibodies.** The administered Anti-D quickly binds to any fetal red blood cells that have entered the mother's bloodstream and clears them out. By destroying these cells immediately, the medication **suppresses the mother's immune system, completely preventing it from mounting a permanent immune response and forming long-term immune memory.**
- This protective treatment does not change the blood group of the mother or the fetus. Because the provided immunity is only **temporary,** the injections must be repeated for all future pregnancies or exposures. Most importantly, **Anti-D immunoglobulin is strictly a preventive measure; it successfully prevents sensitization, but it cannot reverse it if the mother has already been sensitized.**

The mechanism whereby Rh immunoglobulin globin prevents sensitization of the D antigen is not completely understood, but one effect of the anti-D antibody is to inhibit antigen-induced, B lymphocyte antibody production in the expectant mother. The administered anti-D antibody also attaches to D antigen sites on Rh-positive fetal RBCs that may cross the placenta and enter the circulation of the expectant mother, thereby interfering with the immune response to the D antigen.

رسالة من الفريق العلمي:

عن أبي هريرة رضي الله عنه أن رسول الله صلوات الله عليه وآله وسلم قال :
من قال :

**لا إله إلا الله وحده لا شريك له
له الملك .. وله الحمد
وهو على كل شيء قدير**
(في يوم مئة مرة)

**كانت له عدل عشر رقاب
وكتب له مئة حسنة ، ومحيت عنه مئة سيئة
وكانت له حرزا من الشيطان يومه ذلك حتى يمسي
ولم يأت أحد بأفضل مما جاء ، إلا رجل عمل أكثر منه**
(متفق عليه)

For any feedback, scan the code or click on it.



Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1			
V1 → V2			