RESEARCH PAPER

Impact of Hh (Bombay) Phenotype on Safe Blood Transfusion and Patient Outcomes: A Review

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Received: 20th Feb, 2026 | **Revised:** 4th Mar, 2026 | **Accepted:** 25th Mar, 2026 | **Available Online:** 10th Apr, 2026

ABSTRACT

The Hh phenotype, commonly known as the Bombay blood group, is a rare and clinically significant blood type characterized by the absence of the H antigen on red blood cells. Unlike individuals with the conventional ABO blood group system, Bombay phenotype individuals possess anti-H antibodies, making them incompatible with all standard ABO blood groups, including O. This rare phenotype presents major challenges in transfusion medicine, particularly in emergency settings where compatible blood is difficult to procure. This review explores the genetic basis, epidemiology, immunohematological characteristics, and clinical implications of the Hh phenotype, emphasizing its impact on safe blood transfusion practices and patient outcomes. Strategies such as rare donor registries, autologous transfusion, and improved screening techniques are also discussed to enhance patient safety.

Keywords: Hh phenotype, Bombay blood group, rare blood group, anti-H antibodies, blood transfusion compatibility, hemolytic transfusion reaction, FUT1 gene mutation, immunohematology, rare donor registry, blood bank management.

How to cite this article: Anbu Murugan SP, Habeeb Raja S, Akshayaa AS, Gracia Wiselin WG, Parimaleshwari R, Ifthikhar MB. Impact of Hh (Bombay) Phenotype on Safe Blood Transfusion and Patient Outcomes: A Review. Int J Drug Deliv Technol. 2026;16(29s):554-558. DOI: 10.25258/ijddt.16.29s.72

Source of support: Nil.

Conflict of interest: The authors declare no conflict of interest.

1. Introduction

Blood transfusion is a life-saving medical intervention that depends on strict compatibility between donor and recipient blood groups to prevent adverse immune reactions. In routine clinical practice, the **ABO** and **Rh** blood group systems are the primary determinants of compatibility. However, rare blood group phenotypes, such as the Hh (Bombay) phenotype, introduce additional complexity and risk into transfusion practices due to their unique immunohematological characteristics.

The Bombay phenotype, first identified in Mumbai (formerly Bombay), India, is characterized by the complete absence of the H antigen on the surface of red blood cells. The H antigen serves as the fundamental precursor for the formation of A and B antigens; therefore, its absence prevents the expression of A or B antigens regardless of an individual's ABO genotype. As a result, individuals with this phenotype are typically misclassified as blood group O in routine testing, unless specific confirmatory tests are performed.

A critical clinical feature of the Bombay phenotype is the presence of naturally occurring **anti-H antibodies** in the plasma. These antibodies are highly potent and can react with any red blood cells that possess the H antigen, including those of the O blood group, which normally contains the highest amount of H antigen. Consequently, transfusion of any standard ABO blood type into a Bombay phenotype individual can lead to severe, potentially fatal hemolytic transfusion reactions.

This unique incompatibility makes transfusion management extremely challenging. Patients with the Bombay phenotype can only safely receive blood from donors with the same phenotype, which is exceedingly rare. In emergency situations, the unavailability of compatible blood can delay

treatment, increase the risk of complications, and adversely affect patient outcomes. Therefore, accurate identification, proper blood grouping, and access to rare donor registries are essential components in ensuring safe transfusion practices for individuals with this rare blood group.

2. Genetic Basis of Hh Phenotype

The synthesis of the H antigen, which is essential for the expression of ABO blood group antigens, is controlled by the **FUT1 (fucosyltransferase 1)** gene. This gene encodes an enzyme responsible for adding fucose to a precursor substance on the red blood cell membrane, thereby forming the H antigen. The presence of this antigen is crucial because it acts as the structural foundation upon which A and B antigens are subsequently formed.

In individuals with the Bombay (Hh) phenotype, the **FUT1 gene is either mutated or functionally inactive**, resulting in the absence of a functional fucosyltransferase enzyme. Due to this defect, the biochemical pathway required for H antigen synthesis is disrupted. As a consequence, **no H antigen is produced on the surface of red blood cells**.

Since the H antigen is a necessary precursor for the formation of both A and B antigens, its absence prevents their expression, even if the individual genetically carries A or B alleles. Thus, although their genotype at the ABO locus may suggest blood groups A, B, or AB, they do not express these antigens phenotypically and instead appear similar to group O in routine testing.

Genetically, individuals with the Bombay phenotype are homozygous recessive (**hh**), meaning they inherit a non-functional FUT1 gene from both parents. In contrast, individuals with at least one functional allele (**Hh or HH**) are capable of producing the H antigen and, consequently, expressing A or B antigens depending on their ABO genotype.

This genetic defect not only alters the red blood cell antigen profile but also leads to the production of strong **anti-H antibodies** in the plasma, which has significant implications for blood transfusion compatibility and clinical management.

3. Epidemiology

The Bombay (Hh) phenotype is an exceptionally rare blood group worldwide, making it one of the most clinically significant rare phenotypes in transfusion medicine. Its global incidence is estimated to be approximately **1 in 1,000,000 individuals**, highlighting its extreme rarity in most populations. However, in India, the frequency is relatively higher, occurring in about **1 in 10,000 individuals**, with certain regions reporting even greater prevalence.

This increased occurrence in India is largely attributed to **consanguineous marriages**, where individuals marry within the same family or close genetic lineage. Such practices increase the likelihood of inheriting identical recessive genes from both parents. Since the Bombay phenotype results from a homozygous recessive condition (**hh genotype**), consanguinity significantly raises the probability that both parents carry and pass on the defective **FUT1 gene** to their offspring.

Additionally, **genetic clustering** within specific communities or populations contributes to its higher regional prevalence. In such groups, limited genetic diversity and repeated intermarriages within the same community allow rare alleles, like the non-functional FUT1 gene, to persist and become more common over generations. This phenomenon explains why certain populations in India and nearby regions show a relatively higher frequency of the Bombay phenotype compared to the global average.

The rarity of this phenotype has important clinical implications, particularly in blood transfusion, as the limited number of compatible donors makes it challenging to manage patients requiring urgent or repeated transfusions.

4. Immunohematological Characteristics

Individuals with the Bombay (Hh) phenotype possess a distinct immunohematological profile that sets them apart from all conventional ABO blood groups. The most defining feature is the **complete absence of H antigen** on the surface of red blood cells. Since the H antigen is the essential precursor required for the formation of A and B antigens, its absence automatically results in the **lack of A and B antigens** as well. Therefore, despite their genetic background, these individuals do not express any of the standard ABO antigens on their red blood cells.

In response to this absence, the immune system of Bombay phenotype produces **naturally occurring anti-H antibodies**, which are typically of the **IgM type**. These antibodies are highly potent and capable of activating the complement system, leading to rapid destruction of incompatible red blood cells. In addition to anti-H antibodies, their serum also contains **anti-A and anti-B antibodies**, similar to individuals with blood group O, but with a much stronger and broader reactivity due to the presence of anti-H.

The most critical implication of this antibody profile is its effect on transfusion compatibility. Unlike

individuals with blood group O—who are often considered universal donors—Bombay phenotype individuals **cannot receive blood from any ABO group, including O**. This is because O group red blood cells still carry a significant amount of H antigen on their surface, which will react with the recipient's anti-H antibodies. Such a reaction can trigger severe and potentially life-threatening **hemolytic transfusion reactions**.

Therefore, individuals with the Bombay phenotype can only safely receive blood from donors with the same phenotype, making transfusion management particularly challenging and emphasizing the importance of accurate diagnosis and specialized blood bank support.

5. Challenges in Blood Transfusion

5.1 Compatibility Issues

- Cannot receive blood from A, B, AB, or O groups
- Only compatible with **Bombay phenotype blood**

5.2 Risk of Hemolytic Transfusion Reactions

- Transfusion of incompatible blood leads to:
  - Acute hemolysis
  - Renal failure
  - Shock
  - Death (in severe cases)

5.3 Difficulty in Blood Availability

- Rare donor availability
- Lack of awareness in blood banks
- Delay in emergency transfusion

6. Impact on Patient Outcomes

6.1 Delayed Treatment

The rarity of the Bombay (Hh) phenotype often leads to significant delays in medical management, particularly when blood transfusion is required. Since compatible blood can only be obtained from another individual with the same phenotype, locating a suitable donor may take considerable time. As a result, **planned surgical procedures may need to be postponed** until compatible blood is arranged and secured. In critical cases, this delay can worsen the patient's condition, leading to **increased morbidity**, prolonged hospitalization, and a higher risk of complications due to inadequate or delayed treatment.

6.2 Increased Mortality Risk

In emergency situations such as **trauma, severe accidents, or obstetric hemorrhage**, immediate blood transfusion is often essential to save a patient's life. However, for individuals with the Bombay phenotype, the unavailability of compatible blood can become a life-threatening barrier. Transfusion with incompatible blood is not an option due to the risk of severe hemolytic reactions, leaving clinicians with limited alternatives. Consequently, the **lack of timely access to compatible blood significantly increases the risk of mortality**, especially in acute and high-blood-loss conditions.

6.3 Psychological Burden

Beyond physical health challenges, individuals with the Bombay phenotype often experience a considerable **psychological burden**. Awareness of having a rare blood type can lead to **anxiety and fear**, particularly regarding emergency situations where blood may not be readily available. Patients may also feel vulnerable due to their **dependence on rare donor networks or registries**, which are not always easily accessible. This ongoing uncertainty can impact mental well-being and quality of life, emphasizing the need for counseling, awareness, and support systems alongside medical management.

7. Diagnostic and Screening Approaches

7.1 Routine Blood Grouping Limitations

Routine blood grouping in most laboratories is based primarily on the detection of A and B antigens using standard **forward (cell) typing** methods. Since individuals with the Bombay (Hh) phenotype lack A and B antigens on their red blood cells, they appear similar to **group O** during initial testing. As a result, they are often **misclassified as O blood group** if only routine ABO typing is performed.

This misclassification can have serious clinical consequences because, unlike true O group individuals, Bombay phenotype individuals possess **anti-H antibodies**, which react strongly with the H antigen present on O group red blood cells. Therefore, relying solely on routine blood grouping without further confirmatory tests may lead to incompatible transfusions and severe hemolytic reactions.

7.2 Specialised Testing

To accurately identify the Bombay phenotype, additional and more specific laboratory tests are required:

Forward and Reverse Grouping Discrepancy:

In detailed blood grouping, both forward typing (testing patient RBCs with known antisera) and reverse typing (testing patient serum with known RBCs) are performed. In Bombay phenotype individuals, a discrepancy arises because:

Forward typing suggests group O (no A or B antigens)

Reverse typing shows strong agglutination with all test cells, including O cells

This unusual pattern indicates the presence of **anti-H antibodies** and raises suspicion of the Bombay phenotype.

Anti-H Lectin Testing (using *Ulex europaeus*):

This is a confirmatory test that specifically detects the presence of the H antigen. The plant-derived lectin from *Ulex europaeus* binds selectively to the H antigen on red blood cells.

- In normal individuals (including group O), agglutination occurs
- In Bombay phenotype individuals, **no agglutination is observed**, confirming the absence of the H antigen

- **Molecular Genotyping (FUT1 Gene Analysis):**
  Advanced diagnostic techniques involve analyzing the **FUT1 gene**, which is responsible for H antigen synthesis. Detection of mutations or inactivation of this gene confirms the **hh genotype**.
  Molecular methods provide a highly accurate and definitive diagnosis, especially useful in complex or ambiguous cases.

8. Strategies for Safe Transfusion

8.1 Rare Donor Registries

- National and international databases help locate compatible donors.
- Essential for emergency preparedness.

8.2 Autologous Blood Donation

- Preoperative blood storage by the patient.
- Useful for planned surgeries

8.3 Family Screening

- Family members may share the phenotype.
- Useful for donor identification.

8.4 Cryopreservation of Rare Blood

- Long-term storage of Bombay phenotype blood units.
- Enhances availability.

8.5 Awareness and Training

- Educating healthcare professionals and blood banks.
- Inclusion in transfusion protocols.

9. Advances in Transfusion Medicine

Advances in Transfusion Medicine

Recent advancements in transfusion medicine have significantly improved the identification, management, and clinical outcomes of patients with rare blood groups such as the Bombay (Hh) phenotype. These developments focus on enhancing diagnostic accuracy, increasing the availability of compatible blood, and improving communication between donors and healthcare systems.

- **Molecular Typing Techniques Improve Identification:**
  Traditional serological methods sometimes fail to accurately identify rare blood group phenotypes. The introduction of **molecular typing techniques**, such as DNA-based assays, has revolutionized blood group identification. By analyzing genes like **FUT1**, these methods can precisely detect mutations responsible for the absence of the H antigen. Molecular typing not only ensures an accurate diagnosis of the Bombay phenotype but also helps in identifying rare donors and preventing misclassification, thereby enhancing transfusion safety.

Development of Rare Blood Bank Networks:

The establishment of **rare blood bank networks** at national and international levels has greatly improved access to compatible blood for patients with uncommon blood groups. These networks maintain databases of individuals with rare phenotypes, including the Bombay blood group, and facilitate coordination between blood banks. In emergency situations, these systems enable rapid identification and transportation of compatible blood units, reducing treatment delays and improving patient survival rates.

- **Digital Platforms Connecting Rare Donors Globally:**
  With the advancement of digital technology, **online platforms and mobile applications** now play a crucial role in connecting rare blood donors with patients in need. These platforms allow real-time registration, tracking, and communication between donors, hospitals, and blood banks across regions and countries. For individuals with the Bombay phenotype, such digital connectivity is particularly valuable, as it expands the donor pool beyond local limitations and ensures quicker access to life-saving transfusions.

10. Future Perspectives

- Expansion of rare donor registries
- Gene therapy (potential future approach)
- Artificial blood substitutes (under research)
- Improved diagnostic kits for early detection

11. Conclusion

The Hh (Bombay) phenotype poses significant challenges in transfusion medicine due to its rarity and unique immunohematological profile. Ensuring safe transfusion requires accurate diagnosis, availability of compatible donors, and robust healthcare infrastructure. Strengthening rare donor registries, enhancing awareness, and adopting advanced diagnostic tools are critical to improving patient outcomes. Early identification and strategic planning can significantly reduce morbidity and mortality associated with transfusion in Bombay phenotype individuals.

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