Review Article

Research progress on febrile non-hemolytic transfusion reaction: a narrative review

Hekong Wang[1#], Dangli Ren[2#], Hongtao Sun[2], Jiqin Liu[3]

[1]Department of Procurement Service, the Characteristic Medical Center of the Chinese People's Armed Police Force, Tianjin, China; [2]Institute of Nerve Trauma and Repair, the Characteristic Medical Center of the Chinese People's Armed Police Force, Tianjin, China; [3]Department of Clinical Laboratory, the Characteristic Medical Center of the Chinese People's Armed Police Force, Tianjin, China

Contributions: (I) Conception and design: H Wang, J Liu; (II) Administrative support: J Liu; (III) Provision of study materials or patients: H Wang; (IV) Collection and assembly of data: D Ren; (V) Data analysis and interpretation: H Wang, J Liu; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Hongtao Sun. Institute of Nerve Trauma and Repair, the Characteristic Medical Center of the Chinese Peoples Armed Police Force, 220 Chenglin Road, Dongli District, Tianjin, China. Email: chenmo333@163.com; Jiqin Liu. Department of Clinical Laboratory, the Characteristic Medical Center of the Chinese People's Armed Police Force, 220 Chenglin Road, Dongli District, Tianjin 300300, China. Email: 15900326882@163.com.

Background and Objective: About 1% of patients who receive blood transfusions will develop transfusion reactions. Febrile non-hemolytic transfusion reaction (FNHTR) is the most common type of transfusion reaction. It not only leads to misdiagnosis and delayed treatment, but also incurs a huge economic burden. This article reviews FNHTR systematically, aiming to make clinicians have a more comprehensive understanding of FNHTR and reduce the occurrence of this side effect.

Methods: A comprehensive search of the PubMed, Embase, and Cochrane Library databases was performed. Medical Subject Headings (MeSH) included Blood Transfusion, Transfusion Reaction, and Febrile Non-Hemolytic Transfusion Reaction. The searches and literature screening were performed by 2 researchers; any differences of opinion or results were resolved through negotiation.

Key Content and Findings: The pathophysiological mechanisms of FNHTR mainly included immune and non-immune pathways. The former was associated with antibodies against human leukocyte antigen (HLA) produced in transfused patients, while the latter was associated with cytokines released from blood products during storage. Women with a reproductive history and those patients with multiple blood transfusions were more likely to experience FNHTR. Primary hematologic disease, malignant disease, and transfusion with over 6 units of leukocyte-depleted packed red blood cells were independent risk factors for the development of FNHTR. FNHTR could be diagnosed by accompaniment of the fever symptom (body temperature ≥38 ℃, maybe an increase of body temperature of more than 1 ℃ compared with that before blood transfusion) during or within 4 hours after transfusion, or the presence of chills, shakes, headache, and nausea, among other symptoms. FNHTR should be mainly differentiated from other types of transfusion reactions with similar symptoms. Prophylactic strategies for the routine use of antipyretic drugs before transfusion remain controversial. Removal of leukocyte components from blood could reduce the incidence of FNHTR significantly.

Conclusions: The pathogenesis of FNHTR is mainly associated with anti-HLA antibodies and cytokines released from blood products during storage. Specific markers and effective detection methods for FNHTR are still lacking. Treatment for FNHTR is currently limited to antipyretic drugs, sedation, and other symptomatic treatment measures. More studies are warranted to focus on the pathological mechanism of FNHTR.

Keywords: Blood transfusion; transfusion reaction; febrile non-hemolytic transfusion reaction; review

Submitted Sep 13, 2022. Accepted for publication Nov 17, 2022.
doi: 10.21037/atm-22-4932
View this article at: https://dx.doi.org/10.21037/atm-22-4932

Introduction

Blood transfusion is a commonly used treatment in clinical practice. It has been reported that about 15% of patients receive blood component transfusions during hospitalization (1,2). Transfusion reaction is the most common complication of blood transfusion, with about a 1% overall incidence (3). Although the incidence is low, severe transfusion reactions can be fatal, with a mortality rate of 1/200,000–420,000 blood product units (4,5). Transfusion reactions could cause the adverse events in patients as well as a heavy financial burden on the healthcare system (6). Common transfusion reactions include allergic transfusion reaction, acute hemolytic transfusion reaction, delayed hemolytic transfusion reaction, delayed serological transfusion reaction, febrile non-hemolytic transfusion reaction (FNHTR), hypotensive transfusion reaction, sepsis transfusion reaction, transfusion-related circulatory overload, and transfusion-related acute lung injury (7).

Among the above transfusion reactions, FNHTR has the highest incidence (8,9), with an overall incidence of 1,000–3,000 per 100,000 (3). However, the incidence of FNHTR is related to the blood component transfused and whether it is a leukoreduced blood product (10). Moreover, the incidence of FNHTR for red blood cells and platelets has previously been reported as 0.33% and 4.6%, respectively (11). A study showed that the incidence of leukoreduced red blood cells before transfusion was 0.08%, and that of non-leukoreduced platelets was as high as 27.2% (12). FNHTR can result in fever, chills, tachycardia, and other symptoms in patients, which may also be confused with other febrile transfusion reactions and cause misdiagnosis. Once fever and other symptoms occur after transfusion, the routine treatments include suspension of blood transfusion and subsequent investigation. Therefore, in addition to delaying blood transfusion therapy, FNHTR also increases the implementation of unplanned clinical treatment measures, which may incur extensive consumption of medical resources and economic burden (13). A study in 2017 showed that among patients with FNHTR, 40% did not complete the established blood transfusion plan, 25% underwent chest imaging, 79% underwent microbial culture, and 15% were admitted directly to the hospital for further diagnosis and treatment of FHNTR, with an additional medical cost of $160/patient (10).

Therefore, it is of great clinical significance to conduct further studies on FNHTR. This article reviews and summarizes FNHTR from the aspects of epidemiology, pathophysiological mechanism, diagnosis and differential diagnosis, and prevention and treatment measures, with the intention to achieve more in-depth and comprehensive understanding of FNHTR among clinicians and reduce the occurrence of the most common transfusion reaction. We present the following article in accordance with the Narrative Review reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-4932/rc).

Methods

Retrieval strategies

A comprehensive search of the PubMed, Embase, and Cochrane Library databases was performed from database inception to May 2022. The MeSH terms used for search included Blood Transfusion, Transfusion Reaction, and Febrile Non-Hemolytic Transfusion Reaction. The literature inclusion criteria were as follows: (I) reports involving the epidemiology, pathophysiological mechanisms, diagnosis and differential diagnosis, preventive or therapeutic measures of FNHTR; (II) the article was an original study; (III) the language of the literature was English. The exclusion criteria were as follows: article types such as reviews, conference abstracts, and case reports. The searches were conducted by 2 researchers individually. After removal of duplicate literature, the articles were screened according to the relevance of the content. Different opinions or results were resolved through negotiation between the 2 researchers. The detailed search strategies were showed in *Table 1*.

Literature review

Pathophysiological mechanism

At present, it is generally accepted that the pathophysiological mechanism of FNHTR mainly includes 2 pathways: an immune pathway and a non-immune pathway (14). The former is associated with antibodies against human leukocyte antigen (HLA) produced in transfused patients, while the latter is associated with cytokines released from blood products during storage, and the number of cytokines is positively correlated with the length of blood product storage (10). Cytokines are associated with inflammatory responses including FNHTR. Addas-Carvalho *et al.* (15) detected higher serum levels of interleukin (IL)-1beta *in vivo* and higher promoter activity in FNHTR patients. Other potential mechanisms include human platelet antigen (HPA) and gene polymorphism.

Table 1 The search strategy summary

Items	Specification
Date of search	May 18, 2022 for the first time and Oct. 13, 2022 for the second time
Databases and other sources searched	PubMed, Embase, and Cochrane Library
Search terms used	Blood Transfusion, Transfusion Reaction, and Febrile Non-Hemolytic Transfusion Reaction
Timeframe	From database inception to Oct. 13, 2022
Inclusion and exclusion criteria	The literature inclusion criteria were as follows: (I) reports involving the epidemiology, pathophysiological mechanisms, diagnosis and differential diagnosis, preventive or therapeutic measures of FNHTR; (II) the article was an original study; (III) the language of the literature was English. The exclusion criteria were as follows: article types such as reviews, conference abstracts, and case reports
Selection process	HKW and DLR conducted the selection independently and consensus were reached through negotiation

FNHTR, febrile non-hemolytic transfusion reaction.

Anti-HLA antibodies

Muñiz Díaz *et al.* (16) serologically tested 100 patients with FNHTR, the majority of whom antibodies against HLA were detected in the blood, yet there were rare platelets and granulocyte-specific antibodies. A previous study had shown that one of the triggers of FNHTR is HLA-mediated antigen-antibody reactions (14). HLA antibodies are produced in the blood of patients after multiple blood transfusions or pregnancy in women. When the re-transfusion is conducted, HLA antibodies react with the binding of transfused leukocytes or platelets, which could result in the decomposition and release of pyrogens from leukocytes or platelets, and further cause fever and other symptoms. Further, if the donors have HLA antibodies inside their body, they could be transfused into the patients during blood transfusion and also lead to febrile reactions (17).

Leukocyte-derived cytokine

Except for the antigen-antibody pathway, cytokines with immunoinflammatory effects are considered the mediators of FNHTR. Two studies in the 1990s (18,19) showed that the cytokines involved include tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), IL-6, and IL-8, the main source of which came from the stored blood product itself. Moreover, the longer the storage time, the higher the cytokine levels. The fevers of FNHTR patients were found to be caused by the transfusion of blood products containing high levels of cytokines. The possible mechanism is that these cytokines are endogenous pyrogens and act directly on the thermoregulatory centers through the blood-cerebrospinal fluid barrier to raise the set-point temperature threshold (20). Due to the numerous pyrogenic cytokines, a large-scale screening of cytokines that may be involved in FNHTR was conducted as research progressed. Larsen *et al.* (13) examined a variety of cytokines in the blood from 20 patients who developed FNHTR after transfusion of leukoreduced blood cells, including IL-1b, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, IL-17, IL-18, TNF-a, TNF-b, sTNF-RI, sIL-6Ra, IFN-c, GM-CSF, and MCP-1. The results showed no statistically significant differences in inflammatory markers compared to pre-transfusion levels, except for the significant increment of IL-6. However, it was not suggested that only IL-6 is involved in the pathogenesis of FNHTR. There were several common cytokines that were not detected in this study, which may have been caused by the fact that the transfusion was leukoreduced blood cell and these leukocyte-derived cytokines were removed prior to transfusion. Meanwhile, it was also suggested that IL-6 is likely to be the most difficult to clear as well as the main endogenous pyrogen in the study.

Platelet antigen

Most of the above cytokines are derived from leukocytes. Previous studies have demonstrated that transfusion of leukoreduced blood products reduces the incidence of FNHTR (21,22); however, they are not completely avoided. Some researchers believe that besides leukocyte-derived cytokines, HPA, as a potential membrane antigen, may play an important role in FNHTR. In a study in 2017, HPA-2, HPA-3, and HPA-15 in the blood of 120 patients who

developed FNHTR were examined by the researchers with the specific polymerase chain reaction (PCR) and electrophoresis, for which the results showed that HPA-2 was significantly different between the FNHTR group and the control group in patients with infectious diseases or febrile neutropenia. It was suggested that HPA-2 may induce the development of FNHTR in patients with the above 2 complications (23).

Gene polymorphism

In addition to blood factors, there is a view that blood transfusion has the same point as transplantation, which is the transplantation of allogeneic cells or organ/s into the recipient. Graft-versus-host disease in organ transplantation is caused by an immune response, which is similar to transfusion reactions. A prospective cohort study in 2019 included 19 patients with transfusion reactions (15 patients with FNHTR) and 20 healthy controls. The genotyping analysis on genotype SNPs in the *CTLA4* gene was conducted by the investigators, which showed that 4 SNPs demonstrated differences in allele frequencies between patients and controls (24). The study suggested that because SNPs in costimulatory molecules may affect immunoregulatory mechanisms, it could play an important role in the pathogenesis of FNHTR.

In summary, although the pathophysiological mechanisms of FNHTR are basically clear, certain aspects remain unclear. Firstly, how to remove HLA antibodies from blood donors is a focus of ongoing research. Secondly, for leukocyte-derived cytokines, future studies should aim to clarify the certified factors involved in FNHTR in leukoreduced and non-leukoreduced blood products, respectively. Thirdly, the pathogenic mechanism and risk factors for HPA should be further clarified, and HPA-2 genotyping can be included in pretransfusion testing programs to improve transfusion safety. Finally, the relationship between transfusion-related gene polymorphisms and transfusion reactions have been proposed. There are some polymorphisms of inflammatory cytokine genes associated with FNHTR. An association of IL1RN*2.2 genotype with the occurrence of precocious FNHTR was detected by using polymerase chain reaction and restriction digestion or sequencing methods (15).

Risk factors

Gender and transfusion history

A total of 192 voluntary donors for HLA-associated antibodies were tested in a study in 2021, which showed that plasma from pluripara donors had a higher chance of containing anti-HLA antibodies, compared with nulliparous female and male donors (25). In addition, if blood products differ in HLA content from that of the patient, HLA antibodies could develop in the patient after transfusion and FNHTR may occur with the next infusion of the same HLA antigen (26). Therefore, FNHTR is more likely to occur in women with a reproductive history (27) and in patients with a history of multiple blood transfusions (28).

Risk factors identified in clinical studies

Menis *et al.* (29) included 4,336,338 elderly patients who underwent blood transfusion during hospitalization in a 2015 study. The statistical results showed that 2,517 developed FNHTR, for which the incidence was associated with age, gender, blood transfusion volume, and blood composition. The FNHTR rates decreased with advancing age in patients more than 65 years old. Patients who received red blood cell and platelet transfusions had a significantly higher incidence of FNHTR compared with those who received plasma transfusions alone. The results of multivariate regression analysis showed that massive transfusion, women, history of transfusion for more than 1 year, lymphoma, and leukemia were independent risk factors for FNHTR. Yanagisawa *et al.* (30) included 522 pediatric transfusions in a retrospective study of 2016. Multivariate regression analysis showed that the primary hematological diseases, malignant diseases, and transfusion with over 6 units of leukocyte-depleted packed red blood cells were independent risk factors for the development of FNHTR.

In clinical practice, when blood transfusion is necessary for pluripara, patients with a history of blood transfusion, massive blood transfusion, and patients combined with the above risk factors for their condition, the treating physician should pay special attention to the relevant symptoms and signs of patients; transfusion reactions should be identified promptly, their cause should be investigated, and effective intervention implemented.

Diagnosis and differential diagnosis

Exclusion is generally used for the diagnosis of FNHTR in clinical practice. FNHTR was defined by the International Society of Blood Transfusion and the International Hemovigilance Network (IHN) as the presence of fever (body temperature ≥38 ℃, or an increase of more than

1 ℃ from the pretransfusion temperature) during or within 4 hours after transfusion, or with fear of cold, chills, headache, and nausea and other symptoms, to the exclusion of hemolytic transfusion reactions, bacterial contamination, and other potential factors (31). Hemolytic transfusion reactions should be excluded after febrile transfusion reactions, and relevant tests should include Coombs' test and microscopic examination of plasma. Septic transfusion reactions, particularly following platelet transfusions, should be excluded in patients who do not improve after discontinuation of blood transfusions or use of antipyretics, have a body temperature rise of 2 ℃ or higher, or have new clinical signs of bacterial infection (32). FNHTR can be diagnosed when there are no other probable causes, such as underlying febrile illness, as well as the negative assessment and tests associated with hemolysis (3). The diagnostic criteria for FNHTR have been approximately the same in previous clinical studies. The following diagnostic criteria was used in a study (33) of 2004: (I) definite clinical symptoms, including a body temperature rise of 1 ℃ or more, with or without symptoms such as fear of cold and chills; and (II) the hemolytic transfusion reactions, allergic transfusion reactions, transfusion-related acute lung injury, and septic transfusion reactions are excluded. FNHTR was defined by Wang *et al.* (34) as fever (the body temperature increases ≥1 ℃), which can be associated with symptoms such as fear of cold, chills, hypertension, tachycardia, and dyspnea, without other clinical explanations. In some studies, the time for onset of FNHTR-related symptoms was specified, and it was usually used within 4 hours after transfusion (13). The severity of FNHTR is generally divided into 4 grades in accordance with the degree of body temperature elevation: Grade I ≤38 ℃; Grade II <39 ℃; Grade III <40 ℃; and Grade IV ≥40 ℃ (35).

FNHTR should be mainly differentiated from other types of transfusion reactions with similar symptoms. Acute hemolytic transfusion reactions may present with acute fever, with symptoms such as chills and dyspnea. However, hemolysis-related low back pain, hemoglobinuria, acute renal failure, shock, and other specific symptoms and signs may occur. Besides, a positive direct antiglobulin (Coombs') test can assist in making the definitive diagnosis (36). Severe allergic transfusion reactions may present with tracheospasm, respiratory distress, decreased blood pressure, and other systemic symptoms (37). However, histamine released from allergic reactions can cause rash, itching, urticaria, local angioedema, and other skin manifestations (38). Septic transfusion reaction is caused by bacterial contamination of blood products (platelets are the most common), with the most common symptoms of fever and chills, and specific manifestations are shown as the signs associated with systemic inflammatory response syndrome (SIRS), which can be diagnosed by bacterial culture and gram staining (39). Transfusion-related acute lung injury (TRALI) may have symptoms similar to FNHTR, such as fever, tachycardia, or hypertension; however, most patients may present with acute respiratory distress syndrome (ARDS) caused by the lung injury, including dyspnea and hypoxemia (40).

Preventive and therapeutic measures

For the prevention of FNHTR, the strategy of routine use of antipyretic drugs before transfusion is controversial. Some clinicians agree with the approach, while some researchers worry that the drug will mask other early symptoms of serious transfusion reactions. The use of pretransfusion antipyretics for the first time was investigated in a study of 2004, and the transfusion of nearly 120,000 units of blood products were reviewed and summarized by the researchers. The results showed that about 80% of patients had used prophylactic antipyretics before transfusion, with an overall incidence of 0.09% for FNHTR. The investigators believe that the application of antipyretic drugs before transfusion reduces the incidence of FNHTR, which could avoid unnecessary transfusion of blood from multiple donors to patients, and concurrently reduce waste. In addition, there is no evidence that antipyretic drugs mask other symptoms of serious transfusion reactions, such as acute hemolysis, septic shock, or TRALI (14). However, in 2005, 385 pediatric patients were transfused with 7,900 units of leukoreduced irradiated blood products, and the results showed that prophylactic antipyretic agents did not reduce the incidence of FNHTR (41). Recently, 3 randomized controlled trials (RCTs) were included in a published meta-analysis, the combined results of which suggested that routine use of paracetamol before transfusion does not prevent FNHTR. However, the effectiveness of the prevention strategy should be further evaluated in patients with a history of transfusion reactions (42). Another systematic review similarly found no evidence to support the prophylactic use of antipyretic agents, which did not recommend using prophylactic agents before transfusion of leukoreduced blood products (43). In recent years, the prevention and treatment strategies of FNHTR have shifted towards pathogenesis. A study had shown that removing leukocyte components from the

blood can significantly reduce the incidence of FNHTR when patients are transfused with packed red blood cells or platelets (34). However, the effectiveness of leukoreduction methods has been inconsistent in previous literature reports. Uhlmann *et al.* (44) investigated 36,303 patients with allogeneic red blood cell transfusion in 2001, and the statistical results showed that there was no significant difference in the incidence of FNHTR between transfused leukoreduced red blood cells and non-leukoreduced red blood cells. However, several subsequent published studies have shown that transfusion of leukocyte-depleted platelets or red blood cells could reduce the incidence of FNHTR by 50% (45-47). The timing of leukocyte removal can be prior to the storage or use of blood products. A study conducted in 2012 showed that pre-storage leukoreduction was superior to post-storage in reducing FNHTR (34). The current level of evidence for pre-storage leukoreduction is 1A (3), which removes not only donor leukocyte-derived cytokines, but also HLA and other antigens (8), to inhibit immune and non-immune pathways caused by FNHTR development. When the leukoreduction link is performed after blood product storage, patients present with a moderate inflammatory response, which indicates that leukocytes themselves and their secreted substances are likely to be involved in the pathogenesis of FNHTR (48). In 2021, a new study showed that ambient temperature during leukoreduction of blood products had an effect on the number of residual leukocytes and the incidence of FNTHR. Some 70 units of erythrocytes were divided into a room temperature group (22±2 ℃) and hypothermia group (4±2 ℃) by the researchers. After leukoreduction, the number of residual leukocytes was 0.1×10^6/U and 0.02×10^6/U in the room temperature group and hypothermia group, respectively. In addition, the incidence of FNHTR in patients transfused with hypothermic leukoreduced red blood cells (1/588) was significantly lower than that in room-temperature leukoreduced red blood cells (1/2,000) in the study. However, the difference did not reach the statistical significance (P=0.14) (49).

When the patient has fever, chills, and other symptoms after transfusion, and is suspected of FNHTR, the current conventional treatment measures include the following: First, immediately stop the blood transfusion, check medical documents, ABO blood group, and conduct the direct antiglobulin test (DAT). After hemolysis, sepsis transfusion reactions, and transfusion-related acute lung injury have been excluded, paracetamol and other antipyretic drugs may be given for fever, and pethidine may be given for fear of cold and persistent chills (50).

Conclusions

FNHTR has the highest incidence of all types of transfusion reactions and places a huge burden on patients and healthcare systems. In terms of pathogenesis, it is believed that it could be mainly associated with anti-HLA antibodies and cytokines released from blood products during storage. The future studies should clarify the specific factors that are involved in FNHTR in leukoreduced and non-leukoreduced blood products, respectively. In addition, the relationship between HPA and transfusion-related gene polymorphisms and transfusion reactions should be investigated in further in-depth study. A breakthrough is sought for the diagnosis and treatment of FNHTR. The risk factors include massive blood transfusion, women with a reproductive history, history of multiple blood transfusions, and previous hematologic disorders. The diagnosis of FNHTR is made by exclusion. There is still a lack of specific markers and effective detection methods. In clinical practice, hemolytic, septic, allergic transfusion reactions, and TRALI should be excluded for patients with fever, fear of cold, chills, and other symptoms after blood transfusion. It could not only delay the treatment of patients, but also increase medical costs. Future studies should start with the pathophysiological mechanism of FNHTR, explore specific diagnostic markers, achieve early and accurate diagnostic capability, and reduce unnecessary examination measures. In terms of preventive measures, the current evidence does not recommend to the routine use of antipyretic drugs before transfusion. The blood products, such as red blood cells and platelets, are effectively reduced in the incidence of FNHTR by removing white blood cells at low temperatures before storage. Treatment for FNHTR is currently limited to fever reduction, sedation, and other symptomatic treatment measures.

Acknowledgments

Funding: This work was supported by the Key Scientific Research Projects of Military Logistics (No. BWJ20J002).

Footnote

Reporting Checklist: The authors have completed the

Narrative Review reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-4932/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-4932/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Carson JL, Stanworth SJ, Dennis JA, et al. Transfusion thresholds for guiding red blood cell transfusion. Cochrane Database Syst Rev 2021;12:CD002042.
2. Godbey EA. Whole Blood Transfusion: Past, Present, and Future. Clin Lab Med 2021;41:659-67.
3. Delaney M, Wendel S, Bercovitz RS, et al. Transfusion reactions: prevention, diagnosis, and treatment. Lancet 2016;388:2825-36.
4. Abdallah R, Rai H, Panch SR. Transfusion Reactions and Adverse Events. Clin Lab Med 2021;41:669-96.
5. Bolton-Maggs PH. Bullet points from SHOT: key messages and recommendations from the Annual SHOT Report 2013. Transfus Med 2014;24:197-203.
6. Riley W, Smalley B, Pulkrabek S, et al. Using lean techniques to define the platelet (PLT) transfusion process and cost-effectiveness to evaluate PLT dose transfusion strategies. Transfusion 2012;52:1957-67.
7. Wang Y, Rao Q, Li X. Adverse transfusion reactions and what we can do. Expert Rev Hematol 2022;15:711-26.
8. Goel R, Tobian AAR, Shaz BH. Noninfectious transfusion-associated adverse events and their mitigation strategies. Blood 2019;133:1831-9.
9. Grandi JL, Grell MC, Areco KCN, et al. Hemovigilance: the experience of transfusion reaction reporting in a Teaching Hospital. Rev Esc Enferm USP 2018;52:e03331.
10. Cohen R, Escorcia A, Tasmin F, et al. Feeling the burn: the significant burden of febrile nonhemolytic transfusion reactions. Transfusion 2017;57:1674-83.
11. Geiger TL, Howard SC. Acetaminophen and diphenhydramine premedication for allergic and febrile nonhemolytic transfusion reactions: good prophylaxis or bad practice? Transfus Med Rev 2007;21:1-12.
12. Wood EM, Fox LC. Hot and bothered: management and outcomes for patients with febrile nonhemolytic transfusion reactions. Transfusion 2017;57:1639-41.
13. Larsen R, Sandhu N, Heegaard NHH, et al. Changes in circulating inflammatory markers following febrile non-haemolytic transfusion reactions to leucoreduced red cells. Vox Sang 2018;113:76-9.
14. Heddle NM. Pathophysiology of febrile nonhemolytic transfusion reactions. Curr Opin Hematol 1999;6:420-6.
15. Addas-Carvalho M, Salles TS, Saad ST. The association of cytokine gene polymorphisms with febrile non-hemolytic transfusion reaction in multitransfused patients. Transfus Med 2006;16:184-91.
16. Muñiz Díaz E, Madoz P, Pastoret C, et al. Non-hemolytic transfusion reactions of the febrile type. Sangre (Barc) 1990;35:18-25.
17. Giannoli C, Nguyen TK, Dubois V. HLA and transfusion: new approaches with Luminex™ technology. Transfus Clin Biol 2011;18:218-23.
18. Muylle L, Joos M, Wouters E, et al. Increased tumor necrosis factor alpha (TNF alpha), interleukin 1, and interleukin 6 (IL-6) levels in the plasma of stored platelet concentrates: relationship between TNF alpha and IL-6 levels and febrile transfusion reactions. Transfusion 1993;33:195-9.
19. Stack G, Snyder EL. Cytokine generation in stored platelet concentrates. Transfusion 1994;34:20-5.
20. Dinarello CA. Cytokines as endogenous pyrogens. J Infect Dis 1999;179 Suppl 2:S294-304.
21. Kadar JG. Leukocyte-reduced blood products. Curr Opin Hematol 1998;5:381-5.
22. Rajesh K, Harsh S, Amarjit K. Effects of Prestorage Leukoreduction on the Rate of Febrile Nonhemolytic Transfusion Reactions to Red Blood Cells in a Tertiary Care Hospital. Ann Med Health Sci Res 2015;5:185-8.
23. Chen DP, Wen YH, Lu JJ, et al. Human platelet antigens are associated with febrile non-hemolytic transfusion reactions. Clin Chim Acta 2017;474:120-3.
24. Wen YH, Lin WT, Wang WT, et al. Association of

CTLA4 Gene Polymorphism with Transfusion Reaction after Infusion of Leukoreduced Blood Component. J Clin Med 2019;8:1961.
25. Priyadarsini AJ, Dhawan HK, Sharma RR, et al. Prevalance of Anti-HLA antibodies in parous female blood donors: A pilot study from tertiary care hospital of North India. Asian J Transfus Sci 2021;15:16-20.
26. Brown CJ, Navarrete CV. Clinical relevance of the HLA system in blood transfusion. Vox Sang 2011;101:93-105.
27. Ortolano GA, Russell RL, Angelbeck JA, et al. Contamination control in nursing with filtration: part 2: emerging rationale for bedside (final) filtration of prestorage leukocyte-reduced blood products. J Infus Nurs 2004;27:157-65.
28. Mempel W, Böck M. Substitution of thrombocyte concentrates in polytransfused patients. Beitr Infusionsther 1993;31:81-5.
29. Menis M, Forshee RA, Anderson SA, et al. Febrile non-haemolytic transfusion reaction occurrence and potential risk factors among the U.S. elderly transfused in the inpatient setting, as recorded in Medicare databases during 2011-2012. Vox Sang 2015;108:251-61.
30. Yanagisawa R, Shimodaira S, Sakashita K, et al. Factors related to allergic transfusion reactions and febrile non-haemolytic transfusion reactions in children. Vox Sang 2016;110:376-84.
31. Wood EM, Ang AL, Bisht A, et al. International haemovigilance: what have we learned and what do we need to do next? Transfus Med 2019;29:221-30.
32. Jacobs MR, Smith D, Heaton WA, et al. Detection of bacterial contamination in prestorage culture-negative apheresis platelets on day of issue with the Pan Genera Detection test. Transfusion 2011;51:2573-82.
33. Ezidiegwu CN, Lauenstein KJ, Rosales LG, et al. Febrile nonhemolytic transfusion reactions. Management by premedication and cost implications in adult patients. Arch Pathol Lab Med 2004;128:991-5.
34. Wang RR, Triulzi DJ, Qu L. Effects of prestorage vs poststorage leukoreduction on the rate of febrile nonhemolytic transfusion reactions to platelets. Am J Clin Pathol 2012;138:255-9.
35. Yanagisawa R, Tatsuzawa Y, Ono T, et al. Analysis of clinical presentations of allergic transfusion reactions and febrile non-haemolytic transfusion reactions in paediatric patients. Vox Sang 2019;114:826-34.
36. Tinegate H, Birchall J, Gray A, et al. Guideline on the investigation and management of acute transfusion reactions. Prepared by the BCSH Blood Transfusion Task Force. Br J Haematol 2012;159:143-53.
37. Simons FE, Ardusso LR, Bilò MB, et al. World Allergy Organization anaphylaxis guidelines: summary. J Allergy Clin Immunol 2011;127:587-93.e1-22.
38. Harvey AR, Basavaraju SV, Chung KW, et al. Transfusion-related adverse reactions reported to the National Healthcare Safety Network Hemovigilance Module, United States, 2010 to 2012. Transfusion 2015;55:709-18.
39. Eder AF, Goldman M. How do I investigate septic transfusion reactions and blood donors with culture-positive platelet donations? Transfusion 2011;51:1662-8.
40. Vlaar AP, Juffermans NP. Transfusion-related acute lung injury: a clinical review. Lancet 2013;382:984-94.
41. Sanders RP, Maddirala SD, Geiger TL, et al. Premedication with acetaminophen or diphenhydramine for transfusion with leucoreduced blood products in children. Br J Haematol 2005;130:781-7.
42. Ning S, Solh Z, Arnold DM, et al. Premedication for the prevention of nonhemolytic transfusion reactions: a systematic review and meta-analysis. Transfusion 2019;59:3609-16.
43. Duran J, Siddique S, Cleary M. Effects of Leukoreduction and Premedication With Acetaminophen and Diphenhydramine in Minimizing Febrile Nonhemolytic Transfusion Reactions and Allergic Transfusion Reactions During and After Blood Product Administration: A Literature Review With Recommendations for Practice. J Pediatr Oncol Nurs 2014;31:223-9.
44. Uhlmann EJ, Isgriggs E, Wallhermfechtel M, et al. Prestorage universal WBC reduction of RBC units does not affect the incidence of transfusion reactions. Transfusion 2001;41:997-1000.
45. King KE, Shirey RS, Thoman SK, et al. Universal leukoreduction decreases the incidence of febrile nonhemolytic transfusion reactions to RBCs. Transfusion 2004;44:25-9.
46. Paglino JC, Pomper GJ, Fisch GS, et al. Reduction of febrile but not allergic reactions to RBCs and platelets after conversion to universal prestorage leukoreduction. Transfusion 2004;44:16-24.
47. Yazer MH, Podlosky L, Clarke G, et al. The effect of prestorage WBC reduction on the rates of febrile nonhemolytic transfusion reactions to platelet concentrates and RBC. Transfusion 2004;44:10-5.
48. Pagano MB, Ness PM, Chajewski OS, et al. Hypotensive transfusion reactions in the era of prestorage leukoreduction. Transfusion 2015;55:1668-74.
49. Mittal S, Chacko MP, Varughese S, et al. Laboratory

and clinical comparison of the efficacy of prestorage leukoreduction of red cells at cold versus room temperature. Transfusion 2021;61:2556-65.
50. Martí-Carvajal AJ, Solà I, González LE, et al. Pharmacological interventions for the prevention of allergic and febrile non-haemolytic transfusion reactions. Cochrane Database Syst Rev 2010;2010:CD007539.

Cite this article as: Wang H, Ren D, Sun H, Liu J. Research progress on febrile non-hemolytic transfusion reaction: a narrative review. Ann Transl Med 2022;10(24):1401. doi: 10.21037/atm-22-4932

