Working Party on Rare Donors Case Studies 2025 - # (ISBT will add)

A pregnancy with Anti-U, a challenge in countries with developing rare donor programs

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Clinical History

28-year-old pregnant woman **(week 32 of pregnancy)**

Afro-descendant ethnicity

Four (4) pregnancies **three (3) abortions**, one (1) birth

No transfusion history

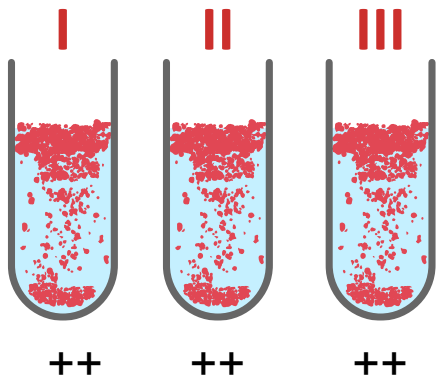
High-risk pregnancy due to **absent prenatal care**, with diagnosis of false labor, **high risk of bleeding during childbirth** (reported in medical history due to medical evaluation), and the threat of preterm birth.

Fetus with signs of hemolytic disease (HDFN)

Serologic History

Without serologic history

Current Sample Presentation Data



ABO/Rh
O RhD Negative

DAT
Negative

Antibody Screen Method
Column Agglutination Test
(BioRad ID-System)

Antibody Screen Results
Positive with all cells
(2+)

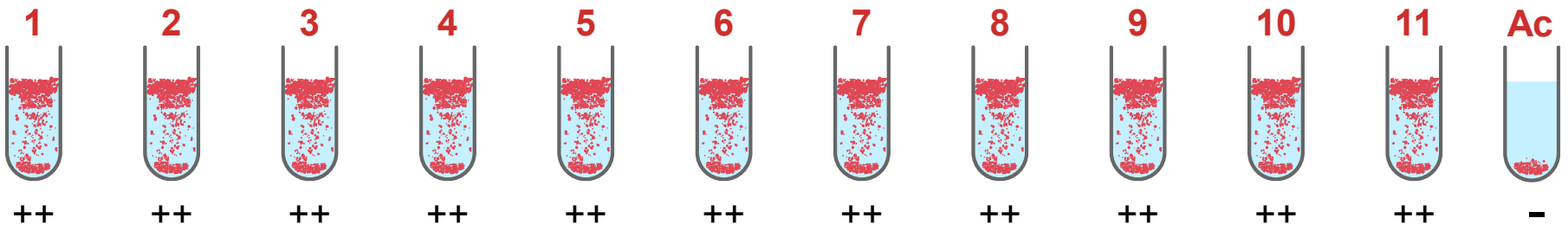
Antibody Identification Method
Column Agglutination Test
(BioRad ID-System)

Antibody Identification Preliminary Results
Positive with all cells *(2+ all cells)* with negative auto-control

RBC Crossmatch
All six units crossmatched were incompatible

Current Sample Presentation Data

Representative Image of the Antibody Identification Panel



Panel at room temperature

Negative with negative auto-control

Panel AHG 37 ºC

Positive with all cells *(2+)* with negative auto-control

Panel papain-treated cells

Positive with all cells *(2+)* with negative auto-control

Treated cells with 200mM DTT

Positive with all cells *(2+)* with negative auto-control

Antibody Identification Method

Column Agglutination Test
(BioRad ID-System)

Adsorption with allogeneic red cells

Negative

Antibody titration

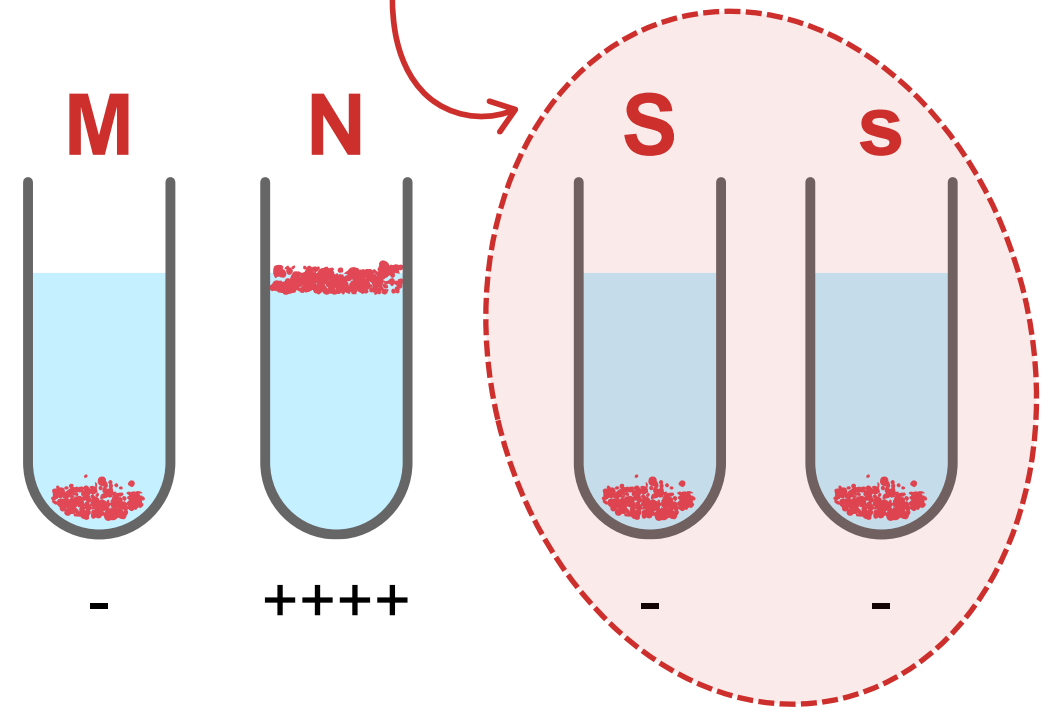
Anti-U titer 16

Phenotyping Results

Phenotyping was performed with Column Agglutination Test (BioRad ID-System)

C– c+ E– e+ K– k+ Kp(a–b+) Jk(a+b–) Le(a–b+) Lu(a–b+) M– N+ **S– s–** Fy(a–b+) P1+ H+

With the phenotyping and antibody identification panel, the hypothesis was a U– phenotype with anti-U alloantibody.



Phenotyping Results

S– s– Phenotype

The S– s– phenotype is the result of two distinct molecular backgrounds
The U– negative phenotype is associated with an absence of GPB or with altered forms of GPB

S–s–U–

Results from a large deletion in *GYPB* (Del Exons 2-6)

Allele *GYPB*01N*

Alloantibody to a high-prevalence GPB antigen, mainly to the U antigen

S–s–U+^{var}

var= variant
Results expression of GPB variants

Allele *GYPB(P2)* and *GYPB(NY)*

Alloantibody *"anti-U-like"*

Reference: *Transfusion. 2012 Mar;52(3):622-8. doi: 10.1111/j.1537-2995.2011.03318.x. Epub 2011 Aug 31. PMID: 21880045.*

Genotyping Results

Genotyping was performed using Immucor Array Imaging System and Precise Type Human Erythrocyte Antigen (HEA) BeadChip test kit.

Chip	Sample	Status	RhCE-P103S	RhCE-109Ins	RhCE-A226P	RhCE-G336C	RhCE-L245V	K1/K2	Kp	Js	FYA/FYB	GATA	FY-265	JKA/JKB	GPA	GPBS	GPB-Int5	GPB-230	LUA/LUB	DIA/DIB	COA/COB	DO-793	DO-323	DO-350	LWA/LWB	SC1/SC2	HbS173
HEAK7264_1	Negative QC	Valid NC	NTD	NTD	NTD	NTD	NTD	NTD	NTD	NTD	NTD	NTD	NTD	NTD	NTD	NTD	NTD	NTD	NTD	NTD	NTD	NTD	NTD	NTD	NTD	NTD	NTD
HEAK7264_2	CHEA Ref pA Positive QC	Valid HEA Ref-pA	AA	AA	AA	AA	AA	AA	AA	AA	AA	AA	AA	AA	AA	AA	AA	AA	AA	AA	AA	AA	AA	AA	AA	AA	AA
HEAK7264_3	C. HEA Ref pB Positive QC	Valid HEA Ref-pB	BB	AB	BB	BB	BB	BB	BB	BB	BB	BB	BB	BB	BB	BB	BB	BB	BB	BB	BB	BB	BB	BB	BB	BB	BB
HEAK7264_4	Propositus	LS(3)	AA	AA	AA	AA	AA	BB	BB	BB	BB	AB	AA	AA	BB	LS	LS	LS	BB	BB	AA	BB	AA	AA	AA	AA	AA

GPBS, *GPB-Int5*, and *GPB-230*, three polymorphisms that evaluate Glycophorin B gene (*GYPB*), have low signal on genotype (LS: Signal: Signal intensity below recommended minimum). In this case, this result may be indicative of *GYPB* deletion.

Also, the patient has a heterozygous GATA mutation with an *FY*B/FY*B* genotype.

Genotyping Results

Genotyping was performed using Immucor Array Imaging System and PreciseType Human Erythrocyte Antigen (HEA) BeadChip test kit.

Predicted Phenotype																																				
Chip	Sample	Status	c	C	e	E	V	VS	K	k	Kp^a	Kp^b	Js^a	Js^b	Fy^a	Fy^b	Jk^a	Jk^b	M	N	S	s	U	Lu^a	Lu^b	Di^a	Di^b	Co^a	Co^b	Do^a	Do^b	Hy	Jo^a	LW^a	LW^b	Sc1	Sc2	HbS
HEAK7264_4	Propositus	LS(2)	+	0	+	0	0	0	0	+	0	+	0	+	0	+	+	0	0	+	LS	LS	0	0	+	0	+	+	0	0	+	+	+	+	0	+	0	0
Details: Predicted phenotype U-																																					

The genotype results confirm the following:

- The predicted phenotype is **S– s– U–** due to the deletion of *GYPB (GYPB*01N)*. These results are concordant with the serologic phenotype.
- Phenotype Fy(a–b+) due to *FY*B* homozygous with heterozygous GATA mutation.

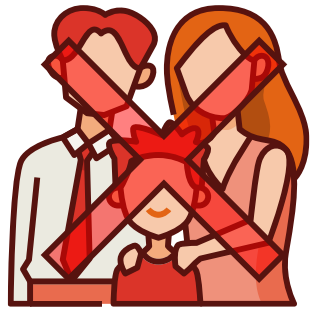
Challenge with the Current Presentation

The treating clinician ordered two RBC units:

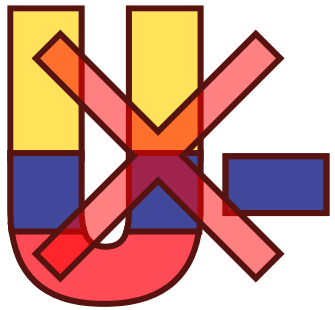
- One for the pregnant woman due to the **risk of bleeding during childbirth.**
- One for the newborn due to the signs of **hemolytic disease**.

The requested phenotype was

O RhD negative U–



No family members were available. The patient's family, eligible to be blood donors, was more than 12 hours away in a rural area of Colombia with difficult travel access.



No U–donors were identified in Colombia.

Other alternatives

*Alternatives to stimulate erythropoiesis

Erythropoietin + intravenous iron were administered

*Alternatives to reduce bleeding during childbirth were evaluated by the clinicians.

Challenge with the Current Presentation

Rare donor program and availability of blood with rare phenotypes

At the time of the case, the District Institute of Science, Biotechnology and Innovation in Health-IDCBIS- Rare Donor Program had recently started. Colombia didn't have rare donors with the U– phenotype.

Due to the patient's diagnosis and the Fetus's signs of hemolytic disease, the clinicians considered the availability of U– blood transfusion urgent. Therefore, they comprehensively evaluated the patient and opted for an autologous blood donation. An international blood search was not considered since urgent delivery scheduling was required, and the patient met the clinical evaluation criteria for autologous donation.

IDCBIS

Unique Donor Program

Solution to Blood Needs

In interdisciplinary work with the obstetrician and the hematologist of the public hospital who referred the case, the blood bank's haemovigilance doctor and other blood bank professionals determined that the pregnant woman could make a blood donation (the only alternative to guarantee the availability of red blood cell units during childbirth).

Solution to Blood Needs

IDCBIS apheresis equipment was transferred to the public hospital, and strict clinical follow-up was carried out.

The patient donated two units of red blood cells without clinical complications

According to information from the referring hospital, one unit was transfused to the patient and one to the newborn. IDCBIS requested additional information on the clinical and immunohematological follow-up of the mother and newborn but did not obtain it.

What are the short-term and long-term transfusion needs?

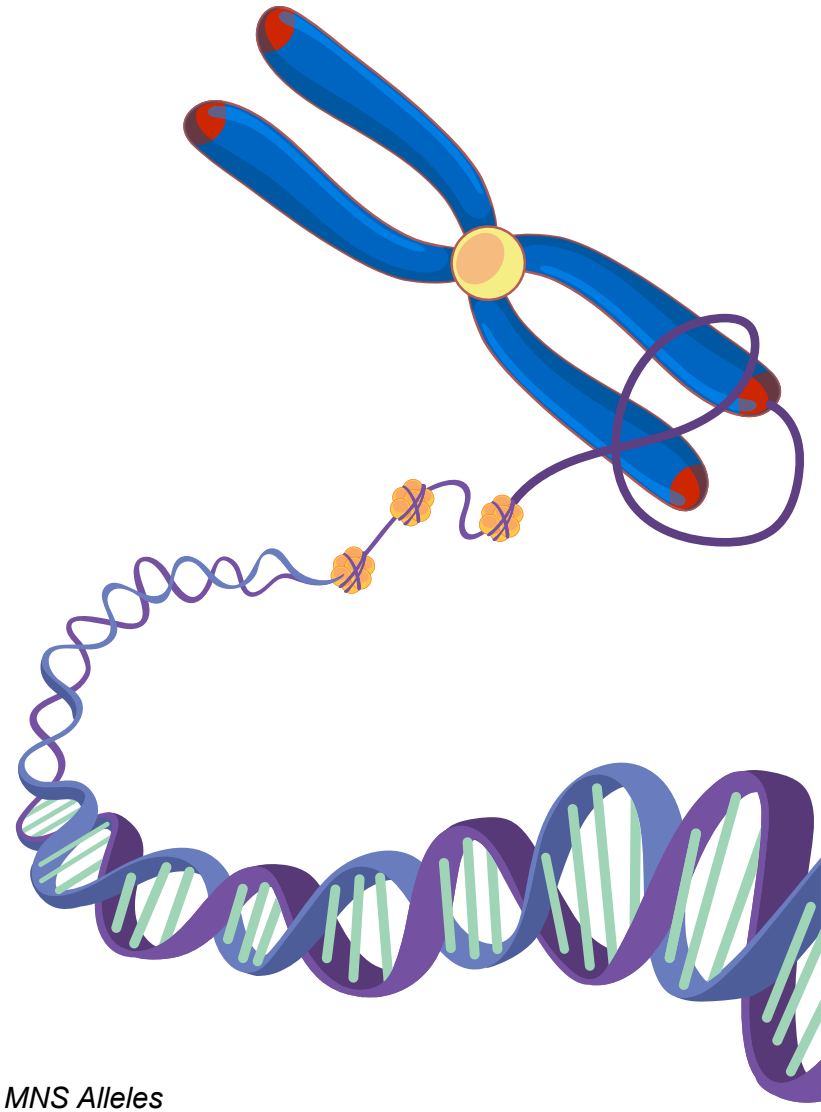
According to clinical history, the patient doesn't need long-term transfusion.

Family Study Information

The patient was advised on the importance of conducting a family study and becoming a blood donor in the future. However, due to her cultural beliefs, the patient stated that she was uninterested and only her husband should make the decision for her to become a potential blood donor.

ISBT Terminology of the System

ISBT Terminology of the System			
System	MNS (ISBT 002)		
Chromosome	4q31.21		
Gene Name	***GYPA***	***GYPB***	***GYPE****
Number of exons	7	5 plus 1 pseudoexon	4 plus 2 pseudoexons
Initiation codon	Exon 2	Exon 2	Exon 2
Stop codon	Exon 7	Exon 6**	Exon 6**
Entrez Gene ID:	2993	2994	2996
LRG sequences genomic	NG_007470.3	NG_007483.2	NG_009173.1
LRG sequences transcript	NM_002099.5	NM_002100.5	NM_002102.3



**GYPE*, *"…which is adjacent to GYPB, may not encode an RBC membrane component, but participates in gene rearrangements resulting in variant alleles"* (Marion E Reid *et al.*) .
**Exon numbering accounts for the presence of pseudoexons in *GYPB* and *GYPE*

Reference: *https://www.isbtweb.org/resource/002mnsalleles.html*
Red Cell Immunogenetics and Blood Group Terminology, Blood Group Allele Tables, 002 MNS Alleles
Marion E. Reid, Christine Lomas-Francis and Martin L. Olsson. The Blood Group Antigen FactsBook. ISBN 978-0-12-415849-8.

Brief Review of the Blood Group System

MNS (ISBT 002) Blood Group	
System	MNS (ISBT 002)
General Information	The MNS blood group system consists of 50 antigens carried on glycophorin A (GPA), glycophorin B (GPB) or on hybrids of these glycophorins. These proteins are single pass type I membrane glycoproteins that are heavily O-glycosylated. GPA carries an N-glycan. GPA consists of 150 amino acids
Products	Glycophorin A (GPA; MN sialoglycoprotein) Glycophorin B (GPB; Ss sialoglycoprotein)
Expresion	Renal endothelium and epithelium

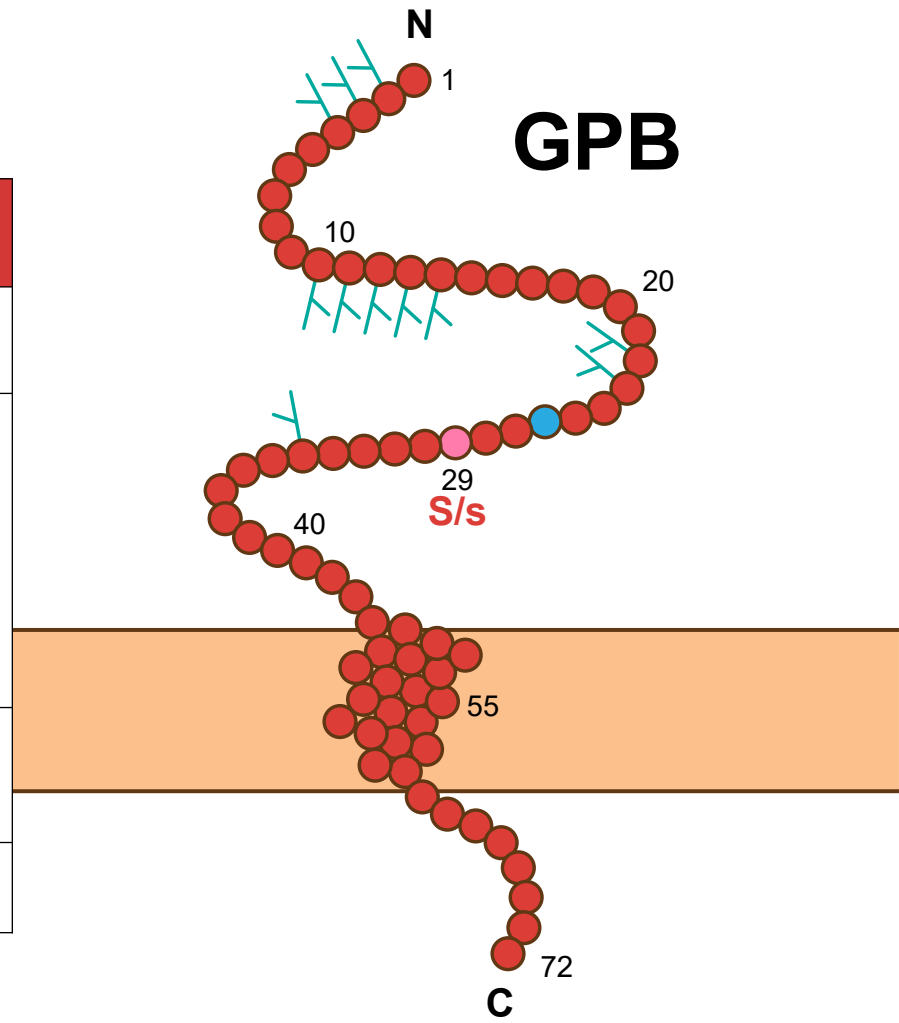


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Image adapted from: Daniels Geoff. Human Blood Groups. Human Blood Groups. ISBN 978-1-118-49359-5

Brief Review of the U Blood Group Antigen

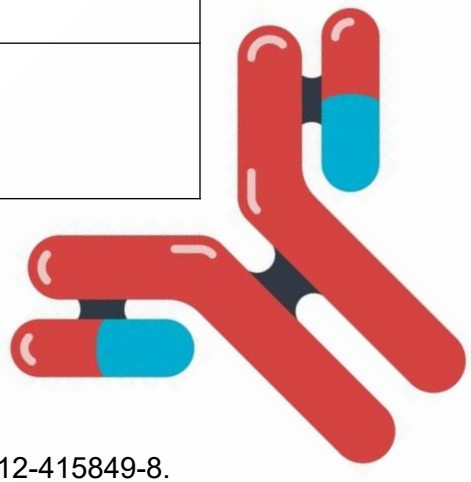
The U antigen was discovered in 1953 and its name comes from its **universal distribution**.
Expression of the U antigen involves GPB and another protein, probably RhAG.

MNS (ISBT 002) Blood Group U Antigen									
Antigen	Expression		Effect of enzymes and chemicals on U antigen on intact RBCs					Prevalence %	
	Cord RBC	Altered	Ficin/Papain	Trypsin	α-Chymotrypsin	DTT 200 mM	Acid	Caucasians	Afro-descendant
U	Expressed	GPB variants and on regulator type of Rh_{null}, and on Rh_{mod} RBCs	Resistant	Resistant	Resistant	Resistant	Resistant	99,9 %	99 %

Reference:
Marion E. Reid, Christine Lomas-Francis and Martin L. Olsson. The Blood Group Antigen FactsBook. ISBN 978-0-12-415849-8.
Bio-Rad Laboratories. Characteristics of blood group antibodies. H005165(898800190) 10/2024

Brief Review of the Characteristics of Anti-U

MNS (ISBT 002) Blood Group U Antibody							
Antibody	Inmunoglobulin class		*in vitro* characteristics			Associated with	
	IgM	IgG	Saline	IAT	Papain 37°C	HDFN	HTR
Anti-U	Not reported	Yes	No	Yes	Unaffected	Mild to severe	Mild to severe
Autoantibody has been identified to cause Warm Autoimmune Hemolytic Anemia							



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Bio-Rad Laboratories. Characteristics of blood group antibodies. H005165(898800190) 10/2024

Conclusion

28-year-old Afro-descendant pregnant woman with rare phenotype U– and alloantibody anti-U; a fetus with signs of HDFN.

Key Point: Panagglutination + negative auto-control + S– and s– phenotype suggest a **U– phenotype and anti-U**.

The patient's genotype confirms the **deletion of *GYPB* (*GYPB*01N*),** which is consistent with the findings of the serological tests (phenotype, panels incubated at different temperatures, panels with enzymes, and DTT).

Conclusion

The pregnant woman/patient donated two units of RBC in an apheresis process. The interdisciplinary work with clinicians and blood bank staff allowed us to conduct the necessary clinical follow-up for the pregnant woman and the fetus.

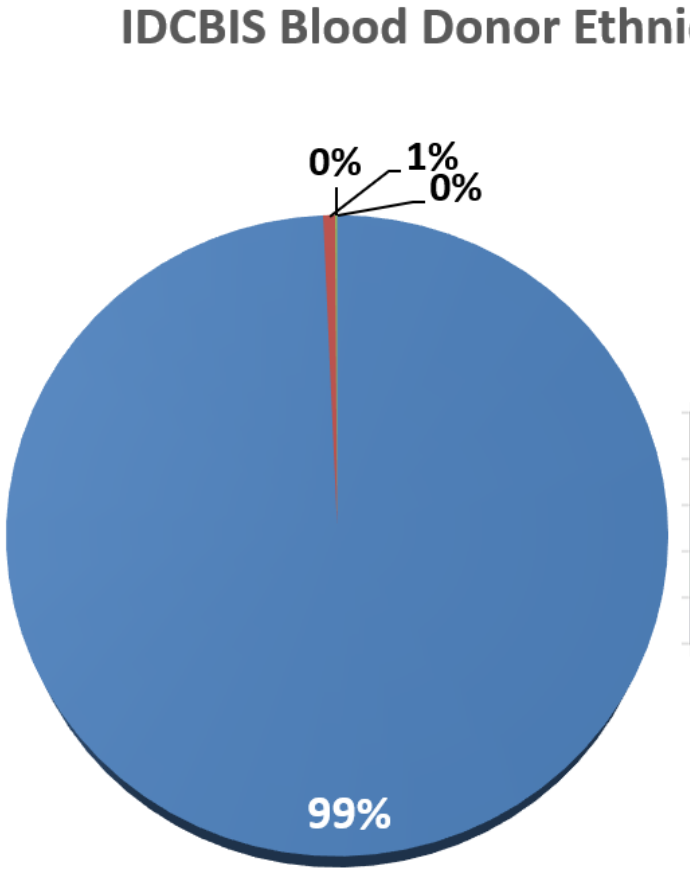
The patient is also RhD-negative and is of childbearing age. If allogeneic transfusion is required, they should receive RhD-negative blood. This situation dramatically reduces the chances of finding donors. At IDCBIS, the prevalence of O RhD-negative donors is 4.60 %. However, given the ethnic background of blood donors it is less likely that a U– RhD-Negative unit would be found (probability 1: 21,739 with a 99.9 % prevalence of the U antigen).

Summary of Case Challenges

- Pregnancy with absent prenatal care, **Afro-descendant** patient with a rare phenotype **U–** with anti-U.
- Cultural beliefs that limit both autologous and altruistic blood donation and a family study.
- An institutional rare donor program, IDCBIS Unique Donor Program, recently started.

Summary of Case Challenges

99,2 % of **IDCBIS blood donors** auto-describe themselves as mestizos and **only 0.6 % as Afro-descendants**. Finding phenotypes associated with Afro-descendant populations is challenging in our blood bank. In this context, it is necessary to design strategies for increasing the promotion and loyalty of donors of Afro-descendant, Indigenous, and other genetic backgrounds or to promote recruitment strategies in regions with more prevalence of Afro-colombian and Indigenous people.



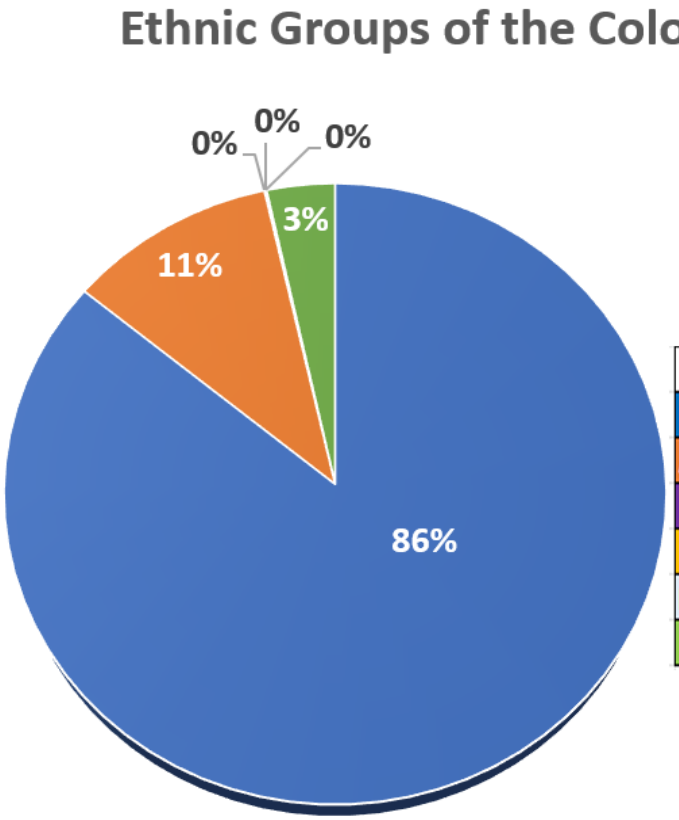
IDCBIS Blood Donor Ethnicity	%
Mestizos	99,2
Afrocolombian	0,6
Caucasians	0,1
Indigenous	0

Reference: Database, Advanced Immunohematology Unit, IDCBIS.

Lessons Learned by the Case

Colombia is a country with a high diversity of geographic and population regions. Currently, it is recognized that the Colombian population is made up of Caucasians and Mestizos (in Colombia, Mestizos are mainly descendants of Amerindians and Caucasians, predominantly Spanish from the colonial era), Afro-Colombians (Afro-descendants, mulattoes, palenqueros, and raizales), Indigenous people, and the Rom population (gypsies).

Population studies are necessary to characterize the distribution of erythrocyte antigens and identify rare phenotypes in the Colombian population. Some have been conducted for approximately 30 years. Still, the migration processes within the country and migration from other Latin American countries are challenging and may impact the current characteristics of the Colombian population.



Ethnicity	%
Mestizos , Caucasians or without ethnic affiliation	85,94
Afrocolombian and Mulato	10,52
Raizal of the Archielago of San Andres	0,08
Palenquero de San Basilio	0,02
Rom	0,01
Indigenous	3,43

Reference:
https://geoportal.dane.gov.co/servicios/atlas-estadistico/src/Tomo_I_Demografico/3.4.-poblaci%C3%B3n-por-grupos-%C3%A9tnicos.html

Lessons Learned by the Case

When devising recruitment and loyalty strategies for rare donors, it is imperative to **consider their sociocultural characteristics**. This tailored approach not only respects their individuality but also **enhances the effectiveness of our strategy**.

Young immunohematologists must be familiar with the findings associated with rare phenotypes and the strategies for determining the specificity of antibodies directed against high-incidence antigens.

Lessons Learned by the Case

Strengthening interdisciplinary work for comprehensively managing patients with rare phenotypes is necessary.

Educating clinicians on the challenges and alternatives for transfusion management of rare patients is also essential.

References

- *Marion E. Reid, Christine Lomas-Francis and Martin L. Olsson.* The Blood Group Antigen FactsBook. 2012 ISBN 978-0-12-415849-8.
- *Daniels, Geoff.* Human Blood Groups. Human Blood Groups.2013 ISBN 978-1-118-49359-5
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- *Caudill JL, Gillard L.* HDFN Resulting from Anti-U: Alternatives to Allogeneic Intrauterine Transfusion. Lab Med. 2022 Jul 4;53(4):e79-e82. doi: 10.1093/labmed/lmab099. PMID: 34791347. Caudill JL, Gillard L. HDFN Resulting from Anti-U: Alternatives to Allogeneic Intrauterine Transfusion. Lab Med. 2022 Jul 4;53(4):e79-e82. doi: 10.1093/labmed/lmab099. PMID: 34791347.
- *Yin Q, Srivastava K, Brust DG, Flegel WA.* Transfusion support during childbirth for a woman with anti-U and the RHD*weak D type 4.0 allele. Immunohematology. 2021 Mar;37(1):1-4. doi: 10.21307/immunohematology-2021-001. PMID: 33962485; PMCID: PMC8108908.