



# Febrile Nonhemolytic Transfusion Reactions

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## Definition

- A. Febrile nonhemolytic transfusion reactions (FNHTRs) are the development of an otherwise unexplained temperature increase of  $\geq 1^{\circ}\text{C}$  or  $2^{\circ}\text{F}$  from baseline or the onset of chills or rigors in a patient who is receiving a transfusion.
- B. FNHTRs also may develop in patients who have completed a transfusion within the past four to six hours.

## Incidence

- A. FNHTRs are reported in 0.5%–5% of all transfusions.
- B. FNHTRs are the most common complication of platelet transfusion.
  - 1. Incidence ranges from 1.7% to 31%.
  - 2. Higher incidences are seen in patients who have received multiple prior transfusions.
- C. Incidence may decrease with increased use of prestorage leukocyte-reduced blood products.
- D. Higher incidence of blood transfusion reactions occurs in patients with hematologic and malignant diseases.

## Risk Factors

- A. Previous transfusion
- B. Prior pregnancy
- C. History of previous FNHTR
- D. History of hematologic disorder or malignancy

## Pathophysiology

- A. Reaction is mediated by donor leukocytes and cytokines.

- 1. Transfusion recipient develops antibodies to human leukocyte antigens (HLAs) from prior exposure via previous transfusion or prior pregnancy. This process is called alloimmunization.
- 2. Recipient reacts to
  - a. HLAs on donor platelets and leukocytes
  - b. Platelet-specific antibodies.
- 3. The presence of donor leukocytes in transfused red blood cells and platelets is a major contributor to the development of refractoriness and alloimmunization in patients who have received multiple transfusions.
- 4. Cytokines are produced and accumulated during the storage of blood products by the leukocytes that contaminate red blood cell and platelet concentrates.
  - a. One unit of red blood cells contains approximately 1–2 billion leukocytes.
  - b. One unit of random donor platelets contains about 50 million leukocytes.
  - c. One unit of pheresed platelets contains between 1 million and 1 billion leukocytes.

- B. Macrophages, lymphocytes, and endothelial cells secrete cytokines.
- C. Leukocytes in platelet concentrates stored at room temperature generate and release pyrogenic cytokines that may directly cause febrile reactions.
  - 1. Transfusion of cytokines that have developed during storage is a major factor in platelet transfusion reactions.
    - a. Interleukin-1 $\beta$  (IL-1), IL-6, IL-8, and tumor necrosis factor- $\alpha$

have been measured in platelet supernatant.

- b. IL-1, IL-6, IL-8, and tumor necrosis factor- $\alpha$  mediate inflammatory responses and may act as direct pyrogens.
- c. Cytokines appear to be transfused with the plasma component of the blood product.
- 2. FNHTRs in red blood cell transfusions primarily are the result of HLA incompatibility of the donor leukocytes, which contaminate the red blood cell product.
- D. Leukoreduction removes more than 99.9% of leukocytes from cellular blood components.
- E. Reducing the number of leukocytes transfused with blood products can decrease incidence of FNHTRs.
  - 1. Blood products labeled as “leukocyte reduced” must meet certain criteria for maximum residual leukocyte content.
    - a. Red blood cells— $1.0 \times 10^6$
    - b. Platelets, pheresis— $1.0 \times 10^6$
    - c. Platelets— $1.6 \times 10^5$  per unit.Four to six units of pooled platelets must contain  $\leq 1.0 \times 10^6$  residual leukocytes.
  - 2. The U.S. Department of Health and Human Services’ Advisory Committee on Blood Safety and Availability recommended in February 2001 that universal prestorage leukoreduction of all nonleukocyte cellular blood components

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Digital Object Identifier: 10.1188/02.CJON.171-172