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Review Article

Investigating the Refractory Platelet Transfusion: Understanding the Underlying Factors, Diagnosis, and Effective Treatment Strategies

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Abstract

This review article provides a comprehensive overview of platelet transfusion-refractory (PTR), a condition in which patients do not respond well to platelet transfusions, leading to increased bleeding and complications. It discusses various aspects of PTR such as its causes, prevention, diagnosis, management, and potential complications. While immune-mediated reactions are the primary cause, non-immunologic, patient-related, and donor-related factors can also contribute. Preventing PTR involves methods such as HLA matching, platelet count monitoring, and prophylactic transfusions; however, alternative approaches require further research. Accurate diagnosis is crucial, with treatment strategies depending on the cause often requiring platelet transfusions from HLA-matched donors or immunosuppressive therapies. Complications included bleeding, infection, and adverse drug reactions, highlighting the need for proper management and monitoring. Future research should focus on patient-specific risk factors, alternative prevention methods, and blood product safety. Understanding immune-mediated reactions and other causes, prevention, diagnosis, management, and potential complications can improve outcomes in patients needing platelet transfusions. In conclusion, PTR is a complex condition that healthcare professionals must handle carefully. Ongoing research is crucial to advancing knowledge, enhancing care, and improving patient outcomes.

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1. INTRODUCTION

Langerhans Platelets play a crucial role in blood circulation by facilitating clot formation and preventing excessive bleeding following an injury (1, 2). Individuals with specific medical conditions, including cancer, leukemia, and aplastic anemia, may experience a reduction in their capacity to generate platelets. For such patients, platelet transfusion therapy is frequently required to restore platelet levels and alleviate the symptoms associated with low platelet counts. The decision to administer platelet transfusions is typically made by a healthcare provider considering the patient's unique requirements and medical background (3, 4). Platelet transfusion refractory (PTR) can be attributed to various causes, such as immune-mediated platelet destruction (which can occur as a result of HLA alloimmunization or the formation of platelet-specific antibodies), non-immunological platelet destruction (which can be attributed to conditions such as sepsis, disseminated intravascular coagulation, or splenomegaly), inherited platelet disorders (including Glanzmann thrombasthenia, Bernard-Soulier syndrome, and storage pool deficiency), and medication-related effects (such as heparin and quinine). Although non-immune factors can play a role in refractoriness, immune-mediated causes, specifically alloimmunization, have been identified as significant contributors to this phenomenon (5, 6). Clinicians should consider these diverse causes when managing patients with PTR. Despite notable progress, there is still an unmet need in immune-mediated platelet transfusion refractoriness. The establishment of standardized protocols for platelet cross-matching, identification of reliable predictors of refractoriness, and exploration of novel immunomodulatory agents are areas requiring further investigation. Additionally, comprehensive studies are needed to assess the impact of refractoriness on patient outcomes, including bleeding risk and overall survival, to guide clinical decision-making and optimize transfusion strategies (7-9).

2- DEFINITION OF PLATELET TRANSFUSION REFRACTORINESS

Platelet transfusion therapy has been thoroughly investigated over six decades. PTR is a condition in which patients do not respond adequately to platelet transfusions, leading to an insufficient increase in platelet counts. It is characterized by the inability of platelet transfusions to achieve the desired therapeutic effect, that is, to raise platelet levels and ensure proper hemostasis (10, 11). The criteria for diagnosing PTR may vary; however, it is typically defined as a corrected count increment (CCI) of less than 5,000-7,500 platelets per microliter following transfusion. CCI is determined by subtracting the pre-transfusion platelet count from the post-transfusion count, dividing it by the number of platelet units transfused, and adjusting it based on the patient's body surface area.

CCI= [(post-transfusion platelet count </μL>) - (pre-transfusion platelet count </μL>)] x (body surface area < m^2>) / (number of platelets transfused < $x10^{11}$/μL>)

Another formula used to assess PTR is the Platelet Production Index (PPI), which involves dividing the post-transfusion platelet count by the number of hours since transfusion completion. A PPI value below 5,000 platelets per microliter per hour indicated refractoriness.

PPI = post-transfusion platelet count – pre-transfusion platelet count

The Percent Platelet Recovery (PPR) is a laboratory parameter used to evaluate the effectiveness of platelet transfusions by measuring the proportion of transfused platelets that successfully circulate and function in the recipient's bloodstream, typically assessed at 1 hour and 24 hours post-transfusion (12, 13). ABO similar platelets have more platelet recovery and survival. ABO-identical and ABO-non-identical platelet transfusions have comparable ability in controlling episodes of hemorrhage up to World Health Organization (WHO) grade two. To ensure the effectiveness of platelet injection, it is advisable to evaluate additional factors, such as the functional properties of platelets in the donor, as well as anti-HLA and anti-HPA antibodies (14). Additional criteria used to diagnose PTR include:

Number of transfusions: Refractoriness may be diagnosed if a patient has undergone a specific number of platelet transfusions (typically 4-6) within a defined period (e.g., 1-2 weeks) without achieving the desired increase in the platelet count

Platelet-specific antibodies: The presence of platelet-specific antibodies, which can be detected through laboratory tests such as platelet antibody detection assay or human platelet antigen (HPA) typing, can contribute to the diagnosis of PTR**.**

Clinical evaluation: Factors such as bleeding symptoms, underlying medical conditions, and concurrent medications are considered during PTR diagnosis (3, 11, 13, 15, 16). Table 1 compares the corrected count increment (CCI), platelet production index (PPI), and percent platelet recovery (PPR) parameters along with their definitions and corresponding formulas. In addition, the table includes the references used for each parameter.

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Table 1. Comprehensive table parameters that could be related to evaluation of Plt transfusion.

Parameter	Definition	Formula	Reference
CCI	Corrected count increment measures the post-transfusion increase in the recipient's platelet count per unit of transfused platelets, adjusted for the patient's body surface area.	(Posttransfusion platelet count - Pretransfusion platelet count) / Number of transfused platelets x 10 / Body surface area	Murphy et al., 1987
PPI	Platelet production index measures the rate of platelet production by the bone marrow in response to thrombocytopenia.	(Platelet count increment at 24 hours - Platelet count increment at 1 hour) / Hours elapsed between transfusion and 24-hour count x Body weight	Slichter et al., 1974
PPR	Percent platelet recovery measures the proportion of transfused platelets that successfully circulate and function in the recipient's bloodstream.	[(Posttransfusion platelet count - Pretransfusion platelet count) / Number of transfused platelets] x 100%	Stanworth et al., 2009
TTP	Time to platelet recovery measures the time it takes for the patient's platelet count to recover to a certain level after transfusion.	Not applicable	Wandt et al., 1998
PTI	Platelet transfusion interval measures the time between platelet transfusions.	(Time elapsed since last transfusion) / Number of platelet transfusions received	Smith et al., 2019
MPI	Mean platelet increment measures the average increase in platelet count per unit of transfused platelets.	(Posttransfusion platelet count - Pretransfusion platelet count) / Number of transfused platelets	Valeri et al., 1965

Other relevant parameters related to the evaluation of platelet transfusions were also discussed.

3- UNCOVERING THE MECHANISMS BEHIND THE REFRACTORINESS TO PLATELET TRANSFUSION

Refractory platelet transfusion can result from a range of factors involving both immune and non-immune mechanisms. Table-2 provides a summary of the causes of PTR, categorizing them into non-immune- and immune-mediated factors.

3-1-Nonimmune-mediated mechanisms

Identifying the nonimmune factors that contribute to PTR is essential for healthcare professionals to develop effective management strategies and improve patient outcomes One significant non-immune cause is the sequestration of platelets in the spleen. In certain individuals, the spleen may enlarge because of various underlying medical conditions, such as liver disease or specific types of cancer (15). Spleen enlargement can capture a substantial portion of transfused platelets, hindering their circulation in the bloodstream, reducing the response to platelet transfusions, and inhibiting their intended therapeutic impact. Another non-immune factor contributing to PTR is the swift clearance of platelets. Specific medications, such as chemotherapeutic drugs or antibiotics, can accelerate the breakdown of platelets in the body, resulting in a shorter lifespan and diminished efficacy of transfused platelets (16, 17). Furthermore, bone marrow suppression resulting from chemotherapy or radiation therapy can impede the production of new platelets, thereby reducing the effectiveness of platelet transfusions in elevating platelet counts. Another complication associated with PTR is sepsis, which presents a significant challenge in managing septic patients owing to an increased risk of bleeding and complicating their medical condition. Studies have shown a direct link between sepsis and PTR with complex and multifactorial underlying mechanisms. Sepsis-induced inflammation is believed to trigger platelet dysfunction and thrombocytopenia, leading to impaired clotting and an increased bleeding risk. Additionally, sepsis-related coagulopathy and disseminated intravascular coagulation may contribute to PTR. Early identification and management of sepsis are critical for preventing PTR and enhancing overall patient outcomes (18-23).

Moreover, various studies have investigated the correlation between sepsis, drug use, and PTR. For example, a study conducted by Zarychanski et al. in 2013 revealed that septic patients receiving specific medications such as nonsteroidal anti-inflammatory drugs (NSAIDs) and antiplatelet agents were at a higher risk of developing PTR(24). Additionally, a study conducted by Warkentin et al. highlighted the connection between sepsis and the administration of heparin, a blood-thinning medication that can result in platelet dysfunction and refractoriness. These findings underscore the significance of drug use when managing septic patients with PTR. Therefore, the use of NSAIDs, antiplatelet agents, and heparin has been linked to an elevated risk of developing this condition(25).

PTR caused by drugs is a widely recognized phenomenon, often observed in patients undergoing chemotherapy or taking specific medications, such as heparin and quinine. These drugs can lead to non-immune-mediated platelet destruction, resulting in decreased platelet counts and compromised clotting abilities (figure 1). The exact

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Table 2. This table summarize both the nonimmune-mediated and immune-mediated causes of RPT.

Cause	Definition	Contributing Factors
Spleen sequestration	Rapid removal of transfused platelets by an enlarged spleen	Splenomegaly due to conditions such as cirrhosis or hematologic malignancies
Rapid platelet clearance	Increased destruction of transfused platelets due to various factors	Infection or inflammation, medications, metabolic disorders
Bone marrow suppression	Decreased production of platelets by the bone marrow	Chemotherapy, radiation therapy, myelodysplastic syndrome
Drug-induced	Direct toxicity or immune-mediated destruction of platelets	Heparin, quinine, sulfonamides
Inherited platelet disorders	Genetic abnormalities affecting platelet production or function	Bernard-Soulier syndrome, Glanzmann thrombasthenia
Disseminated Intravascular Coagulation (DIC)	Abnormal activation of clotting factors leading to systemic clotting and consumption of platelets	Septic shock, trauma, obstetric complications
Infection or viral contamination	Introduction of bacteria or viruses into the bloodstream, leading to platelet destruction	Bacterial sepsis, cytomegalovirus
Hemodilution	Dilution of transfused platelets in the recipient's blood volume	Massive transfusion, fluid overload
Alloimmunization	Development of antibodies against transfused platelets due to donor-recipient antigen mismatch	Previous transfusions, pregnancy, transplantation
Autoimmunization	Development of antibodies against the recipient's own platelets, leading to destruction of transfused platelets	Idiopathic thrombocytopenic purpura, systemic lupus erythematosus

mechanisms by which these drugs cause platelet dysfunction are not fully understood, but they may disrupt platelet production, function, or lifespan. In certain instances, antibiotics such as Vancomycin or Ceftriaxone have also been linked to platelet dysfunction and PTR (26).). It is crucial to recognize that the underlying cause of PTR can differ from person to person, and a comprehensive assessment is essential to determine the specific factors involved. Managing this condition requires discontinuation of the causative agent, if feasible, and the opting for alternative treatments such as plasma or cryoprecipitate transfusions to aid in clotting support (25, 27-30). Furthermore, certain drugs may trigger the production of antibodies that attack platelets, aggravating this issue and leading to immune-mediated platelet destruction. Research has investigated the correlation between drug use and this phenomenon, such as Arnold et al.'s study on the role of quinine and quinidine in immune-mediated platelet destruction and subsequent refractoriness to transfusions. Another study by Aster et al. focused on the effects of NSAIDs and antibiotics on platelet function and their potential contribution to the PTR. Therefore, healthcare professionals should exercise caution when prescribing medications to septic patients and explore alternative treatment options to minimize the likelihood of PTR (31, 32).

PTR can be attributed to Disseminated Intravascular Coagulation (DIC), a multifaceted disorder characterized by simultaneous abnormal clotting and bleeding. DIC is typically triggered by underlying conditions, such as sepsis, trauma, or malignancies. When DIC develops, it can lead to the excessive consumption and depletion of platelets, resulting in a reduced response to platelet transfusions (33, 34). Apart from the previously mentioned causes, several

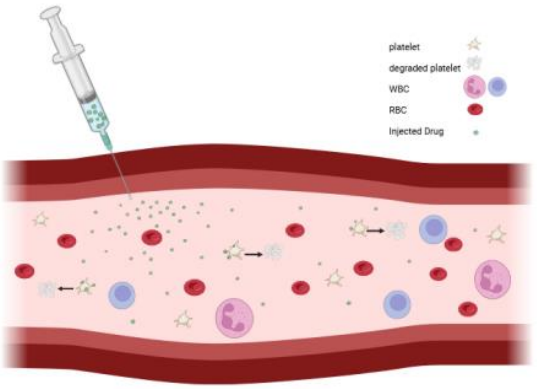

Figure 1. Understanding RPT caused by drugs: A Common Side Effect of Certain Medications. This image delves into the realm of Drug-Induced Thrombocytopenia (DITP), a well-recognized phenomenon that affects patients undergoing chemotherapy or those prescribed certain medications like heparin and quinine. These drugs have the potential to trigger non-immune-mediated platelet destruction, ultimately leading to a significant decline in platelet counts and a compromised ability to form blood clots WBC: White blood cell, RBC: Red blood cell.

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Table 3- List of drugs known to induce refractory platelet transfusion, along with their classification (immune or non-immune), mechanism, and frequency

Drug Name	Classification	Mechanism	Frequency
Heparin	Immune	Formation of heparin-dependent antibodies	Moderate to High
Quinine	Immune	Formation of quinine-dependent antibodies	Low to Moderate
Quinidine	Immune	Formation of quinidine-dependent antibodies	Low to Moderate
Vancomycin	Immune	Formation of vancomycin-dependent antibodies	Low to Moderate
Penicillin	Immune	Formation of penicillin-dependent antibodies	Low to Moderate
Cephalosporins	Immune	Formation of cephalosporin-dependent antibodies	Low to Moderate
Rifampin	Immune	Formation of rifampin-dependent antibodies	Low to Moderate
Sulfonamides	Immune	Formation of sulfonamide-dependent antibodies	Low to Moderate
Methyldopa	Immune	Formation of methyldopa-dependent antibodies	Low to Moderate
Procainamide	Immune	Formation of procainamide-dependent antibodies	Low to Moderate
Amoxicillin	Immune	Formation of amoxicillin-dependent antibodies	Low to Moderate
Ranitidine	Non-immune	Direct platelet inhibition and destruction	Low to Moderate
Nonsteroidal Anti-Inflammatory Drugs	Non-immune	Direct platelet inhibition and destruction	Low to Moderate
Antibiotics	Non-immune	Direct platelet inhibition and destruction	Low to Moderate
Chemotherapy Agents	Non-immune	Direct platelet inhibition and destruction	Low to Moderate
Antiplatelet Medications	Non-immune	Direct platelet inhibition and destruction	Low to Moderate
Antidepressants	Non-immune	Direct platelet inhibition and destruction	Low to Moderate

other potential factors can contribute to PTR. These additional causes include the following.

- **Infection or viral contamination:** Certain viral infections, such as cytomegalovirus (CMV) or human immunodeficiency virus (HIV), can affect platelet function and lead to PTR (23, 35-37) .
- **Hemodilution:** Dilutional thrombocytopenia can occur when a patient undergoes extensive fluid administration during surgery or massive blood transfusions. The dilution of platelets in the bloodstream can lead to a decrease in their concentration, thereby reducing the effectiveness of platelet transfusions (34, 38-40).

3-2- Immune-mediated mechanisms

Immune-mediated factors, particularly alloimmunization, have been identified as significant contributors to PTR. Immune refractory after platelet transfusion is a situation in which patients do not respond to platelet transfusions because of the production of antibodies against donor platelets. This can lead to thrombocytopenia and an elevated risk of bleeding in affected individuals (41, 42). To discuss the immunogenicity of platelets, it is important to note that they possess class I HLA molecules, platelet- To discuss the immunogenicity of platelets, it is important to note that they possess class I HLA molecules, platelet-particular glycoproteins, and a limited number of ABO antigens on their exterior. Antibodies can target and bind to these antigens on transfused platelets, leading to their removal from patient circulation. Class I HLA molecules are present on platelets and most nucleated cells, whereas class II molecules are primarily found on cells that are involved in antigen presentation. Platelets predominantly express HLA-A and HLA-B alleles, while antibodies against HLA-C are not a significant cause of immune-based refractoriness glycoproteins, and a limited number of ABO antigens on their surface. Antibodies can target and bind to these antigens on transfused platelets, leading to their removal from patient circulation. Class I HLA molecules are found on platelets and the majority of nucleated cells, while class II molecules are primarily found on cells that engaged in antigen presentation. Platelets mainly express HLA-A and HLA-B alleles, while antibodies against HLA-C are not notable factor of immune-based refractoriness (42-44). The human platelet antigen (HPA) system, which exhibits less antigenic variability than the Human Leukocyte Antigen (HLA) system, is seldom linked to refractoriness. In many cases, antibodies against HPA are detected alongside HLA antibodies (45-47). Additionally, ABO blood group antigens on the surface of platelets play a role in PTR by determining the matching between the donor and patient. The number and level of immunogenicity of ABO blood group antigens on platelets vary among individuals, affecting the risk and severity of immune reactions that can occur during transfusions (48, 49). If a patient has high levels of anti-A or anti-B antibodies, this can result in substantial clearance of donor platelets that possess matching ABO antigens. To prevent this problem, transfusion of platelets with identical ABO antigens is recommended approach (50-53). As mentioned earlier, specific medications can stimulate the production of antibodies in the body, leading to platelet attacks. This immune response is a drug-induced antibody-mediated reaction.

Drug-induced antibodies can be formed when drugs interact with platelet membrane glycoproteins. Certain commonly

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Table 4. Overviews on researches on Anti-HLA Class I alloantibodies in PTR published over the past 5 years.

Title	Authors	Journal	Year	Main Findings
HLA alloimmunization in patients with hematologic malignancies receiving platelet transfusions: impact on transfusion outcomes and implications for personalized medicine	Patel AA, et al.	Ther Adv Hematol	2017	The study shows that HLA alloimmunization is associated with an increased risk of platelet transfusion refractoriness in patients with hematologic malignancies and highlights the importance of HLA matching in transfusion therapy.
Alloimmunization to HLA antigens in transfused patients with bone marrow failure syndromes	Ono Y, et al.	Int J Hematol	2018	The authors examine the prevalence and clinical significance of HLA alloimmunization in transfused patients with bone marrow failure syndromes and suggest the importance of HLA matching in these patients.
HLA alloimmunization in solid organ transplant recipients: impact on transfusion support and clinical outcomes	Kato S, et al.	Transfus Apher Sci	2019	The article discusses the impact of HLA alloimmunization on transfusion support and clinical outcomes in solid organ transplant recipients and highlights the need for personalized transfusion therapy based on HLA typing.
Diagnostic approach to HLA alloimmunization in platelet transfusion refractoriness patients	Cho YU, et al.	Blood Res	2020	The review article summarizes the diagnostic approach to HLA alloimmunization in platelet transfusion refractoriness patients, including the use of serological and molecular methods, and highlights the emerging therapeutic options for these patients.
HLA alloimmunization in pediatric patients with hematologic malignancies: incidence, risk factors, and impact on transfusion outcomes	Huang J, et al.	Pediatr Blood Cancer	2020	The study examines the incidence, risk factors, and impact of HLA alloimmunization on transfusion outcomes in pediatric patients with hematologic malignancies and suggests that HLA matching may reduce the risk of platelet transfusion refractoriness in these patients.
Effectiveness of HLA-matched platelet transfusions in reducing refractoriness rates and improving clinical outcomes in patients with myelodysplastic syndromes	Kao RH, et al.	BMC Hematol	2021	The retrospective study shows that HLA-matched platelet transfusions are effective in reducing refractoriness rates and improving clinical outcomes in patients with myelodysplastic syndromes and highlights the importance of personalized transfusion therapy based on HLA typing.
Prevalence and clinical significance of HLA alloimmunization in patients with sickle cell disease receiving chronic transfusion therapy	Kanias T, et al.	Blood Adv	2021	The study examines the prevalence and clinical significance of HLA alloimmunization in patients with sickle cell disease receiving chronic transfusion therapy and suggests that HLA matching may improve transfusion outcomes in these patients.
HLA alloimmunization in renal transplant candidates: impact on donor selection and transplant outcomes	Salazar-Paramo M, et al.	Transplant Proc	2021	The article discusses the impact of HLA alloimmunization on donor selection and transplant outcomes in renal transplant candidates and highlights the importance of personalized transfusion and transplantation therapy based on HLA typing.
Association between HLA antibody specificity and platelet transfusion refractoriness in hematologic malignancy patients	Li Y, et al.	BMC Hematol	2022	The retrospective study investigates the association between HLA antibody specificity and platelet transfusion refractoriness in hematologic malignancy patients and suggests that a better understanding of HLA antibody specificity may improve transfusion outcomes in these patients.
HLA mismatching in unrelated cord blood transplantation: impact on engraftment and survival	Yoshida K, et al.	Blood Adv	2022	The article discusses the impact of HLA mismatching on engraftment and survival in unrelated cord blood transplantation and highlights the importance of HLA matching in improving transplant outcomes.

implicated drugs can result in rapid thrombocytopenia, which typically resolves shortly after the withdrawal of medication. Additionally, there are independent of drugs antibodies that are not necessary for the availability of a drug to demonstrate activity (54-57). Recently, several studies have presented compelling evidence to support the occurrence of drug-induced antibody-mediated PTR. For example, a study conducted by Arnold et al. in 2013 examined a case of severe thrombocytopenia following treatment with a particular medication. Upon further investigation, the presence of drug-dependent antibodies specifically targeting platelets was identified, resulting in ineffective platelet transfusions to increase the patient's platelet count (31). Likewise, a separate study conducted by Johnson et al. in 2016 investigated patients who experienced PTR despite receiving multiple platelet units. By conducting detailed laboratory investigations, the researchers successfully identified drug-induced antibodies in these patients that were responsible for the destruction of platelets. This study emphasizes the significance of acknowledging and comprehending the role of drug-induced antibodies in the occurrence of platelet transfusion refractoriness (58). Additionally, a more recent study by Lee et al. in 2020 investigated the clinical characteristics and outcomes of patients with drug-induced antibody-mediated PTR. Researchers have observed that specific medications, including heparin and quinine, are commonly associated with the development of these antibodies (59). These

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Table 5. Overviews on researches on Anti-HPA alloantibodies in PTR published over the past 5 years.

Title	Authors	Journal	Year	Main Findings
HPA alloimmunization: current perspectives on its clinical significance and management	Bayat B, et al.	Crit Rev Clin Lab Sci	2017	The review summarizes the current knowledge regarding HPA alloimmunization, its mechanisms, clinical significance, and management options.
Platelet transfusion refractoriness due to HPA antibody-mediated alloimmune thrombocytopenia: new solutions for an old problem	Nazy I, Arnold DM	Platelets	2017	The article discusses the pathophysiology of HPA antibody-mediated alloimmune thrombocytopenia, diagnostic approaches, and emerging treatments.
The clinical significance of anti-human platelet antigen antibodies in transfusion medicine	Curtis BR, McFarland JG	Transfusion	2018	The authors provide an overview of the clinical significance of anti-HPA antibodies, including their association with bleeding disorders, immune thrombocytopenia, and transfusion reactions.
Management of patients with platelet-specific alloantibodies who require surgery or invasive procedures	Arnold DM, et al.	Br J Haematol	2018	The article reviews the management strategies for patients with platelet-specific alloantibodies who require surgery or invasive procedures, including preoperative assessment, transfusion support, and emerging therapies.
Frequency and specificity of human platelet antigens among blood donors in the Chinese population	Ye L, et al.	Vox Sang	2019	The study investigates the frequency and specificity of human platelet antigens (HPAs) among Chinese blood donors and highlights the importance of HPA matching in transfusion medicine.
Anti-platelet antibodies in patients with bone marrow failure syndromes	Shalev H, et al.	Am J Hematol	2019	The authors examine the prevalence and clinical significance of anti-platelet antibodies in patients with bone marrow failure syndromes, including immune thrombocytopenia and aplastic anemia.
Severe neonatal alloimmune thrombocytopenia caused by anti-HPA-3a alloantibody	Kao RH, et al.	Pediatr Neonatol	2020	The case report describes a rare case of severe neonatal alloimmune thrombocytopenia caused by anti-HPA-3a alloantibody and the successful management of the newborn using HPA-matched platelets.
Diagnostic approach to platelet transfusion-refractory patients with suspected HPA alloimmunization	Ruiz-Delgado GJ, et al.	Curr Opin Hematol	2020	The review article discusses the diagnostic approach to platelet transfusion-refractory patients with suspected HPA alloimmunization, including the use of serological assays, genotyping methods, and emerging technologies.
Incidence and clinical implications of anti-HPA-1a alloimmunization in fetomaternal alloimmune thrombocytopenia: a systematic review	Bakchoul T, et al.	Transfus Med Rev	2021	The systematic review examines the incidence and clinical implications of anti-HPA-1a alloimmunization in fetomaternal alloimmune thrombocytopenia, highlighting the need for early diagnosis and tailored management strategies.
HPA alloimmunization in pregnant women: implications for personalized medicine in transfusion therapy	Leparc GFS, et al.	J Clin Apher	2022	The authors review the current knowledge on HPA alloimmunization in pregnant women and its implications for personalized medicine in transfusion therapy, including the use of HPA-matched platelets and emerging therapeutic options.

findings emphasize the importance of raising awareness, detecting the condition early, and implementing suitable management strategies to enhance platelet transfusion outcomes in affected patients (42, 60-62). This table includes a complete list of drugs known to induce PTR along with their classification (immune or non-immune), mechanism, and frequency (Table 3). It is important to emphasize that the frequency mentioned in the table can vary based on individual patient factors as well as the specific dosage and duration of drug use.

3-2-1- Alloimmune factors

Alloimmune disorders, particularly PTR, arise when the body's immune system identifies transfused platelets as foreign and initiates an immune response. This immune reaction results in the destruction of transfused platelets, making them ineffective in treating platelet-related disorders (63). The alloimmune response mechanism involves the recipient's immune system producing antibodies that target specific antigens on the transfused platelets. These antibodies can directly destroy platelets or trigger an immune response involving other immune cells, thereby leading to platelet destruction. Various factors, such as prior exposure to platelet transfusions, pregnancy, and immune-related disorders contribute to the development of PTR. Understanding the mechanisms underlying alloimmune disorders is essential for devising strategies to prevent and manage this condition. Alloantibodies can recognize specific

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Table 6. Overview of flowcytometry in the diagnosis and management of immune refractory platelet

Study Title	Main Findings
Cid J et al. Flowcytometry: an aid to diagnosis and monitoring of alloimmunization in neonatal thrombocytopenia. Transfusion 2002; 42: 1413-9.	Flowcytometry is a reliable method for detecting antiplatelet antibodies in patient samples, and can be used to monitor changes in antibody levels over time.
Arnold DM et al. A systematic evaluation of the role of prophylactic platelet transfusions in patients with hematologic malignancies undergoing autologous hematopoietic cell transplantation. Blood 2012; 120: 768-76.	Flowcytometry is a valuable tool for identifying patients at risk of developing immune refractory platelet transfusion, and for determining appropriate transfusion thresholds based on individual patient characteristics.
Duquesnoy RJ. Antibody-mediated immune responses to platelets. Curr Opin Hematol 1998; 5: 338-43.	Flowcytometry can be used to detect and characterize antibody-mediated immune responses to platelets, which are key factors in the development of immune refractory platelet transfusion. It may also be useful in guiding treatment decisions.
Zeller MP et al. Monitoring of platelet transfusion therapy in patients with refractoriness to platelet transfusions by flow cytometry. Vox Sang 2001; 80: 72-8.	Flowcytometry is a useful tool for monitoring the efficacy of different treatment regimens in patients with immune refractory platelet transfusion, and can help guide decisions regarding the timing and frequency of transfusions.

human leukocyte antigens (HLA) or platelet-specific antigens (HPA), resulting in platelet destruction either through complement-mediated lysis or antibody-dependent cellular cytotoxicity (64-68). Numerous studies have highlighted the crucial role of alloimmunization against HLA and HPA antigens as the primary and most significant causes of PTR (Tables 4,5 And Figure 2,3).

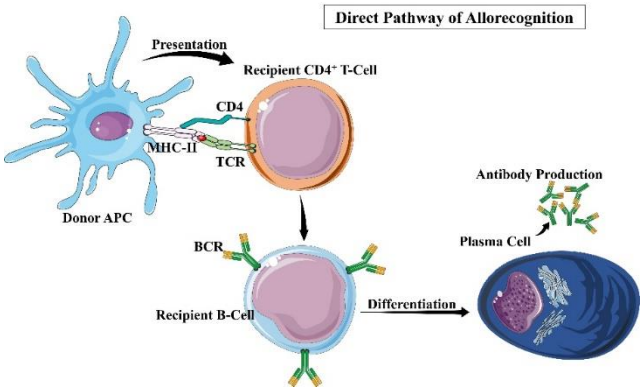

Figure 2. Models of direct allorecognition that can lead to platelet alloimmunization. Major Histocompatibility Complex (MHC) class II molecules on donor antigen-presenting cells (APC) and the T-cell receptor (TcR) on recipient CD4 + T cells interact directly to provide direct allorecognition. In addition to helping B cells differentiate into plasma cells and produce anti-MHC class I antibodies, this also activates T cells. This route is eliminated when platelet concentrates undergo leukoreduction.

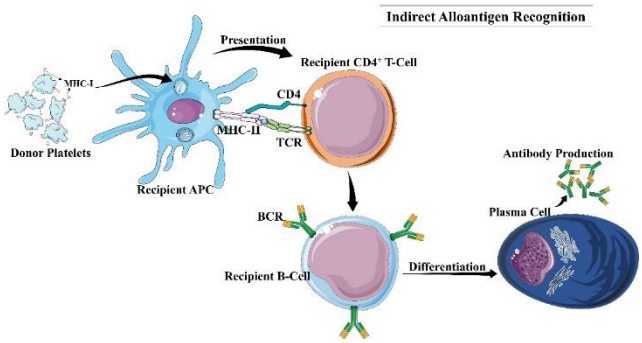

Figure 3. Models of indirect allorecognition that can lead to platelet alloimmunization. MHC class I molecules are on donor platelets. In this process, the recipient's antigen-presenting cells (APCs) absorb MHC class I alloantigens from the donor platelets. These antigens are then processed and displayed on the recipient APCs using MHC class II molecules. This triggers the activation of helper T cells and stimulates the production of alloantibodies by plasma cells.

3-2-2- Autoimmune factors

Autoimmunization occurs when a patient's immune system generates antibodies against their own platelets. This autoantibody production can lead to the destruction of both the newly transfused and the recipient's platelets, causing refractory thrombocytopenia (69). The precise mechanism behind autoimmunization resulting in PTR remains complex and not fully comprehended. However, it is believed that exposure to foreign platelets during transfusion triggers an immune response, leading to the production of autoantibodies against the platelet receptors (11). Subsequent transfusions can be challenging as these

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Table 7. **Comparing some of the methods used to identify compatible platelet units for alloimmunized patients.**

Method	Description	Pros	Cons
Crossmatching	Mixing patient serum with donor platelets to check for compatibility	Highly specific and reliable	Time-consuming and requires specialized laboratory setup
HLA matching	Matching human leukocyte antigens (HLA) between the patient and donor platelets	Can improve platelet survival and reduce alloimmunization	Limited availability of HLA-matched platelets
Washed platelets	Platelets are washed to remove plasma components, reducing the risk of transfusion reactions	Reduces the risk of allergic reactions	May result in lower platelet recovery and efficacy
Serologic testing	Testing for specific antibodies in the patient's serum	Identifies specific antibodies	Limited ability to predict platelet compatibility
Single-donor apheresis platelets	Platelets obtained from a single donor through apheresis	Lower risk of alloimmunization	Limited availability and potential for shortages
Low leukocyte count products	Platelet units with reduced numbers of white blood cells	Decreases the risk of febrile non-hemolytic reactions	Increased risk of bacterial contamination
HPA-matched platelets	Matching human platelet antigens (HPA) between the patient and donor platelets	Reduces the risk of alloimmunization	Limited availability of HPA-matched platelets
Gamma irradiation of platelets	Platelets are treated with gamma irradiation to prevent graft-versus-host disease (GVHD)	Eliminates the risk of GVHD	May impair platelet function

antibodies may target and destroy the freshly transfused platelets. Several factors contribute to the development of autoimmunization and subsequent PTR, including underlying medical conditions, genetic factors, and the patient's transfusion history (70). In patients with Systemic lupus erythematosus (SLE), a chronic autoimmune disease, the development of autoantibodies increases their susceptibility to PTR following platelet transfusions (71). It has been reported that up to 20% of SLE patients receiving platelet transfusions may develop alloimmunization against HLA antigens or autoimmunization against platelet glycoproteins. Consequently, this can lead to the destruction of both transfused and recipient's platelets, leading to PTR (72). Immune thrombocytopenic purpura (ITP), characterized by low platelet counts due to platelet destruction by autoantibodies, is a common hematological manifestation observed in patients with systemic lupus erythematosus (SLE). Therefore, in individuals with SLE, it is essential to be mindful of the possibility of developing allo- or auto-immunization, which can lead to PTR. It is vital to closely monitor platelet counts and antibody levels following transfusion, and implementing appropriate management strategies, such as immunosuppressive therapy and plasma exchange, is crucial. Studies have revealed that ITP patients and platelets should only be used if the patient is bleeding These patients have an increased risk of developing alloimmunization against transfused platelets, which can ultimately lead to transfusion refractoriness. This further underscores the importance of vigilant monitoring and tailored management approaches to optimize transfusion outcomes in patients with autoimmune-related platelet disorders (73, 74). In a study conducted by Vrbensky et al., it was observed that certain patients with ITP who received platelet transfusions developed alloantibodies against HLA, which are present on transfused platelets. These alloantibodies can lead to refractoriness to subsequent transfusions, resulting in severe bleeding and poor outcomes. Another study published in 2019 proposed that some cases of refractory thrombocytopenia after platelet transfusion may have been caused by antibodies directed against soluble HLA molecules. The study reported three cases of patients with hematologic malignancies who experienced severe thrombocytopenia following platelet transfusions despite having no history of alloimmunization. Subsequent testing revealed the presence of circulating IgG antibodies against soluble HLA molecules, which blocked platelet uptake and survival in vitro. These findings highlight the complexities of immune responses and their impact on platelet transfusion outcomes, underscoring the need for further research and tailored management strategies in such cases(75-77).

3-3- Inherited platelet disorders

Inherited platelet disorders, which are genetic conditions characterized by abnormalities in the function or production of platelets and the blood cells responsible for

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Table 8. Summarizing the immunomodulatory therapies commonly used for immune-mediated refractory platelet transfusion.

Therapy	Mechanism of Action	Examples
Intravenous immunoglobulin (IVIG)	Provides high doses of immunoglobulins to reduce autoantibody production	Octagam, Gamunex-C
Corticosteroids	Potent anti-inflammatory agents that suppress the immune response	Prednisone, Dexamethasone
Rituximab	Monoclonal antibody that targets CD20 on B cells to reduce autoantibody production	Rituxan
Cyclosporine	Immunosuppressive drug that inhibits T cell activity	Sandimmune, Neoral
Azathioprine	Immunosuppressive drug that inhibits white blood cell production	Imuran
Mycophenolate mofetil	Immunosuppressive drug that inhibits white blood cell production	CellCept

clotting, can play a role in PTR, where platelets do not adequately respond to transfusions. Several studies have explored the association between inherited platelet disorders and PTR. A study conducted by Greinacher et al. (2011) investigated the prevalence and consequences of inherited platelet disorders in PTR patients. The findings revealed that certain inherited platelet disorders, such as Glanzmann thrombasthenia and Bernard-Soulier syndrome, were linked to an elevated risk of PTR. These disorders affect platelet adhesion and aggregation, leading to impaired clot formation and reduced responsiveness to transfusions. Similarly, another study by Nurden et al. (2011) delved into the molecular mechanisms underlying inherited platelet disorders and their implications for PTR. The researchers discussed various genetic mutations and their impact on platelet function, highlighting the importance of genetic testing in diagnosing these disorders and guiding appropriate management strategies. These studies emphasize the significance of considering inherited platelet disorders in cases of PTR. Healthcare professionals should be aware of these genetic conditions and their potential effects on platelet function to ensure precise diagnosis and appropriate management for patients. (78-80).

4- DIAGNOSIS OF IMMUNE-MEDIATED PLATELET TRANSFUSION REFRACTORINESS

When a patient is suspected to be refractory to platelet transfusions, two essential questions need to be addressed: first, whether the patient is genuinely refractory, and second, whether the refractoriness is a result of immune or nonimmune factors. Once refractoriness is confirmed, healthcare professionals must consider both immune and nonimmune factors as potential causes. To diagnose refractoriness following platelet transfusion, various tests and examinations are utilized by healthcare professionals. Among these diagnostic methods, complete blood counts are commonly employed to monitor the patient's platelet levels and assess their response to the transfusions. To determine this response, post-transfusion platelet counts are taken within 10 to 60 minutes after the transfusion. Although a 1-hour count is considered ideal, obtaining it can be challenging, so a 10-minute count is often used as an alternative. However, the evidence supporting a reduced 1-hour count as a reliable indicator of immune refractoriness remains inconsistent. Further research is necessary to better understand and establish accurate diagnostic criteria for immune refractoriness following platelet transfusions (42, 81). Conducting a comprehensive history and physical examination can aid in ruling out nonimmune factors contributing to PTR. However, in patients with hematologic disorders, it is essential to consider that both immune and nonimmune factors may coexist as potential causes of the condition. Therefore, a thorough assessment and evaluation of all possible factors are necessary to accurately diagnose and manage PTR in these individuals (42). The use of screening tests to assess the presence of HLA or HPA antibodies in new patients is a subject of discussion. Currently, a standard enzyme-linked immunosorbent assay (ELISA) is extensively employed due to its high accuracy and rapidity in determining the presence of HLA or HPA antibodies in the patient's serum Previously, lymphocytotoxic assays were utilized in HLA antibody testing. However, solid-phase testing has largely replaced them due to their efficiency and ability to identify multiple HLA antibody specificities, a capability that cytotoxic assays could not distinguish. Solid-phase testing has proven to be more effective and has become the preferred method in modern HLA antibody testing (42, 50, 82). The solid-phase assay utilizes beads coated with specific HLA antigens, and the binding of antibodies is measured based on fluorescence intensity. However, there is significant variability among laboratories in determining the Mean Fluorescence Intensity (MFI) threshold that indicates positive or clinically significant antibodies. To address this issue, an adapted version of the solid-phase assay was introduced, focusing on complement-fixing antibodies. This adaptation has demonstrated a correlation with antibody-mediated rejection in solid organ transplants, offering valuable

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Table 9. Outlining the various approaches to management of RPT, including their benefits and risks

Treatment/Management Option	Benefits	Risks
Corticosteroids (e.g. prednisone)	Effective at reducing inflammation and swelling in the kidneys	Increased risk of infection, weight gain, increased blood sugar levels, osteoporosis, mood changes
Immunosuppressants (e.g. cyclophosphamide, azathioprine)	Can help prevent the immune system from attacking the kidneys	Increased risk of infection, liver damage, nausea/vomiting, hair loss
Plasmapheresis	Removes harmful antibodies from the blood	Risk of bleeding or infection, temporary decrease in blood pressure, fatigue
Rituximab	Targets specific immune cells responsible for attacking the kidneys	Increased risk of infection, infusion reactions (e.g. fever, chills), respiratory tract infections
IVIG	Risk of allergic reactions, kidney damage, thrombotic events	Rapid onset of action, high efficacy, relatively low risk of infectious complications
Corticosteroids	Risk of increased infection risk, osteoporosis, weight gain, hypertension	Rapid onset of action, high efficacy, relatively low cost
Washed platelets	Risk of bacterial contamination, increased storage time, more expensive	Reduced risk of transfusion reactions, improved patient outcomes
Low leukocyte count products	Risk of decreased transfusion efficacy, longer storage times, more expensive	Reduced risk of FNHTRs, improved patient outcomes
HPA-matched platelets	Risk of alloimmunization to other HPAs, more expensive	Reduced risk of alloimmunization to specific HPAs, improved patient outcomes
Gamma irradiation of platelets	Risk of decreased shelf-life, potential damage to platelets, increased cost	Reduced risk of GVHD, improved patient outcomes
Cyclosporine	Risk of nephrotoxicity, increased infection risk, hypertension	High efficacy, relatively rapid onset of action, useful for refractory cases
Single-donor apheresis platelets	Risk of bacterial contamination, higher cost, longer processing time	Improved patient outcomes, reduced need for multiple transfusions
TPO-RAs	Risk of thrombotic events, increased infection risk, potential for bone marrow fibrosis	High efficacy, reduction in bleeding symptoms, reduced need for platelet transfusions
Microparticle platelet	Risk of thrombotic events, headache, fatigue, nausea	High efficacy, reduction in bleeding symptoms, reduced need for platelet transfusions
Splenectomy	Risk of post-splenectomy sepsis, increased infection risk, thrombotic events	High efficacy in selected cases, resolution of symptoms
Stem cell transplantation	Risk of graft-versus-host disease (GVHD), infection, mortality	Curative in select cases, improved survival rates
Mycophenolate mofetil	Risk of infection, GI toxicity, bone marrow suppression	High efficacy, relatively low cost

insights for clinicians in assessing transplant risks and outcomes. Nevertheless, standardizing MFI thresholds for solid-phase assays remains a challenge, and further research is necessary to establish consistent guidelines across laboratories (42).). However, further research is required to validate the effectiveness of this assay for platelet-refractory patients with weak to moderate HLA antibody levels. Tzong-Shi Chiueh et al. in 2023 presented a study investigating platelet transfusions and the potential for alloimmunization, wherein antibodies develop against donated platelets. The study employs a filtration enzyme-linked immunosorbent assay (ELISA) to detect such antibodies in patients who have undergone platelet transfusions. The results demonstrate that the use of a leukoreduction filter during the transfusion process significantly reduces the risk of alloimmunization. Based on their findings, the study suggests that routine screening for alloantibodies may be necessary in patients receiving frequent platelet transfusions, and the consideration of using leukoreduction filters should be an essential part of the transfusion process (83).

While antibody screening tests can identify the presence of antibodies against donor platelets, flow cytometry is a frequently employed diagnostic tool for confirming immune PTR in patients. It has the capacity to not only confirm the diagnosis but also specify the nature of the antibodies involved. Flow cytometry offers valuable insights into the immune response, enabling healthcare professionals to better understand the underlying mechanisms and tailor appropriate management strategies for patients with immune PTR (84). It is essential to acknowledge that various methods are employed to identify compatible platelet units, and the choice of method may vary depending on the patient's specific condition and clinical context. Among

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these methods, flow cytometry stands out as a valuable tool in diagnosing and managing immune PTR. It enables doctors to swiftly and accurately determine the underlying cause of the patient's symptoms, facilitating the development of an appropriate and effective treatment plan. By utilizing flow cytometry, healthcare professionals can make well-informed decisions to optimize patient outcomes and address platelet transfusion challenges more efficiently (85, 86). Furthermore, flow cytometry can serve as a diagnostic tool for immune PTR by analyzing the patient's blood for specific markers indicative of an immune response against transfused platelets. These markers include the presence of anti-platelet antibodies and activated T cells in the patient's bloodstream (87, 88). By analyzing changes in these markers over time, doctors can determine if a particular treatment is working or if additional interventions are needed. Table 6 provides an overview of some studies and references that may be helpful in understanding the role of flow cytometry in the diagnosis and management of immune PTR.

5- NAVIGATING THE RISKS AND CHALLENGES OF IMMUNE-MEDIATED PLATELET TRANSFUSION REFRACTORINESS

Platelet transfusion is a commonly used treatment for various medical conditions. However, it can lead to complications, one of which is immune PTR. Patients may experience excessive bleeding from minor injuries, nosebleeds, or detect blood in their urine or stool. The risks associated with immune PTR include a higher likelihood of hemorrhage and the need for more frequent and higher doses of platelet transfusions. Consequently, patients may require additional medical interventions, such as surgical procedures or medications, to control bleeding effectively. It is essential for healthcare professionals to be vigilant in monitoring patients who undergo platelet transfusions to detect any signs of immune refractory response and promptly address it to minimize potential complications (36, 89, 90). The development of immune PTR is affected by multiple factors, such as years and pre-existing health issues, and the frequency of transfusions. Additionally, medications and prior transfusions can increase the risk of this condition. To mitigate complications, healthcare providers must closely monitor patients who undergo platelet transfusions, regularly assessing platelet counts and other relevant parameters. Prompt management of any adverse reactions is essential to prevent immune refractory. In certain cases, alternative treatments such as stem cell transplantation may be considered, although this possibility exists, it has not been done so far (4, 91-93). In cases where patients are refractory to platelet transfusion, alternative treatments may be explored. Likewise, immunosuppressive therapy has been employed as a treatment for patients with refractory thrombocytopenia, showing varying levels of effectiveness (94). However, these treatments come with their own risks and limitations and should only be utilized under the guidance of experienced healthcare providers.

6- Strategies for preventing immune-mediated Platelet transfusion refractoriness

Enhancing the management of immune PTR demands a comprehensive approach that integrates expertise from hematology, transfusion medicine, and immunology. This condition poses significant challenges, given that alloimmunization can result in platelet refractoriness in approximately 30% of patients who undergo multiple transfusions (95). Several approaches can be employed to prevent immune refractory reactions following platelet transfusions. Below are some strategies for preventing immune-mediated PTR:

- Minimize unnecessary platelet transfusions (96).
- Ensure the blood type of the donor be compatible with the recipient (97).
- Reduce exposure to HLA/HPA-mismatched platelets by using single-donor platelets (98).
- Use of leukoreduced, washed, and/or irradiated platelets (99).
- Consider prophylactic use of high-dose intravenous immunoglobulin (IVIg) in dose of 0.6 g/kg/d for five days (11).
- Conduct pre-transfusion screening for platelet-specific antibodies (100).

6-1-Determining the cause

Identifying the underlying reason is crucial for formulating suitable treatment approaches. For instance, patients with HLA antibodies may find benefit in receiving HLA matched platelets or undergoing desensitization protocols, whereas those with non-HLA antibodies may exhibit improved response with immunosuppressive therapy (101).

6-2-Blood product management

To ensure effective management of PTR, it may be essential to modify the type and quantity of blood products administered. This could entail using alternative platelet types, like single-donor apheresis platelets or washed platelets. Skillful management of blood products is critical in addressing PTR, and it is important to explore various

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options and approaches to minimize the risks associated with this condition. Here are a few examples of other products and techniques that can be utilized to lower the chances of PTR (Table 7) (102).

6-2-1-Single-donor apheresis platelets:

These platelets are obtained from a single donor using an apheresis machine, which isolates the platelets from other blood components and returns the remaining blood to the donor. Single-donor apheresis platelets offer a higher platelet count per unit volume when compared to pooled platelets. This increase in platelet count may potentially enhance the effectiveness of platelet transfusions in patients who do not respond adequately to standard pooled platelets (103, 104).

6-2-2-Washed platelets:

Washing platelets is a procedure that includes centrifugation and resuspension in saline to eliminate plasma and other potential contaminants that might trigger an immune response. This process reduces the risk of adverse reactions in patients who have developed antibodies against specific blood products or have encountered severe allergic reactions to platelet transfusions (11, 105).

6-2-3-Low leukocyte count products:

Low leukocyte counts products in PTR refer to the utilization of platelet products with fewer white blood cells (leukocytes) in patients who do not respond well to standard platelet transfusions. The aim of this approach is to prevent adverse reactions caused by leukocytes and enhance treatment effectiveness. Recent research has focused on understanding the mechanisms behind the prevention and optimization of treatment using low leukocyte count products in PTR (106). One identified mechanism is the reduction of alloimmunization, where the recipient's immune system perceives transfused platelets as foreign, leading to refractoriness. Leukocytes present in platelet products can trigger this immune response, but by using low leukocyte count products, the risk of alloimmunization is minimized, thus increasing the chances of a successful platelet transfusion. Another mechanism is the prevention of febrile non-hemolytic transfusion reactions (FNHTRs), which are characterized by fever and chills and often result from cytokines released from activated leukocytes during transfusion (107). Employing platelet products with reduced leukocyte counts helps minimize the release of these cytokines, reducing the occurrence of FNHTRs and improving patient outcomes. However, despite the potential benefits, there are challenges associated with the use of low leukocyte count products in PTR. One major challenge is the limited availability of such products. Producing platelet products with reduced leukocyte counts requires specialized techniques, which may not be widely implemented in all blood banks. This limited availability may hinder the widespread adoption of this approach and restrict its use in optimizing treatment for refractory patients (85, 108-110).

6-2-4-Gamma irradiation of platelets:

Gamma irradiation of platelets is a method employed to prevent transfusion-associated graft-versus-host disease (TA-GVHD), which can occur when immunocompromised recipients receive blood products containing viable T lymphocytes. While gamma irradiation does not directly reduce the risk of PTR, it is often used alongside other measures to manage this condition. Recent research has focused on comprehending the mechanisms involved in the prevention and optimization of treatment using this technique. One identified mechanism is the inactivation of lymphocytes, which can cause transfusion reactions. Gamma irradiation effectively eliminates these lymphocytes, thereby reducing the risk of adverse reactions. Overcoming these challenges is crucial to fully harness the benefits of gamma irradiation in the context of PTR (37, 111-113).

6-2-5- HLA-matched platelet transfusions

HLA matching is a valuable method to identify compatible platelets between donors and recipients. It is particularly useful for patients with a history of PTR or those at high risk of alloimmunization. Matching the patient's HLA type with donors having a similar HLA type significantly reduces the risk of alloimmunization and enhances the effectiveness of platelet transfusions, leading to a decreased need for additional transfusions. However, HLA matching comes with challenges, including limited availability of compatible donors, time constraints, and testing costs. Moreover, despite HLA-matched platelets, platelet transfusion refractoriness can still occur due to other factors like non-HLA alloantibodies (91, 114). Identifying HLA match typically requires laboratory testing (115). There are various methods available to determine HLA compatibility between a donor and a recipient, including:

Using fluorescently-labeled monoclonal antibodies, this technique detects HLA antigens on cell surfaces. The cells are then analyzed by flow cytometry, which measures the emitted fluorescence from each cell (116). These methods are commonly employed in clinical settings to establish HLA

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compatibility between a donor and recipient before transplantation (117, 118).

6-2-6- HPA-matched platelet transfusions

HPA matching is a technique used to prevent PTR in patients who require platelet transfusions. This method involves selecting platelets from a donor who lacks the specific HPA (Human Platelet Antigen) that the patient has developed antibodies against, thereby reducing the risk of PTR (119). HPA matching is commonly performed in patients with a history of PTR or those at higher risk of experiencing it. Although the occurrence of HPA antibodies leading to transfusion refractoriness is minimal, this potential needs to be explored when the majority of crossmatches show incompatibility or when HLA-matched transfusions fail. If antibodies against HPA are present, then donors with a known platelet antigen profile might be sought (44). However, the process can be challenging, requiring knowledge of the patient's HPA profile and access to a suitable donor pool. Limited availability of HPA-matched platelets can lead to delays in transfusion and potential complications for the patient. While HPA matching is a valuable strategy for preventing PTR in high-risk patients, its effectiveness in the treatment and management of existing PTR is still uncertain. Some studies suggest that HPA matching in the treatment of PTR may improve platelet recovery and clinical outcomes, but others show no significant benefits. As a result, the use of HPA matching in the treatment of PTR remains a topic of debate, and more research is needed to determine its efficacy in this context. Regarding methods used for identifying HPA compatibility, the following techniques are commonly employed in clinical settings before platelet transfusion or transplantation:

6-2-6-1-Serological typing:

This method uses antibodies to identify specific HPA antigens on the surface of platelets. The cells are mixed with known HPA antibodies, and agglutination or clumping is observed to determine HPA type (120).

6-2-6-2-DNA-based typing:

This approach involves analyzing the DNA sequence of HPA genes. Polymerase chain reaction (PCR) amplifies specific regions of the HPA genes, and sequencing is done to determine the individual's HPA type (121).

6-2-6-3-Functional assays:

These assays measure platelet function in response to certain stimuli like ADP or collagen. Platelets from both the donor and recipient are tested for their response to these stimuli, and any differences may indicate HPA incompatibility (122).

6-3-Immunomodulatory therapies:

Immunomodulatory therapies have emerged as potential treatment options for managing immune-mediated PTR. These therapies aim to enhance platelet transfusion response and increase platelet counts in refractory patients. The timing and dosage of immunomodulatory treatments significantly impact their effectiveness. Initiating therapy early, preferably before platelet transfusion, can help prevent further antibody production and subsequent platelet destruction. Close monitoring of platelet counts and clinical response is crucial to guide treatment decisions and adjust therapy as necessary. Below is a summary table (Table 8) of common immunomodulatory therapies used for immune-mediated platelet transfusion refractory. It is essential to understand that these are just a few examples of available therapies and may not be suitable for every patient. Treatment decisions should always be made in consultation with a healthcare provider (91, 123-126).

6-4- Alternative therapies:

In certain situations, alternative therapies such as thrombopoietin receptor agonists (TPO-RAs) or splenectomy may be considered to enhance platelet production or reduce platelet destruction. In this chapter, we will examine alternative therapies and management strategies for Immune-mediated PTR while also addressing the challenges associated with these approaches (127).

6-4-1- Thrombopoietin receptor agonists (TPO-RAs)

Thrombopoietin receptor agonists (TPO-RAs) have emerged as a promising treatment option for patients with PTR. Drugs like eltrombopag and romiplostim work by stimulating platelet production through binding to the thrombopoietin receptor, activating signaling pathways responsible for megakaryocyte proliferation and differentiation. This mechanism has proven effective in increasing platelet counts for patients with immune thrombocytopenia (ITP), chemotherapy-induced thrombocytopenia, and myelodysplastic syndromes. Despite their effectiveness, TPO-RAs come with certain challenges, such as an increased risk of thrombotic events, particularly

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in patients with pre-existing cardiovascular conditions. Additionally, the long-term safety of these agents is not fully understood, Therefore, while TPO-RAs offer promise in managing PTR, close monitoring and precise management are essential to ensure patient safety and optimize treatment outcomes (128-131).

6-4-2- Microparticle platelet:

Microparticle platelet therapy is a potential treatment approach for PTR, involving the use of small platelet Microparticle platelet therapy is a potential treatment approach for PTR, involving the use of small platelet fragments derived from donated blood. These microparticle platelets are believed to be effective in preventing PTR by stimulating platelet production, supporting platelet function, and inhibiting platelet destruction. A 2017 study published in Transfusion Medicine Reviews reported a significant improvement in platelet count and reduced need for platelet transfusions in patients who previously experienced PTR. This therapy operates by increasing platelet production, activating platelets, facilitating platelet adhesion, and modulating the immune response. However, more research is required to determine the therapy's overall efficacy and safety, as it is not yet widely used or approved by regulatory agencies. Nevertheless, further investigations are necessary to fully comprehend its mechanisms of action, establish optimal dosing and administration strategies, and ensure its safe use under the supervision of qualified healthcare providers (111, 132-134).

6-4-3- Splenectomy:

The spleen plays a crucial role in immune PTR, particularly in patients with chronic immune thrombocytopenia (ITP). As the site of platelet destruction and clearance, splenectomy is often performed to improve platelet counts in ITP patients unresponsive to initial therapies. However, some studies have indicated that splenectomy might worsen immune PTR in specific patients. One proposed mechanism for this phenomenon is that the spleen may act as a reservoir for platelet producing megakaryocytes. Following splenectomy, these megakaryocytes could be redistributed to other organs like the liver, leading to increased platelet destruction and reduced platelet production. Another potential explanation is that splenectomy might trigger changes in the immune system, leading to heightened platelet destruction through mechanisms like autoantibody production or complement pathway activation. Despite the potential risks associated with splenectomy, it remains a viable treatment option for many patients with immune PTR. In conclusion, the relationship between immune PTR and splenectomy is intricate and necessitates further investigation. Healthcare professionals should carefully assess the potential risks and benefits of splenectomy and other treatment options in managing patients with immune PTR (94, 125, 135).

6-4-4- Adoptive T-cell therapy:

Adoptive T-cell therapy has emerged as a highly promising treatment approach for refractory patients, harnessing the potential of platelet-specific T cells to enhance platelet recovery and mitigate the risk of alloimmunization (136). This innovative method aims to overcome the limitations of conventional treatments and deliver improved clinical outcomes for individuals with impaired platelet function. By infusing platelet-specific T cells, adoptive T-cell therapy seeks to restore normal platelet levels in patients who have shown inadequate responses to standard therapies. These infused T cells are engineered to specifically target and eliminate the underlying immune response against platelets, thereby promoting platelet production and enhancing overall platelet recovery (137). This targeted approach holds significant promise in effectively managing refractory cases and reducing the need for repeated transfusions. Additionally, adoptive T-cell therapy addresses the risk of alloimmunization in refractory patients. Alloimmunization, which involves the development of antibodies against transfused platelets, can complicate treatment and limit available options. However, by employing platelet-specific T cells, this therapy helps minimize the likelihood of an immune response against transfused platelets, thus reducing the risk of alloimmunization and its associated complications

6-5- Other Strategies

Despite significant advancements, addressing immune PTR remains a challenging task, with no unanimous agreement on the most effective treatment approaches. Table 9 provides an overview of some commonly employed methods in the management of PTR, outlining potential benefits and risks. Tailored treatment plans that consider individual patient factors, alongside continued research into innovative therapies, will play a pivotal role in enhancing outcomes for individuals with this condition. Below is a compilation of strategies aimed at optimizing the treatment and management of immune-mediated PTR.

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7- CONCLUSION:

This comprehensive review aimed to shed light on the causes, diagnosis, and management of PTR. By exploring both immune-mediated and nonimmune-mediated factors, a deeper understanding of this condition has been achieved. Nonimmune-mediated causes, such as fever, sepsis, drugs, and consumption coagulopathy, have been identified alongside immune-mediated causes involving platelet antibodies and HLA alloimmunization. Armed with knowledge of the root causes, targeted diagnostic and treatment strategies can now be employed to tackle this intricate condition. Advancements in laboratory techniques, including serological testing, flow cytometry, and genotyping, have significantly improved the diagnosis and detection of immune-mediated PTR. These tools enable early identification and appropriate management of patients at risk for platelet refractoriness. Managing the risks and challenges associated with immune-mediated PTR requires a multidisciplinary approach, considering patient history, HLA matching, and transfusion protocols to minimize its occurrence. Implementing preventive measures such as leukocyte reduction, and pre-transfusion compatibility testing can contribute to reducing the incidence of platelet refractoriness. Regarding treatment and management, various options are available, ranging from corticosteroids, immunosuppressants, plasmapheresis, rituximab, and intravenous immunoglobulin (IVIG) to washed platelets, low leukocyte count products, and HPA-matched platelets. Individual patient characteristics and underlying causes of PTR guide the selection of appropriate therapeutic interventions. Optimizing treatment and management strategies involves a personalized approach, tailoring the treatment to each individual's unique needs and reaction to treatment. Emerging therapies such as thrombopoietin receptor agonists (TPO-RAs), microparticle platelets, and stem cell transplantation show promise and warrant further investigation in the realm of PTR.

In conclusion, unraveling the mystery of PTR necessitates a comprehensive understanding of its causes, accurate diagnosis, and effective management strategies. This review has provided valuable insights into the enigma of platelet refractoriness, uncovering both nonimmune and immune-mediated factors. By implementing appropriate prevention measures and employing a targeted approach to treatment, healthcare professionals can improve patient outcomes and enhance transfusion practices.

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Conflict of interest

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