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The Crux

BIMONTHLY FORUM FOR THE LABORATORIANS

CONTENTS

Editorial

Immunohematology is a special branch that studies the reactions that take place between antigens present on blood cells and antibodies present in plasma. Patients undergoing transfusion therapy are tested for their ABO and RhD blood groups and the presence of any antibodies that may cause a reaction between their plasma and donor red cells.

It was not until the year 1900, when Karl Landsteiner at the University of Vienna, discovered why some blood transfusions were successful while others could be deadly. Landsteiner discovered the ABO blood group system by mixing the red cells and serum of each of his staff. He demonstrated that the serum of some people agglutinated the red cells of other, he identified three types, called A, B and C (C was later to be re-named O). Further in 1940-41 Landsteiner and Wiener discovered the Rh blood group system by using the blood of rhesus monkeys to test for the presence of the Rh antigen in human blood. The Rh blood group system classifies blood groups based on the presence or absence of the Rh antigen, also known as the Rh factor.

Whenever there is any blood transfusion or transplant surgery a very important test is being conducted to ensure that the recipient's immune system doesn't create antibodies against the donor's blood cells .This test is termed as crossmatch. There is a short info of it too within.

This issue of *The Crux* also explores the significance of accurate blood group detection through fascinating case studies. We present a rare case of the A_2 blood group, highlighting the challenges of diagnosing this uncommon type, as well as the importance of screening for the Bombay phenotype. These case studies emphasize how crucial it is to correctly identify blood groups to prevent complications and ensure transfusion safety.

Additionally, we provide an informative flowchart in the form of poster **"Add value to forward grouping"**. This poster explains how to proceed forward with the results obtained when you react the patient sample first with Anti A, Anti B, Anti D to detect the subgroups. If subgrouping is done at this time, it will help to identify all individuals with rare blood groups. These people can be thus listed in donors list which would ensure timely transfusion in times of need.

We hope this issue sheds light on the critical importance of Immunohematology in transfusion medicine, helping readers appreciate the complexities of blood group testing and the advancements that continue to improve patient outcomes.

Finally, we haven't forgotten to include a special page dedicated to our "BOUQUET" section, offering a delightful and engaging touch for our readers.

Happy reading!

IMMUNOHAEMATOLOGY

Immunohematology is the study of the relationship between antigens and antibodies in blood transfusions and pregnancy complications. It's a branch of hematology and transfusion medicine.

BLOOD GROUPING ANTIGENS AND ANTIBODIES

ABO BLOOD GROUPS	BLOOD GROUP A	BLOOD GROUP B	BLOOD GROUP AB	BLOOD GROUP O
Red blood cell type	A	B	AB	O
Antigen (on red blood cells)	A antigen	B antigen	A antigen B antigen	none
Antibodies (in plasma)	anti-B	anti-A	none	anti-A anti-B

ABO BLOOD GROUP SYSTEM

It is now known that no two individuals can have similar red cells. They differ in chemical structures on the red cell surface called **Blood Group Antigens**. Antigens are an expression of an inherited gene from the previous generation. Different RBC antigens are inherited by different individuals depending on the inherited gene. Individuals are divided into various blood groups on the basis of the antigens present on their red blood cells.

A red blood cell antigen is harmless to the person who possesses it, but it can endanger someone who does not possess that antigen.
Blood grouping is the process of testing red blood cells to determine which antigens are present on their surface. There are many blood group systems which have been discovered, some of them are ABO, Rh, MNS, Lewis, Lutheran, Kell, Kidd, Duffy. Of these ABO and Rh blood grouping is routinely carried out and tests for other antigens are done in selected cases.
Exposure to a foreign antigen may cause an individual to produce a substance whose function is the destruction of that antigen. The destructive substance which can be demonstrated in the serum is called **antibody**.

There are two types of antibodies produced in an individual

- Naturally occurring antibody: Some antibodies are found in persons who have neither been transfused nor have they been pregnant.
- Immune Antibody: Production of antibody to a blood group antigen is usually preceded by the introduction of foreign red cells either by **transfusion or pregnancy**.

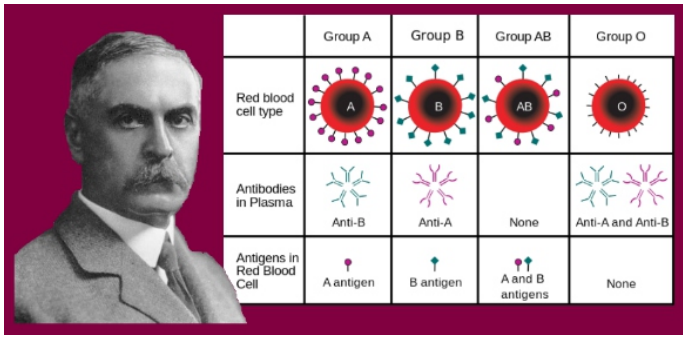
BLOOD GROUPING/TYPING

THE STUDY OF BLOOD GROUPS CAN BE DIVIDED INTO:

1. THE ABO SYSTEM
2. THE RH SYSTEM

ABO SYSTEM

A series of tests reported by Karl Landsteiner in 1900 led to the discovery of ABO blood group system and to the development of routine blood typing procedures.



IMPORTANCE OF ABO GROUPING

The first blood group system to be discovered. ABO remains the most significant for transfusion practice. It is the only system in which the reciprocal (or antithetical) antibodies are consistently and predictably present in the sera of most people who have no exposure to human red cells i.e., Anti-A found in the serum of B group individual.
Because of these antibodies, transfusion of ABO–incompatible blood may cause severe **intravascular hemolysis** (destruction of the red cells inside the blood vessels) as well as the other manifestions of **acute hemolytic transfusion reaction**. Testing to detect ABO incompatibility between a recipient and the donor is the foundation on which all the **pretransfusion testing** is based.

ABO GROUPING

The ABO blood group system divides individuals into four blood groups on the basis of presence or absence of two antigens on the red blood cell surface.
The two antigens are:

1. *A antigen*
2. *B antigen*

The presence and absence of these genes is under genetic control and is determined by three genes A, B & O. Genes A & B code for the corresponding antigen on the red blood cell surface but gene 'O' is an amorph i.e, it does not produce any antigen on the RBC surface. Testing the red cells of an individual for the presence or absence of A and/ or B antigen is known as **ABO grouping**.

The four blood groups based on ABO grouping are: -
GROUP A- Red cells of this group have only the A antigen on their surface
GROUP B- Red cells of this group have only the B antigen on their surface
GROUP A, B- Red cells of this group have both A and B antigens on their surface
GROUP O- Red cells of this group have neither A nor B antigens on their surface

In addition to A and B antigens, red cells of all ABO groups have another antigen 'H'. 'H' is a precursor from which A and B antigens are made by the addition of specific sugars.

ANTISERAS

Whenever any antigen of the ABO system is absent on the red blood cells of an individual the corresponding antibody is present in his / her serum. **These are naturally occurring antibodies**.

GROUP A **individuals have Anti-B in their serum**
GROUP B **individuals have Anti-A in their serum**
GROUP O **individuals have both Anti-A and Anti-B in their serum**
GROUP A, B **individuals have neither Anti-A nor Anti-B in their serum**

As already studied earlier it has been found that certain particles like pollen, food particles, dust etc, have antigenic properties that resemble the A and B antigen and when we ingest these antigens the corresponding anti-A and anti-B antibodies are formed. This concept is used to produce the various antiseras required to detect A and B antigens on the red cells

BLOOD GROUPING- TEST METHODS

FORWARD GROUPING

The individual is first assigned to the four ABO blood groups A, B, A,B or O based on the reaction of his/her cells with the blood grouping sera anti-A and anti-B. This is known as forward grouping.

RED CELLS TESTED WITH		BLOOD GROUP
ANTI-A	ANTI-B	
+ve	-ve	**A**
-ve	+ve	**B**
+ve	+ve	**A,B**
-ve	-ve	**O**

In ABO grouping, the Antisera used for forward grouping test should
1. Contain IgM antibodies in a low protein diluent
2. Agglutinate saline suspended red cells
3. React at room temperature and the reaction should be immediate.

REVERSE GROUPING

Reverse grouping helps in confirming the results of forward grouping. In reverse grouping serum of the individual is tested with known group A and group B red cells to demonstrate the presence or absence of anti-A or anti-B. Any discrepancy in the result of the forward and reverse grouping must be investigated and resolved before concluding an individual's true ABO group.

SERUM TESTED WITH		ANTIBODY PRESENT IN SERUM	BLOOD GROUP
A CELLS	B CELLS		
-ve	+ve	ANTI-B	**A**
+ve	-ve	ANTI-A	**B**
-ve	-ve	NONE	**A,B**
+ve	+ve	ANTI-A & ANTI-B	**O**

Forward grouping is done by slide or tube techniques and reverse grouping is done by the tube technique only.

ABO/Rh group	Forward Typing			Reverse Typing	
	Anti-A	Anti-B	Anti-D	A1 cells	B cells
O neg	0	0	0	4+	4+
O pos	0	0	4+	4+	4+
A neg	4+	0	0	0	4+
A pos	4+	0	4+	0	4+
B neg	0	4+	0	4+	0
B pos	0	4+	4+	4+	0
AB neg	4+	4+	0	0	0
AB pos	4+	4+	4+	0	0

WHAT ARE THE ADVANTAGES AND DISADVANTAGES OF SLIDE V/S TUBE TESTS?

SLIDE TEST

ADVANTAGES	DISADVANTAGES
a. Convenient and swift	a. Weaker variants of antigens may be missed
b. No equipment needed	b. Greater chances of human error in performing the slide test
c. Avidity of the antigen-antibody reaction can be gauged only by the slide test	c. Batch testing is not feasible

TUBE TEST

ADVANTAGES	DISADVANTAGES
a. Weaker variants of the antigens are not missed	a. More time consuming than slide tests
b. Less chance of human error due to the use of standard equipment and preparation of cell suspensions	b. Standardized equipment required
c. Blood banks resort to this method of testing as more number of tests can be performed in a single session	c. Avidity cannot be gauged by tube tests

ANTI-A,B

Anti-A,B is prepared from an O group person and therefore it is more potent than the individual Anti-A and Anti-B. It is observed that certain weaker subgroups of A are not detected by Anti-A and therefore the use of Anti-A,B would eliminate the missing of these weaker sub-groups of A. Anti A,B also confirms the results obtained with Anti-A, Anti-B.

A_1 GROUP

The cells of about 80% of group A population are A_1, while 20% are A_2 or weaker subgroups. Anti- A_1 lectin a seed extract from *Dolichos biflorus* and is used to detect presence or absence of A_1 antigen. If the red cells agglutinate with anti-A_1 lectin then A_1 antigen is present on the cell otherwise A_2 or weaker subgroups of A are present. The other weaker subgroups of A are A_3, $A_{int.}$ A_x.

IMPORTANCE OF SUBGROUPS

Occasionally subgroups can present practical problems. The antigen may be so weak that it is not recognized, and the red cells are mistyped as O; this is dangerous if the cells are of a donor. In case of A_2 or A_2B group individuals, the serum contains anti-A_1 and this is produced by about 1-2% of A_2 persons and about 25% of A_2B persons. Anti-A_1 is also a naturally occurring antibody. So if A_1 cells are given to A_2 or A_2B group individuals then it could cause transfusion reaction due to presence of Anti-A_1 in the serum of these individuals. Hence differentiating A_1 and A_2 becomes essential while grouping a person.

A_1 and A_2 Subgroup*

	Anti-A antisera	Anti-A_1 antisera	Anti-H lectin	ABO antibodies in serum
A_1	4+	4+	0	Anti-B
A_2	4+	0	3+	Anti-B & anti-A_1

LECTINS

Lectins are antibody like material, which react specifically with blood group antigens. Lectins are commonly obtained from seed extracts and hence are known as phytohaemagglutinins (phyto-plants; haem-blood; agglutinin-antibody that brings about agglutination of antigenic particles) and are used as reagents in blood grouping.

ANTI-A_1 LECTIN

Anti-A_1 lectin is used for the detection of red cells of subgroup A_1 and A_1B. **Anti-A_1 lectin prepared from the seeds of Dolichos biflorus agglutinates red cells of Group A_1 and A_1B** does not agglutinate the other weaker subgroups of A and AB.

ANTI-H LECTIN

Anti H lectin, which is prepared out of Ulex europaeus, is used for the detection of secretor characteristics in saliva and can be used for the determination of the H antigen on the red cell surface. Anti-H lectin is found to react most strongly with O red cells and most weakly with A_1B cells.

The reactivity pattern of Anti–H lectin with different red cell antigens are as follows:

$O > A_2 > B > A_2B > A_1 > A_1B$

THE BOMBAY PHENOTYPE

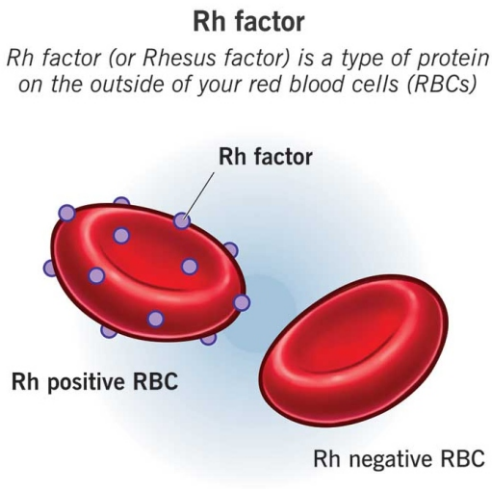
In 1952 Bhende and his associates reported the first case of Bombay phenotype (denoted by '**O_h**'). The term 'Bombay' has been used for the phenotype in which red cells lack H, A, and B antigens because examples of such red cells were first discovered in Bombay, India. The serum of persons of the Bombay phenotype group contains Anti-A, Anti-B and Anti-H. **Due the presence of these antibodies a Bombay phenotype blood group person can receive blood only from another Bombay phenotype individual**. Blood of A, B, AB and O are incompatible. The O_h phenotype is demonstrated by the absence of reaction when the cells are tested with Anti-H lectin, a seed extract from *Ulex europaeus* (used to detect the presence or absence of H antigen).

ACQUIRED B GROUP

Blood group antigens altered by Bacterial Enzymes

Some group A individuals with intestinal obstruction, carcinoma of the colon or rectum and disorder of the lower intestine acquire a B like antigen. The reaction observed between Anti-B and the acquired B antigen is usually weak and often disperses easily. Increased permeability of the intestinal walls allow the passage of bacterial enzyme into circulation. These enzymes act on the terminal sugar of A antigen, causing the patient's red cells to be agglutinated by anti-B (in addition to their original reactivity with Anti-A which is unaffected). This could lead to the blood being mistyped. **However on reverse grouping, the results observed are those expected of a group A person**, i.e., only anti-B is present in the serum. Thus reverse grouping gives the clue that the patient does not belong to blood group B or AB. If the intestinal condition improves, the red cells revert to normal and no longer react with anti-B. Hence a good Anti–B reagent should be truly negative reacting with acquired B characteristics

RH SYSTEM (Rhesus Blood Group System)



The clinical importance of the Rh blood group system stems from the fact that the antigen D of the system is highly immunogenic (ability to produce Anti-D); if a unit of D-positive blood is transfused to a D-negative recipient, the recipient forms Anti-D in some 90% of the cases and thereafter cannot be transfused with D positive red cells.

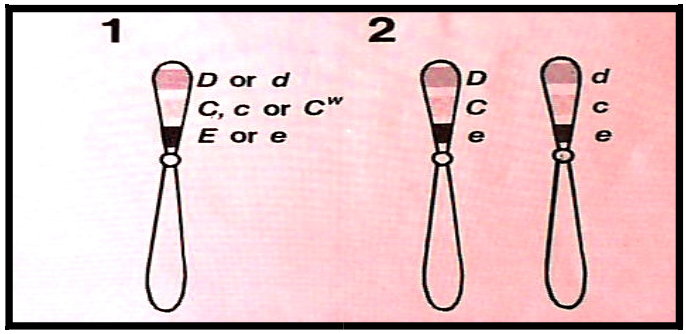
Soon after Anti-D was discovered it was found that D antigen is genetically transmitted.

Rh genes

By the mid–1940s, four additional antigens C, E, c, and e had been recognized as belonging to the Rh system. C is antithetical to c and E to e. There is no antigen antithetical to D.

Weiner proposed a single locus with multiple alleles determining surface molecules that embody numerous antigens. Wiener's nomenclature is now almost obsolete.

In 1943 R. A Fisher proposed that there were three closely linked genes Cc, Dd and Ee and the order of the genes was DCE. It was later found out that d did not occur. Application of the techniques of molecular biology showed that there are only two Rh genes: D, which has no allele and a second gene, CeEe that has many alleles. d is used to indicate the absence of D.



D is by far the most immunogenic of the Rh antigens at least 20 times more immunogenic than c, the next potent antigen.

THE D ANTIGEN

D antigen is the major antigen of the Rh system. The term Rh positive is used to denote the presence of D antigen or its variant D^u (Weak D / Partial D) on the red cell membrane. Red cells, which have neither D nor D^u on their membranes, are termed as Rh negative.

IMPORTANCE OF Rh TYPING

Unlike the ABO system, naturally occurring antibodies are not seen in the Rh system. This is because there are no substances present in nature, which are chemically similar to the D antigen, hence Anti-D is not a naturally occurring antibody.

Anti-D is seen in the serum of Rh-negative persons only after they have been exposed to Rh-positive cells. This may take place only under the following two circumstances:

Transfusion of blood from a Rh positive donor to a Rh negative recipient.

Passage of cells from a Rh positive fetus through the placenta to the Rh negative mother.

Both the above can prove to be fatal. So correct Rh typing is essential to avoid the above from occurring.

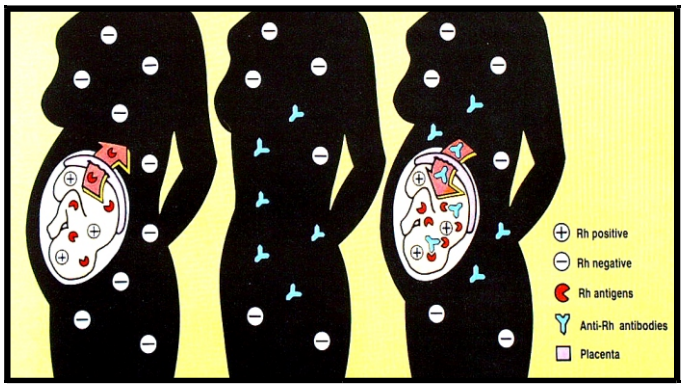
CLINICAL SIGNIFICANCE OF D TYPING

As mentioned earlier with the exception of A and B antigen, the most important of all blood groups antigens is undoubtedly D. The D antigen is highly immunogenic antigen.

1. Transfusion of D (incompatible blood leads to the formation of Anti-D and the presence of this antibody can lead to tragic consequences during subsequent transfusions.
2. Rh incompatibility between mother and fetus can result in hemolytic disease of the newborn.

HEMOLYTIC DISEASE OF THE FOETUS NEWBORN (HDFN) occurs when the fetal red cells have an antigen of paternal origin (D antigen), which the mother lacks (i.e., mother is Rh-ve). At the time of delivery, these fetal red cells enter the maternal circulation. These red cells then immunize the mother, and antibodies (Anti-D) are produced by the mother against these red cells. These newly formed antibodies (Anti-D) cannot harm the infant as it has been delivered, but antibodies still persist in the maternal circulation, so during subsequent pregnancies, these maternal antibodies (Anti-D) enter the fetal circulation. These antibodies then destroy the fetal cells if they have the same antigen (D antigen from paternal origin). The fetus then develops severe anemia and jaundice due to hemolysis of the red cells. Early treatment is necessary to save the child. Although HDFN is sometimes caused by ABO incompatibility, it is most often due to Rh incompatibility.

The first child is affected only if the mother has been previously immunized against that antigen by incompatible transfusion (i.e, transfused with D (Rho) antigen before).



Although transfer of fetal cells during pregnancy or at the time of delivery cannot be prevented, initial immunization to D can be prevented by administration of Anti-D immunoglobulin to the mother.

Due to the above mentioned reasons D typing is extremely important and the correct Rh type of the person must be determined.

D^u (Weak D) CLASSIFICATION

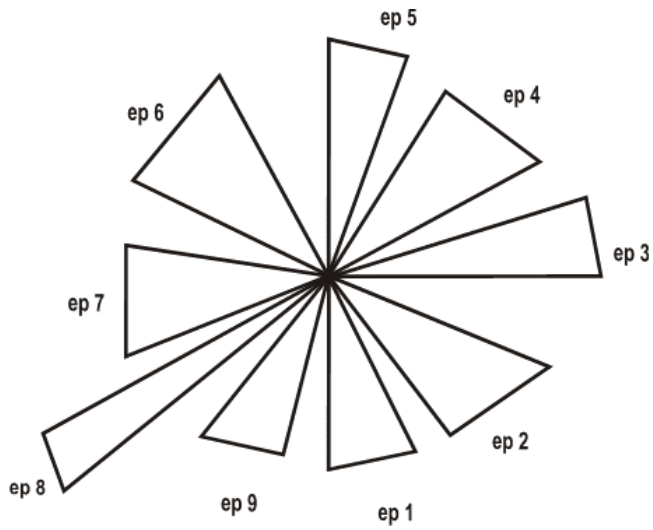
D antigen is the major antigen of the Rh system. The cells which are not immediately agglutinated by Anti-D sera cannot be easily classified as D negative because some of these agglutinate after addition of antiglobulin sera. This weak reactivity is termed as Du. Du is the weak expression of D antigen.

The term Rh positive is used to denote the presence of D antigen or its variant D^u (Weak D / Partial D) on the red cell membrane. Red cells, which have neither D nor D^u on their membranes, are termed as Rh negative.

Subsequent research has shown that the traditional D^u red cells can be classified as;

- **Weak D's**
- **Partial D's**

Let us look at the structure of the D antigen on the nine-epitope model suggested by Lomas et al (1993)



According to new understanding the D antigen is a mosaic (A picture made up of pieces). In a normal Rho D positive individual, the D antigen is in its complete form, with all the nine epitopes present on the red cells.

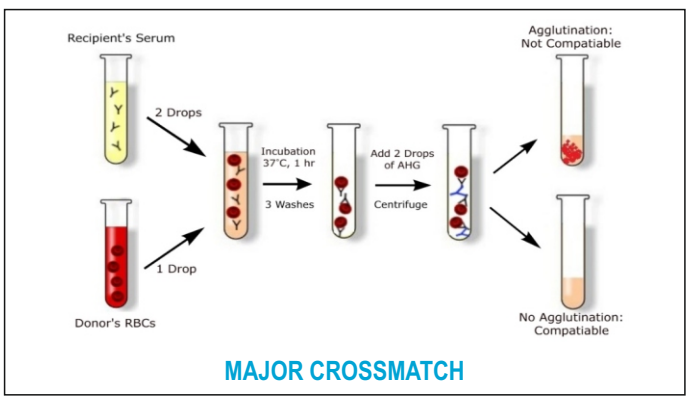
In a 'Weak D' the number of D antigen sites is less as compared to the normal D, but all the epitopes of the antigen are present on the red cells. (ep.1 to ep.9).

In a 'Partial D' however, the number of antigenic sites may be **slightly or significantly less** as compared to the normal D but one or more of the epitopes of the D antigens are missing on such red cells.

CROSSMATCH AND COMPATIBILITY TESTING:

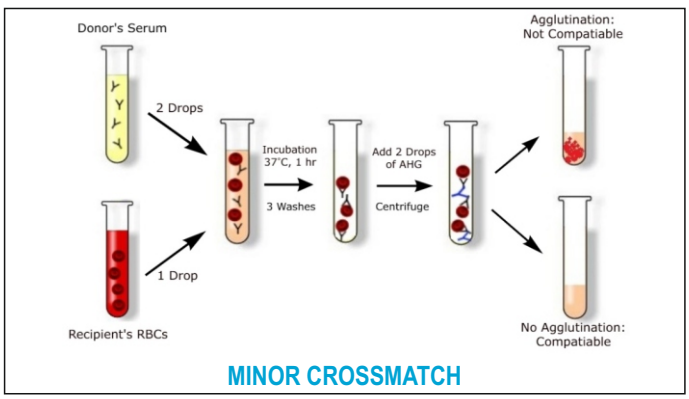
Crossmatching is a test performed before a blood transfusion as part of blood compatibility testing.
The final decision about whether donor blood is safe to transfuse to a patient does not depend only on ABO grouping and Rh typing but it depends on whether the donor and recipient blood are compatible i.e., whether there is any hemolysis or agglutination when they are mixed together due to atypical antibodies.

The compatibility test includes the **MAJOR CROSSMATCH** AND **MINOR CROSSMATCH**.
The MAJOR CROSSMATCH is more important of the two. This test detects antibodies in the recipient's serum, which may destroy the red cells of the donor. If this happens the purpose of the crossmatch is defeated. Hence this crossmatch is known as a **MAJOR CROSSMATCH**.



MAJOR CROSSMATCH

The MINOR CROSSMATCH detects antibodies in the donor's serum, which can destroy the recipient's red cells. Donor antibodies are mostly diluted in vivo by the recipient's plasma. Hence this crossmatch is of minor importance.



MINOR CROSSMATCH

PHASES INVOLVED IN CROSS MATCH

A Crossmatch involves three phases:
1. Room temperature phase or Initial phase
2. Incubation phase
3. Antiglobulin phase

Interpretation of Cross match:
- A positive result showing hemolysis or agglutination during the cross-match test would indicate blood incompatibility.
- A negative result showing no agglutination during the cross-match test would indicate blood compatibility.

CASE STUDIES OF RARE BLOOD GROUPS:

CASE1: Rare case of A_2+ve blood group with Placenta praevia with Obstetric Haemorrhage in mild hypovolemic shock.
(Journal of Clinical and Diagnostic Research. 2014 Feb, Vol-8(2):181-182)

Case Report

A 31-year-old unbooked lady presented to the Obstetric emergency ward and a diagnosis of gravida 2, para 1, living 0 with 27 weeks of gestation with central placenta praevia with ante partum haemorrhage was made. She had undergone a previous caesarean section at term for a transverse lie and the baby was still-born. Patient had been treated for secondary infertility and conceived spontaneously ten years later with the present pregnancy. General examination revealed the patient to be in mild hypovolemic shock with a tachycardia of >130 beats/minute. Her blood pressure was 94/60 mmHg. Haemoglobin was 8.4 gm/dL. Blood group was A+ve but when sent for cross matching was found to be incompatible with all ABO groups. Senior blood bank officers were called in and further tests done indicated a rare subgroup of A_2+ve. No blood in our bank and two other major blood banks was found compatible. Ultimately, four pints of compatible A_2+ve blood was found after screening nearly 600 pints of A+ve blood at the Karnataka Red Cross Blood Bank. Patient had received 3 pints of blood and antenatal steroids. Since she had no further bleeding it was planned to monitor her as an inpatient till she crosses her period of viability or the fetus can sustain in an extra uterine environment, provided she has no further life threatening haemorrhage which would compromise either her or the baby.

Discussion

Massive obstetric haemorrhage is a major contributor towards maternal morbidity and mortality. The main causes are abruptio placentae, placenta praevia and postpartum haemorrhage. Clinicians managing pregnant women should be equipped with the knowledge of blood and blood products and skills for managing massive obstetric haemorrhage.
Most clinicians are, however, unfamiliar with the fact that in 1911, Landsteiner detected the presence of subgroups of A, one of which was exhibiting weaker expression of the A antigen and named the two subgroups A_1 and A_2. Most of the individuals with a rare blood group are coincidently identified when a routine pre-transfusion testing or pregnancy follow-up is performed, if the antibodies corresponding to the rare specificity are present. There is a growing awareness of the impact of the genomics revolution on transfusion medicine and its potential to transform the way blood is selected for transfusion. From antibody-based technology to now single-nucleotide polymorphism (SNP) genotyping for blood, PCR-technology will help in extended matching of RBC units. Such advances in cross-matching of blood can save the lives of many, especially, as in this case, young women of child bearing age and thus reduce maternal mortality.

Conclusion

An awareness of rare blood groups and subtypes will help focus on recruiting minority donors. Though, multiple SNPs are available for ABO typing, providing extended-matched RBC units is unlikely for all patients. But, with advances in genotyping and better blood inventory–management systems more patients will be able to benefit from extended-matched transfusions.

Until then, the challenge lies in integrating such testing into the blood bank environment, standardizing methods and enhancing information systems to use effectively. In India where maternal mortality rates are still high, the major cause being haemorrhage, easily accessible compatible blood transfusion would help decrease these rates. The establishment of a state and national register of donors of rare blood groups and their alleles in India would aid in creating awareness of their existence.

CASE 2:

Bombay Blood Group Phenotype Misdiagnosed As O Phenotype:

Hira Qadir 1, Muhammad Omar Larik 2, Muhammad Ashhal Iftekhar 2
Editors: Alexander Muacevic, John R Adler

https://pmc.ncbi.nlm.nih.gov/articles/PMC11145363/

Case Report

A 32-year-old male with no known underlying medical conditions was involved in a road traffic accident, where he was admitted to another institute for an exploratory laparotomy and mesenteric tear repair. Postoperatively, he received packed red blood cell transfusions. His blood type was determined to be O Rh-positive. A day later, the patient presented to the emergency department of our institute with complaints of severe abdominal pain and decreased urine output. The laboratory parameters on admission to the emergency admission of the patient are done revealing acute kidney injury. The urine analysis results revealed >20 red blood cells, and his peripheral smear revealed spherocytes, polychromasia, and nucleated red blood cells. A blood sample was received in the blood bank for grouping and cross-match. Manual tube testing was used to determine the patient's ABO type. The forward grouping showed no agglutination with monoclonal anti-A, anti-B sera, and reversed grouping using A, B, and O cells showed a +4 agglutination reaction with A, B, and O cells. Blood grouping results were ultimately indicative of the Bombay blood group, with the subsequent testing with anti-H lectin sera revealing the lack of agglutination. Saliva testing could not be performed due to the commercial unavailability of testing kits in Pakistan. Subsequently, his blood group phenotype was labeled as Bombay, indicating the patient's exclusive need to receive blood transfusions from other Bombay donors.

Based on the patient's clinical history, it was concluded that he experienced a hemolytic transfusion reaction due to a mismatched transfusion. Eventually, the patient required a blood transfusion, but unfortunately, the institutional registry did not have any Bombay blood donors present. Therefore, the screening of family members was conducted, and irradiated red blood cells were successfully transfused from his siblings with the same Bombay blood group. His laboratory parameters improved thereafter. He and his family members were then comprehensively counseled about their rare blood type. Due to financial constraints, the patient was discharged against medical advice.

Discussion

There is a reasonable similarity between the Bombay blood phenotype and the O group. This is due to the absence of the A and B antigens, which mimic the O phenotype; however, it is incredibly important to consider the presence of the H antigen in all of the ABO blood types. Thus, transfusion of A, B, or O blood types into patients with the Bombay blood group can result in a classic manifestation of acute hemolytic reactions due to the production of anti-H antigen antibodies. Therefore, patients of the Bombay blood group may only receive transfusions of blood or blood components from donors of the same blood phenotype.

Additionally, another similar and rare blood type is the para-Bombay blood group, with only a handful of cases being reported. The prevalence of this blood group is unexplored in many regions of the world due to its rarity and the insufficiency of available data. At a molecular level, the para-Bombay blood group is characterized by the lack of ABH expression on RBCs, with some expression of ABH antigens in bodily secretions. In contrast, the standard Bombay blood group does not have any ABH antigenic expression on both RBCs and secretions.

There are several therapeutic challenges for patients with the rare Bombay blood group that must be highlighted. The arrangement of donor Bombay blood is extremely difficult, especially in regions where the prevalence and identification of this rare blood group are low or unavailable. In such cases, there have been different strategies explored for such patients, including the use of fresh frozen plasma, crystalloid and colloid infusion, and autologous blood transfusion. Moreover, the role of normovolemic hemodilution as an alternative to transfusion during emergency surgery has also shown effectiveness, particularly in pregnant women. In another case, a Bombay group patient underwent hand surgery and was not able to retrieve Bombay blood from the institute and/or her relatives, highlighting a common issue faced by such patients. However, in light of the stable hemoglobin and progressive recovery, the patient was successfully discharged without the need for transfusion, instigating the possibility of opting out of transfusion in non-emergent settings. These strategies have shown success in the previously mentioned case reports; however, the lack of concrete evidence and established guidelines or protocols raises the need for future research and recommendations on this challenge. The current recommendation encourages the practice of appropriate clinical decision-making, reduction of peri-operative and post-operative blood losses, and engagement in nationwide planning and action.

Ultimately, it is imperative to investigate the patient's past medical and family history before performing any invasive procedures. Patients presenting with any history of previous, eventful post-transfusion reactions or a positive family history of such acute hemolytic reactions post-transfusion, must be further investigated prior to any surgical procedure to ensure the correct blood typing. Moreover, the creation and maintenance of national rare blood group registries is vital in order to avoid the risk of incompatible transfusions, which may result in further complications in patients who are already critically ill. The role of national registries becomes highly essential in emergency or traumatic situations, where there is insufficient time and resources to perform testing for rare blood group types. It is also recommended to immediately start screening the patient's family, especially the first-degree relatives, for rare blood group phenotypes, such as the Bombay blood group. This strategy may be useful in any unforeseen future emergencies, in cases where the Bombay blood patient requires a blood transfusion, preventing the consequent risk of an incompatible transfusion.

Conclusions

In summary, the Bombay blood group phenotype may clinically resemble the O phenotype, due to the lack of A and B antigens in the forward grouping. Individuals with the Bombay blood group can only receive blood transfusions from Bombay donors due to the presence of powerful anti-H antibodies in their serum. This case emphasizes the significance of accurate diagnosis of this rare blood type and also highlights the importance of family screening, counseling, and the establishment of a

local Bombay blood donor registry for therapeutic management.

CASE 3:

Bombay Blood Group: A Report of Two Cases

Asthma Nasir 1, Aiman Minhas 1, Ayisha Imran 1, Omar Chughtai 2, Akhtar S Chughtai 2
Editors: Alexander Muacevic, John R Adler

Case Report

A 20-year-old female delivered at full term by spontaneous vaginal delivery at a tertiary care government hospital presented to our blood bank. Her peripheral blood counts showed a hemoglobin (Hb) level of 6.6g/dL, a total leukocyte count (TLC) of 7.2 x 10^3/uL, and a platelet count of 321x10^3/uL. Her gynaecologist requested a blood transfusion with two packed cells. An outside laboratory reported her blood group as “O positive”. She was transfused with O positive packed cells. Shortly after the transfusion started the patient developed shortness of breath, and the transfusion was stopped immediately. After 24 h, the patient received another transfusion with O negative packed cells (washed RBCs). Unfortunately, after only 50 mL of transfusion, she again developed shortness of breath and swelling of her face.

Her repeat complete blood count showed a Hb of 2.8 g/dL, a TLC of 10.5x10^3 and a platelet count of 220x10^3. We received a request for blood cross-matching at our blood bank.

On blood group typing, her results were graded as shown below.

Forward and reverse grouping of case one.

Agglutination reaction strength is graded as negative (0) / strong positive (4+).

Forward Grouping				Reverse Grouping			Auto-control
Anti-A	Anti-B	Anti-D	Anti-H lectin	A cells	B cells	O cells	0
0	0	4+	0	4+	4+	4+	

The blood group typing results were interpreted as ABO: Bombay phenotype, Rh: Positive.

A family screening of the patient showed that two of her siblings belonged to the 'O positive' blood group, whereas a 16-year-old sister and a 19-year-old brother were also found to possess the Bombay phenotype. Her 19-year-old brother was selected as a potential donor, and a crossmatch showed that he was compatible at the anti-human globulin phase of cross-matching. Eventually, the patient was transfused, and her Hb level increased to 5.3 g/dL after one transfusion.

CASE 4:

Bombay Blood Group: A Report of Two Cases

Asthma Nasir 1, Aiman Minhas 1, Ayisha Imran 1, Omar Chughtai 2, Akhtar S Chughtai 2
Editors: Alexander Muacevic, John R Adler

Case Report

A 35-year-old gravida 3 para 2 female was referred to our blood bank for blood grouping. She had never been transfused, and her obstetrician ordered blood grouping because she was anemic and scheduled for an elective cesarean section. She reported her blood group as O positive but did not provide any record of it.

Forward and reverse blood group typing of case two.

Agglutination reaction strength is graded as negative (0) / strong positive (4+).

Forward group typing				Reverse group typing		
Anti-A	Anti-B	Anti-A,B	Anti-D	A	b	0
0	0	0	4+	4+	4+	4+

Further testing of the patient’s red blood cells with anti-H lectin and running auto control.

Testing with auto control and anti-H lectin.

Agglutination reaction strength is graded as negative (0) / strong positive (4+).

Auto control	Anti-H lectin
0	0

The blood grouping results were interpreted as Bombay phenotype, Rh positive.

Upon further history-taking, the patient reported that she had two siblings, one of whom belonged to the Bombay blood group.

Discussion

The Bombay blood group is rare and often misinterpreted as blood group O. Individuals with blood group O have anti-A and anti-B antibodies and no anti-H. In contrast, the Bombay phenotype possesses both anti-A and anti-B antibodies, and, as these individuals lack H antigens, they also have anti-H antibodies. These anti-H antibodies are naturally occurring immune globulin M (IgM) antibodies that can cause intravascular hemolysis. Therefore, it is extremely important to identify this blood group because the clinically significant anti-H antibodies produced can result in an acute hemolytic transfusion reaction, which can manifest as disseminated intravascular coagulation or acute renal failure and can be fatal. Moreover, these individuals can only be transfused with blood products from donors of the same blood group, and finding a donor when needed is challenging due to the rarity of this phenotype. Under-reporting and non-maintenance of registries of correctly diagnosed cases also contribute to the lack of availability of suitable donors.

Various approaches have been adopted to manage these patients when blood from Bombay donors is not available, including the use of autologous transfusion, fresh frozen plasma, crystalloids, and colloids Another approach is acute normovolemic hemodilution, in which controlled removal of whole blood from the patient is performed immediately before a surgical procedure, followed by the administration of colloid or crystalloid solutions to maintain normal blood volume with a reduced red cell mass. The collected whole blood is then re-infused after the procedure inside the operation theater. One study described the successful use of acute normovolemic hemodilution during an emergency cesarean section in a pregnant female with the Bombay phenotype. Another study reported the management of a gravida patient with bleeding who underwent dilatation and curettage by the administration of colloids and crystalloid; however, no autologous blood transfusion was given]. Pre-operative autologous donation is a reasonable approach in diagnosed cases of the Bombay group for which elective procedures are planned, wherein repeated donations stimulate bone marrow erythrocyte production. Another approach is intraoperative cell salvage, in which blood spilled in the surgical field is collected and re-infused into the patient. However, this method can only be implemented if automated cell salvage devices are available, but it is applicable for both elective and emergency surgical procedures.

Based on this case series, we recommend that government transfusion services operating in regions where the Bombay blood group is prevalent maintain a registry of such individuals, as it could aid in increasing donor availability in times of need. Moreover, family members of such individuals should also be tested to determine whether they have the same blood group. The cases we received at our blood bank were misinterpreted by outside laboratories as blood group O. One of our patients (case one) experienced an acute hemolytic transfusion reaction with a significant decrease in Hb; whereas the other case (case two) had fortunately never been transfused, so no significant morbidity occurred.

Conclusions

As the Bombay blood group phenotype is commonly misinterpreted as blood group O, it is crucial to include testing with 'O' cells in reverse blood grouping in routine blood banking. In all discrepant cases, testing with anti-H lectin and running auto control can lead to the correct diagnosis, which can prevent clinical consequences during routine testing. However, in emergency settings where administration of O-negative units may lead to a subsequent hemolytic transfusion reaction, the differential diagnosis of rare blood groups should always be considered.

CASE 5:

Importance of Weak ABO Subgroups

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Beenu Thakral, Karan Saluja, Meenu Bajpai, Ratti Ram Sharma, Neelam Marwaha
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Case Report

The ABO blood group system was discovered by Karl Landsteiner at the beginning of the 20th century and is the most important system for clinical transfusion medicine. Depending upon the person's ABO blood group, naturally occurring IgM anti-A and/or anti-B may be present in serum, constituting a major barrier against ABO incompatible blood transfusion and organ transplantation. The ABO locus on the long arm of chromosome 9 codes for blood group specific transferases which transfer N-acetyl D-galactosamine and/or D-galactose sugar terminally to the H antigen for the formation of A and/or B antigen respectively. The 2 major subgroups A_1 and A_2 are differentiated on the basis of reactivity of A_1 cells but not A_2 cells with anti-A_1 lectin (Dolichos biflorus). Weak subgroups of A can be defined as those of group A subjects whose erythrocytes give weaker reactions or are nonreactive serologically with anti-A antisera than do those of subjects with A_2 RBCs.2 These weak phenotypes, in majority of the cases result from the expression of an alternate weak allele present at the ABO loci. Weak subgroups of A can be divided into 2 categories depending upon whether the cells are agglutinated with anti A. A_3, A_{end} and A_x are agglutinated, while A_m, A_y and A_{el} cells are not. The above phenotypes can be serologically differentiated from each other by using the following techniques:

a) Agglutination of cells using anti-A, anti-B, anti-A,B and anti-H.
b) Serum grouping of ABO antibodies and the presence of anti-A1.
c) Adsorption elution experiments with polyclonal anti A from group B and group O individuals.
d) Secretor status for the presence of H and/or A antigen in saliva.

Similar to A subgroups, subgroups of B blood group have also been serologically characterized with the exception that there is no B_2, B_{end}, and B_y. Special procedures such as serum glycosyl transferases studies and molecular techniques like polymerase chain reaction (PCR) elucidating the genetic basis of ABO locus, can be used for further differentiation. The annual collection at our center for meeting the requirements of a tertiary care hospital is on an average 36,000 blood units. We present here serological workups in 17 cases of weak subgroups of A and B from the total collection of 112,000 units from January 2001 to December 2003. Repeat donations of 25,313 donor units were excluded from the total collection for analysis of correct incidence of subgroup in our been no similar study from India describing the phenotypic frequencies of weak subgroups of A and B. Their implications for blood transfusion are discussed.

Materials and Methods

Blood samples: Blood was collected in 2 pilot tubes after the collection of blood unit from each donor for forward and reverse grouping. Seven to 8 mL of ACD blood was used for forward grouping and adsorption elution experiments. Serum from a clotted sample was used for reverse grouping.

Blood group serology: Detailed serological workup was done for all donor units where forward and reverse grouping showed discrepant result in the ABO blood group system. All donors typed as weak A subgroups, other than A_1, A_2, and A_{int} were included in this study. ABO grouping was done by standard tube technique after washing the donor and reagent RBCs thrice with 0.9% normal saline. Monoclonal anti-A and anti-B sera from 4 manufacturers (Ranbaxy, Tulip, Span Diagnostics, and Glaxo Laboratories) and anti-A,B sera from 3 manufacturers (Tulip, J Mitra, and Glaxo Laboratories) monoclonal antisera were used to reconfirm the routine findings and the level of discordance of results was noted. Agglutination of donor red cells by anti-A1 (Tulip) and anti-H lectin (Tulip) was also determined. All the results were recorded after microscopic examination.

The strength of agglutination was graded according to the standards mentioned in the literature. Polyclonal antisera of human origin from group B, group A, and group O individuals were used for adsorption to determine these subgroups.5 The technique was performed as described in AABB Technical Manual. Heat elution using 6% bovine serum albumin was done at 56°C for 10 minutes and the eluate was tested against 3 unpooled reagent cells (A and B). In some tubes, agglutination was noted on immediate spin whereas tubes showing no agglutination in the above step were incubated at 37°C for 60 to 90 minutes. In these tubes, agglutination was observed after adding anti-human globulin reagent. Hemagglutination inhibition test for secretor status in saliva was done to determine H, A, or B antigens as described in AABB Technical Manual. This helped us to differentiate between Bel or Bm subgroups.

Results

Fourteen (n=14) cases of weak subgroups of A, and 3 (n=3) of group B were detected serologically out of 86,687 donors tested in a Regional Transfusion Centre at PGIMER, Chandigarh, India. Thus, an overall incidence of weak subgroups was found as 1:5,100 or 0.02% in our donor population. On routine grouping, all of these blood units were typed as O group in the forward and A or B group in the reverse grouping except A_3 and B_3. The strength of agglutination was mixed field in the latter 2 blood groups as compared to A_1/A_2 and B, respectively, when tested with anti-A and anti-B antisera. Weakening of the A or B antigens due to various disease states was ruled out as all the donors cleared the stringent donor's questionnaire and were healthy on physical examination. Hemogram of all these donors was normal and blood group chimerism was excluded by history for all the possible modes of its acquisition. This included twin siblings, homologous stem cell, or organ transplantation. Subgroup classification was determined according to standard terminology.

All the samples were tested under identical conditions by the same investigators using the same reagents. The A subgroup was seen more frequently than B subgroups in our donor population. Among the A subgroups, A_3 and A_x were found at a frequency of 1:14,448 and A_{end} at 1:43,344 out of the total units collected. In the subgroups of B; B_3, B_x, and B_{el} were detected at an equal frequency of 1:86,687.

A_3 subgroup (6 cases) – All these samples reacted equally well with anti-A and anti-A,B but showed few larger agglutinates on a background of large amount of free cells (mixed field reaction).All reacted strongly with anti-H lectin. Out of the 5 samples, 1 had cold reactive (4ºC) anti-A1 antibody in the reverse grouping. Adsorption with anti-A was detected in all the above samples from both group O and B polyclonal sera. Saliva testing showed both A and H antigen in 2 of the samples tested.

A_x subgroup (6 cases) – Red cells in this group reacted strongly with anti-A,B as compared to reactions with anti-A antisera. Four plus (4+) agglutination with anti-H lectin was observed. In the reverse grouping anti-A1 antibodies were detected in all the samples that were maximally reactive at 4°C except 1 sample that was reactive at 37°C. Saliva analysis could be performed only on 2 samples that showed only the H substance. The Ax antigen was characteristically detected on donor's RBCs by adsorption at 4ºC with IgG anti-A antibodies from group O individuals as compared to IgM anti-A antibodies from group B individuals. The eluate prepared from adsorbed group O sera agglutinated 3 unpooled group A cells either at room temperature or after incubation at 37°C. Eluate from the adsorbed group B sera was non-reactive.

A_{end} subgroup (2 cases) – Inclusion in this group required equal and very weak mixed field agglutination with anti-A and anti-A,B but a strong positive reaction with anti-H. The A antigen was detected by adsorption elution experiment using both B and O group sera. The saliva test result in both cases was negative for A but positive for H substance.

Weak B subgroups

B_3 subgroup (1 case) – Inclusion criteria is the same as A_3 subgroup.

B_x subgroup (1 case) – The serological work up is similar to A_x subgroup.

B_{el} subgroup (1 case) – RBCs in this subgroup showed no agglutination with anti-B or anti-A,B antisera. B antigen was detected by adsorption with polyclonal group A sera. Bel was differentiated from B_m by saliva testing, which detected only the H antigen.

Discussion

The ABO blood group system was the first system discovered, a century ago, but occurrence of its weaker variants due to heterogeneity of the A and B alleles still poses an enigma for immunohematologists. ABH antigens are expressed by the epistatic addition of terminal monosaccharide immunodominant sugar to the precursor oligosaccharide H chain. A_1 and A_2 phenotypes account for 99% of all group A individuals. A_1 and A_2 differ from each other both qualitatively and quantitatively, with A1 cells carrying 8.1 to 11.7×10^5 antigenic sites as compared to 2.4 to 2.9×10^5 sites on A_2 RBCs. This difference has been ascribed to the abundance of repetitive type 3A and 4A determinants on A_1 cells as compared to A_2 cells.9 Molecular differences between the A_1 and A_2 alleles make N-acetyl galactosamine transferase in A_2 cells less efficient at branched points than in A_1 cells. From 1% to 8% of A_2 and 22% to 35% of A_2B individuals produce anti-A_1 antibodies in their serum. Similarly A_x individuals almost always have anti-A_1 antibody in their serum whereas A_3, A_{end}, and A_{el} may occasionally have this antibody. This anti-A1 is an antibody to type 3A and 4A branched determinants which these individuals lack. Similar to A_1 and A_2, serum glycosyltransferases in weak subgroups of A show varying activity with weak positivity in A_3 and A_x to negativity in A_{end} and A_{el}. Thus varying antigenic density accounts for different strengths of agglutination reaction with monoclonal anti-A typing reagents. The phenotypic frequencies of these weak subgroups differ between ethnic regions. The A_3 subgroup is most common among all the weak subgroups, with an estimated frequency of 1:1,000 group A Danes,10 1:16,667 French,11 and 1:90,000 Canadian blood donors. The frequency of A_3 seen in our blood donors is comparable to that found in French donors. The A_x was found at a comparable frequency to that of A_3 in our population. The incidence of A_x and A_{end} (1:14,448 and 1:43,344, respectively) in our donor population is higher than that estimated in French donors (1:40,000–1:77,000 and 1:75,000 respectively). This difference could be due to the serological workup in our study as compared to the figures cited in literature through molecular analysis. As compared to weak variants of A, their counterparts in the B blood group are very rare.

Weak B subgroups were found at a higher frequency in our population than that seen in French donors (1:116,667). This difference can be explained, as 38% of our donors have the B blood group. ABO genotyping is a valuable complement to serology for correct determination of ABO blood group status. Mutations in the ABO alleles confer differences in the specificity and activity of transferases that add low levels of A (or B) immunodominant sugars to the precursor H antigen.15 The most common Ax allele has the A1 consensus sequence with a missense mutation encoding a Phe216Ile subsitution.16 Ay phenotype arises due to homozygosity for a recessive regulator gene at a locus independent of that for ABO. Mutations in exons 6 and 7 (constituting 77% of the ABO gene) have been studied for their allelism in majority of the cases.18 Most of the methods have used combinations of PCR and Restriction Fragment Length Polymorphism (RFLP) or PCR with allele-specific primers to define polymorphism. A study by Olsson and colleagues16 identified 15 novel A and B subgroup alleles using allele-specific primers to the previously published 14 definable alleles. These included 2 mutations even outside exons 6 and 7. Thus, molecular genetics makes it possible to define an individual's ABO genotype without laborious family studies. It is a useful tool for resolution of typing discrepancies and is especially valuable for distinguishing acquired variant phenotypes from inherited ones.

Conclusions

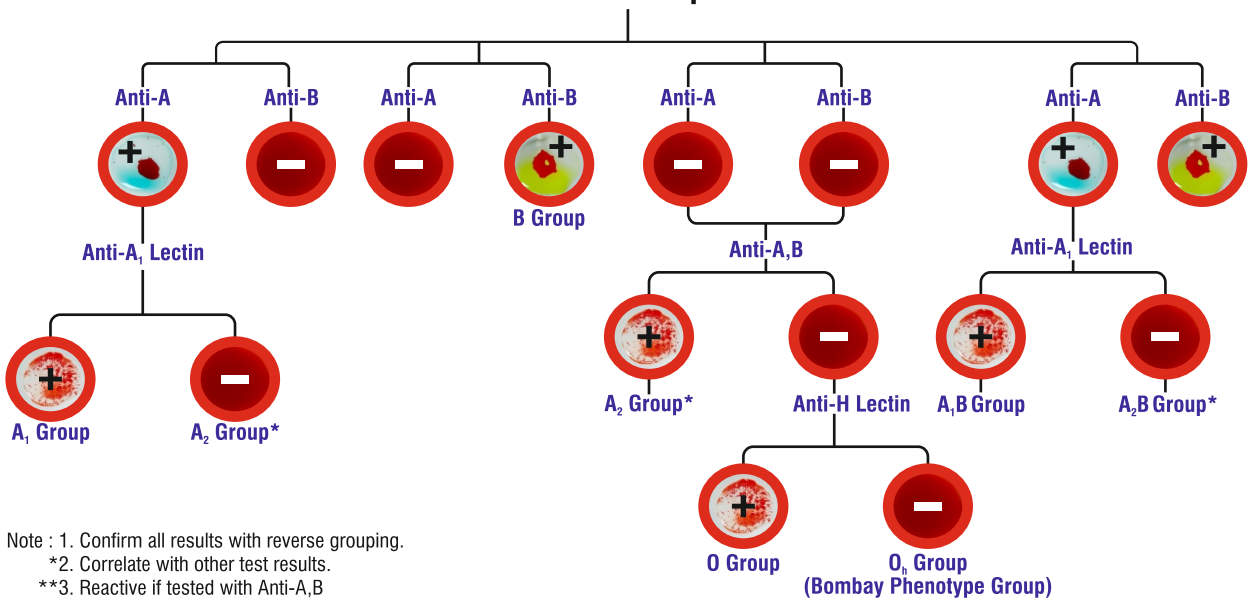
Identification of these subgroups is important because these donors may be mistyped as group O individuals. Wrongly grouped as O, weak subgroups of A or B red cells (if transfused to O group individuals) can show decreased survival. This is due to naturally occurring anti-A and anti-B antibodies in the latter.

Similarly since A_x individuals almost always have anti-A1 antibodies in their serum. If clinically significant, they can lead to fatal transfusion reactions on transfusing their whole blood or plasma to group A individuals. All the donors were personally informed about their group and were given a special blood group card clarifying their donor as well as recipient status. The serologically determined weak ABO phenotypes in our study require confirmation through genomic analysis. This might also bring out some novel mutations in our population leading to these subgroup phenotypes.

ADD VALUE TO FORWARD BLOOD GROUP SCREENING

BLOOD GROUPING

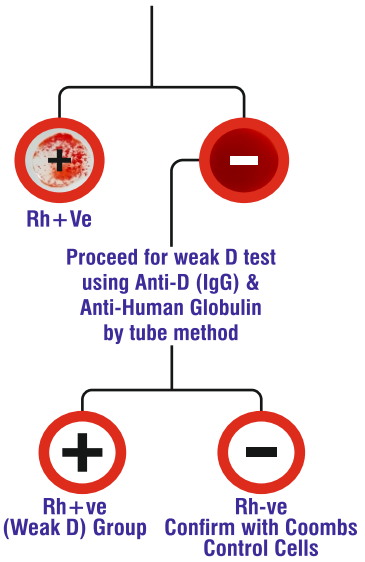
Patient Whole Blood Sample + Antisera



Note : 1. Confirm all results with reverse grouping.
*2. Correlate with other test results.
**3. Reactive if tested with Anti-A,B

Rh Typing

Patient Whole Blood Sample + Anti-D



Blood Group Interpretation Chart

Sample	Anti-A	Anti-B	Anti-A,B	Anti-A1 lectin	Anti-H lectin	Interpretation
Whole Blood	R	NR	**R	R	NT	A_1 Group
Whole Blood	R	NR	R	NR	NT	A_2 Group
Whole Blood	NR	R	** R	NT	NT	B Group
Whole Blood	NR	NR	* R	NT	NT	A_2 Group
Whole Blood	NR	NR	NR	NT	R	O Group
Whole Blood	NR	NR	NR	NT	NR	O_h (Bombay Phenotype) Group
Whole Blood	R	R	**R	R	NT	A,B Group
Whole Blood	R	R	R	NR	NT	A_2B Group

Rh Typing Interpretation Chart

Sample	Anti-D	Weak-D Test (Anti-D IgG)	Interpretation
Whole Blood	R	NT	Rh+ve Group
Whole Blood	NR	R	Rh +ve (Weak D) Group
Whole Blood	NR	NR	Rh-ve Group

R-Reaction/agglutination **NR**-No Reaction/No agglutination **NT**-Not tested

DETECT SUBGROUPS/WEAK D... ENHANCE DONOR LIST... HELP SAVE LIVES

BOUQUET

In Lighter Vein

Teacher: Tomorrow there will be a lecture on sun. Everyone must attend it.

Mary: No madam! I will not be able to attend it.

Teacher: Why?

Mary: My mother will not allow me to go so far!

BOY OR GIRL?

Person 1: Look at that person in Blue Jeans with short hair. Is it a boy or a Girl?

Person 2: She is a girl. She is my Daughter.

Person 1: Oh…I am sorry Sir…I didn't know you were her father.

Person 2: I am not…I am her Mother.

Sister: How did Mum find out you hadn't washed yourself?

Brother: I forgot to wet the soap….

Wisdom Whispers

"Do the difficult things while they are easy and do the great thing while they are small. A journey of a thousand miles must begin with a single step."

❄

"Begin to weave and God will give the thread."

❄

"Never Stop Doing Your Best Just Because Someone Doesn't Give You Credit."

❄

"Never mistake knowledge for wisdom. One helps you make a living; the other helps you make a life."

Brain Teasers

1) **To confirm Bombay phenotype, testing with _____.**
   a) Anti-A1 Lectin is necessary
   b) Anti-H Lectin is necessary
   c) Both are not necessary

2) **Compatibility testing is also known as _____.**
   a) Crossmatch
   b) Weak D testing
   c) None of the above

3) **A positive test results in crossmatch indicates _____ of patient & Donor.**
   a) Incompatibility
   b) Compatibility
   c) None of the above

4) **Anti-D is an _____ antibody.**
   a) Immune
   b) Natural occurring
   c) None of the above

ANSWER: 1:b, 2:a, 3:a, 4:b

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ERYCLONE Anti-D (IgG)
ERYCLONE Anti-D (IgM)
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Reagent Combipacks

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ERYSCREEN PLUS Anti-A, Anti-B, Anti-D (IgG+IgM)
ERYSCREEN TOTAL Anti-A, Anti-B, Anti-A,B, Anti-D (IgG+IgM)

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ERYBANK Anti-A1 lectin
ERYBANK Anti-H lectin

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