

# Hypersensitivity Reactions to Blood Components: Document Issued by the Allergy Committee of the French Medicines and Healthcare Products Regulatory Agency

PM Mertes,<sup>1</sup> A Bazin,<sup>2</sup> F Alla,<sup>3</sup> J Bienvenu,<sup>4</sup> C Caldani,<sup>5</sup> B Lamy,<sup>6</sup> D Laroche,<sup>7</sup> MF Leconte des Floris,<sup>8</sup> J-Y Py,<sup>9</sup> D Rebibo,<sup>10</sup> B Willaert,<sup>11</sup> P Demoly<sup>12</sup>

<sup>1</sup>Service d'Anesthésie-Réanimation, INSERM U961, Hôpital Central, CHU, Nancy, France

<sup>2</sup>Unité Hémo­vigilance, CHU Côte de Nacre, Caen, France

<sup>3</sup>Centre d'investigation clinique - Epidémiologie clinique, Inserm, Centre Hospitalier Universitaire de Nancy, Nancy, France

<sup>4</sup>Centre de Biologie Sud, Inserm U851, Université Lyon, Pierre Bénite, France

<sup>5</sup>Afssaps, DEMEB/Unité Hémo­vigilance, Saint Denis, France

<sup>6</sup>Agence Régionale de Santé de Bourgogne, Dijon, France

<sup>7</sup>Laboratoire de Biophysique, CHU Côte de Nacre, France

<sup>8</sup>Etablissement Français du Sang, Besançon, France

<sup>9</sup>Etablissement Français du Sang Centre Atlantique, Orléans, France

<sup>10</sup>Direction Médicale, Etablissement Français du Sang, La Plaine Saint Denis, France

<sup>11</sup>Afssaps, DEMEB/Unité Hémo­vigilance, Saint Denis, France

<sup>12</sup>Service de Pneumologie et Allergologie, INSERM U657, Hôpital Arnaud de Villeneuve, CHU, Montpellier, France

## ■ Abstract

These guidelines represent a consensus among experts on hypersensitivity reactions occurring after transfusion of blood components. They cover recognition, investigation, treatment, and prevention of such reactions. Implemented in France under the auspices of the French Medicines and Healthcare Products Regulatory Agency (AFSSAPS) and based on current knowledge, research, and experience, they aim to provide effective and easily teachable means of further improving the quality of hemovigilance databases, promote interest in this field, and help identify possible mechanisms and at-risk patient groups.

**Key words:** Anaphylaxis. Blood component. Diagnosis procedure. Hypersensitivity.

## ■ Resumen

Estas guías clínicas representan el consenso alcanzado por los expertos en reacciones de hipersensibilidad que tienen lugar tras la transfusión de hemoderivados. Regulan el reconocimiento, la investigación, el tratamiento y la prevención de dichas reacciones. Aplicadas en Francia bajo el auspicio de la Agencia Reguladora de Medicamentos y Productos Sanitarios (AFSSAPS) francesa y basadas en el conocimiento, la investigación y la experiencia actuales, pretenden presentar un método eficaz y fácil de enseñar para seguir mejorando la calidad de las bases de datos de hemovigilancia, promover el interés por este ámbito y ayudar a identificar los posibles mecanismos y grupos de pacientes de riesgo.

**Palabras clave:** Anafilaxia. Hemoderivado. Procedimiento diagnóstico. Hipersensibilidad.

## Introduction

The French Medicines and Healthcare Products Regulatory Agency (AFSSAPS) is responsible for overseeing all medicinal products marketed for human use in France, including cosmetics, biomaterials, drugs, and biological products such as blood components (BC). Hypersensitivity reactions can occur after the transfusion of any BC, and, although rare, may have very serious consequences. Several pathogenic mechanisms are involved, and no standardized diagnostic procedure is currently available. The reporting of all adverse reactions associated with blood transfusion is mandatory in France, and a comprehensive database now exists. Adverse reactions are reported to a local hemovigilance correspondent (physician), who then records the details (always ensuring patient anonymity) in the on-line electronic e-FIT database, which is in turn analyzed by the AFSSAPS central hemovigilance unit.

In 2008, the AFSSAPS convened a group of experts charged with the task of analyzing nationwide data on hypersensitivity reactions occurring after BC transfusions in order to provide guidelines on the recognition, investigation, treatment, and prevention of such reactions.

The questions put to the group of experts were as follows:

- What defines a hypersensitivity reaction to a BC, how frequently do they occur, and what are the underlying pathogenic mechanisms involved?
- When should an allergic reaction be suspected, and how can the diagnosis be confirmed?
- How should a hypersensitivity reaction to a BC be managed (treatment excluded)?
- How should the resulting data be processed and applied?

Detailed responses to the above questions were provided by BC specialists (hemovigilance correspondents, hematologists, blood transfusion center physicians). Owing to the relative scarcity of publications on this subject, it was felt that, in order to raise interest, promote discussion, and help identify at-risk patient groups, the information obtained should be posted on the AFSSAPS website [1].

## What Defines a Hypersensitivity Reaction to a Blood Component, How Frequently Do They Occur, and What Are the Underlying Pathogenic Mechanisms Involved?

### Definition of an Allergic or Allergic-Type Hypersensitivity Reaction

A diagnosis of allergy is made when suggestive clinical signs appear during or after a transfusion. Indeed, the revised nomenclature for allergy of the European Academy of Allergy

and Clinical Immunology and the World Allergy Organization [2] restricts the diagnosis of allergic hypersensitivity to reactions secondary to an immunological process. The diagnosis of nonallergic hypersensitivity is reserved for cases where an immunological mechanism is not proven. BC specialists are often unfamiliar with the revised nomenclature and still refer to allergic or allergic-like/allergic-type reactions, for any reactions resembling a clinical allergy.

The distinction between an allergic and allergic-type reaction corresponds to the definition of drug hypersensitivity reactions as allergic and nonallergic [2]. The use of these definitions is encouraged; however, for practical reasons, the group of experts acknowledged that nonspecialists may continue to use the term allergy before further investigation.

Allergic reactions to BC comprise not only common hypersensitivity reactions (urticaria/angioedema, bronchospasm, anaphylaxis), but also alloimmunization, febrile nonhemolytic transfusion reaction, transfusion-related acute lung injury, graft-vs-host disease, posttransfusional purpura, and transfusion-associated autoimmune hemolytic anemia, all of which require their own specific investigations and shall not be discussed in the present document.

## Pathophysiology

Allergy is a hypersensitivity reaction mediated through immunological mechanisms that enable an allergen to stimulate the production of antibodies and activation of lymphocytes in a predisposed individual. The antibodies most often involved in the immunologically mediated hypersensitivity response are immunoglobulin (Ig) E (IgE-mediated allergy), produced by plasma cells, and more rarely IgG or IgM. Following the binding of the allergen to the IgE molecules bound on the surface of mast cells and basophils, preformed and newly synthesized mediators are activated and released. This initiates the cascade that results in the clinical manifestation of allergy.

The principal mediators of IgE-mediated allergy primarily responsible for mucocutaneous, cardiovascular, respiratory, and gastrointestinal signs and symptoms are as follows:

- Histamine and tryptase (preformed mediators)
- Leukotrienes and prostaglandins (newly formed mediators)
- Platelet-activating factor and cytokines (eg, interleukin [IL] 4, IL-5, IL-10, IL-13, tumor necrosis factor [TNF]  $\alpha$ )

These mediators and others may be released by non-IgE mechanisms and mimic allergy.

The pathophysiology of reactions to BCs remains poorly understood, insufficiently investigated, and complicated by its multifaceted nature. Three sources of mechanisms have been described, namely, recipient-related, donor-related, and blood-related.

### Recipient-Related Mechanisms

The antibodies of the recipient may react with an allergen contained in the BC. Several examples have been described [4-12], as follows: antierythrocyte (Chido and Rodgers

antibodies), anti-IgA in a patient with IgA deficiency, antihaptoglobin in a patient with haptoglobin deficiency, anti-factor VIII, anti-C3, anti-C4, antialbumin, antifibrinogen, anti-ethylene oxide, anti-hexamethylene diisocyanate, antibody to components of transfusion or sampling devices, antibody to plasma proteins of a different allotype, and antibody to free or plasma protein bound molecules (eg, antipenicillin antibody in a patient who received BC containing  $\beta$ -lactams).

#### Donor-Related Mechanisms

The transfused BC may contain the antibodies or the lymphocytes of a sensitized donor and will trigger a reaction in the recipient if he/she is then exposed to the allergen. Examples have been described [13,14], for example, transfusion of donor food-specific IgE antibodies to a recipient eating the culprit food, transfusion of donor animal dander specific IgE antibodies to a recipient in contact with the animal shortly after the transfusion, transfusion of a BC containing antipenicillin antibody to a recipient later treated with penicillins.

#### BC-Related Mechanisms

The BC may contain mediators accumulated during storage that may trigger a reaction mimicking allergy (nonallergic hypersensitivity). Many examples exist, including histamine (whereby the amount present is proportional to the length of time the BC is stored), bradykinins, serotonin, complement fractions (C3a, C3b), cytokines, chemokines, and other mediators (eg, platelet factor 4,  $\beta$ -thromboglobulin, RANTES, MIP-1 $\alpha$ , and interferon [IFN]  $\gamma$ ).

## Epidemiology

Analysis of the AFSSAPS database on adverse reactions to BCs showed that during the period 2000-2007, reactions

resembling allergy represented 26.1% of all adverse reactions. Using an in-house scale of 0-4 on which 2 is possible and 4 certain, the probability of a reaction being due to a BC was 2-4. The incidence of adverse reactions was 0.6/1000 transfused BCs, although this varied greatly depending on the specific product transfused (Table 1). There were 6 deaths (5.6%) during the same period.

## How Should an Allergic Reaction Be Suspected and the Diagnosis Confirmed?

### Positive Diagnosis

A hypersensitivity reaction is suspected if 1 or more of the following clinical signs appear during or up to 4 hours after the transfusion.

#### Mucocutaneous signs

- Urticaria (localized or generalized)
- Generalized edema
- Pruritus
- Angioedema of the face or mucous membranes (Quincke edema)

#### Cardiovascular signs

- Tachycardia or bradycardia
- Arrhythmia
- Hypotension
- Collapse, cardiac arrest

#### Respiratory signs

- Cough
- Dyspnea, wheezing
- Bronchospasm
- Cyanosis
- Hypoxemia

Table 1. Number of Hypersensitivity Reactions per 1000 Transfused Blood Products

| Type of BC | 2000 | 2001 | 2002 | 2003 | 2004 | 2005 | 2006 | 2007 | 2000-07 |
|------------|------|------|------|------|------|------|------|------|---------|
| RCC        | 0.22 | 0.20 | 0.20 | 0.23 | 0.22 | 0.18 | 0.17 | 0.17 | 0.20    |
| PPC/SPC    | 2.05 | 2.35 | 1.69 | 1.93 | 1.23 | 1.27 | 1.04 | 1.02 | 1.48    |
| PPC-SC     |      |      |      |      |      | 0.68 | 0.84 | 0.73 | 0.75    |
| PPC-A      |      |      |      |      |      |      | 0.20 | 0.29 | 0.26    |
| APC        | 4.68 | 5.01 | 5.04 | 5.40 | 5.59 | 4.95 | 4.35 | 4.33 | 4.91    |
| APC-SC     |      |      |      |      |      | 3.07 | 3.46 | 2.87 | 3.10    |
| APC-A      |      |      |      |      |      |      | 1.02 | 0.83 | 0.89    |
| Plasma     | 0.29 | 0.32 | 0.25 | 0.35 | 0.36 | 0.30 | 0.29 | 0.36 | 0.31    |
| Plasma-SD  | 0.15 | 0.17 | 0.14 | 0.15 | 0.09 | 0.17 | 0.19 | 0.17 | 0.16    |
| Plasma-p   | 0.44 | 0.48 | 0.34 | 0.50 | 0.52 | 0.38 | 0.37 | 0.49 | 0.44    |
| Plasma-A   |      |      |      |      |      |      |      | 0.17 | 0.17    |
| Total      | 0.54 | 0.56 | 0.55 | 0.62 | 0.63 | 0.56 | 0.50 | 0.50 | 0.56    |

Abbreviation: APC, apheresis platelet concentrate; APC-A, apheresis platelet concentrate in preservative solution-amotosalen inactivated; APC-SC, apheresis platelet concentrate in preservative solution; BC, blood component; Plasma-A, plasma-amotosalen inactivated; Plasma-p, plasma-protected; Plasma-SD, plasma-solvent detergent virus inactivated; PPC, pooled platelet concentrate; PPC-A, pooled platelet concentrate-amotosalen inactivated; PPC-SC, pooled platelet concentrate in preservative solution; RCC, red cell concentrate; SPC, standard platelet concentrate.

**Gastrointestinal signs**

- Nausea
- Vomiting
- Diarrhea
- Abdominal pain

**Other clinical signs**

- Malaise, anxiety, feeling of impending doom
- Rhinitis, conjunctivitis
- Dysphagia
- Dysphonia
- Dizziness

In order to facilitate analysis and to define the severity of the reaction, we propose a classification as grade 1, 2, 3, and 4, in accordance with other international anaphylaxis classifications [15-17] (Table 2).

Table 2. Severity of Immediate-Type Hypersensitivity Reactions to a Blood Component

| Grade | Symptoms  |
|-------|---|
| 1     | Generalized mucocutaneous signs: erythema, urticaria, angioedema  |
| 2     | Involvement of at least 2 organ systems: mucocutaneous signs, cardiovascular symptoms (moderate hypotension), respiratory symptoms (cough, dyspnea, bronchospasm), gastrointestinal involvement |
| 3     | Cardiovascular collapse (shock, tachycardia or bradycardia or arrhythmia) with or without symptoms of grade I or II   |
| 4     | Cardiac or respiratory arrest, death (due to inadequate resuscitation)  |

The most common signs of a reaction are mucocutaneous. Less commonly, allergy may be suspected in the presence of isolated cardiovascular, respiratory, or gastrointestinal signs with no evidence of mucocutaneous signs, especially if these occur in combination or are severe.

### Differential Diagnosis

In the absence of mucocutaneous manifestations, a differential diagnosis must be made. A thorough examination of the full range of signs and symptoms, together with consideration of comorbid conditions and prior treatment, will make for a more accurate diagnosis.

The differential diagnoses that should be eliminated in specific situations are as follows:

*Isolated Gastrointestinal Symptoms*

Bacterial contamination often results in gastrointestinal irritation and can be associated with hemodynamic and temperature changes.

*Isolated Respiratory Symptoms*

The appearance of respiratory symptoms and signs should prompt one to consider transfusion-related acute lung injury or fluid overload and the appropriate investigations should be carried out.

*Isolated Shock*

In the event of a shock occurring during transfusion, the diagnoses to be taken into account and systematically investigated without delay are as follows:

- Anaphylactic shock
- Shock due to immunological incompatibility (ABO)
- Septic shock due to bacterial contamination
- Other causes of shock, depending on the clinical context (eg, cardiogenic, hypovolemic)

The diagnosis will eventually be based on the response to appropriate specific treatment, clinical progress, and laboratory results.

## How Should a Hypersensitivity Reaction to a BC Be Managed?

### Approach to the Patient

Patient management should be prompt and in accordance with hospital protocols. The group of experts proposes the immediate and nonimmediate procedures described below:

*Immediate Procedures*

- Stop the transfusion
- Secure intravenous access
- Disconnect and keep the BC, according to hospital protocol
- Check vital signs (pulse rate, blood pressure, temperature, respiratory rate, and oxygen saturation); this should be done at least every 15 minutes or more often, depending on the situation
- Administer supportive drugs according to standard guidelines
- Inform the blood transfusion center immediately (for advice on preventive measures for the future)
- Alert official hemovigilance personnel
- Where there is suspicion of bacterial contamination of the BC, the pack should be sent to the microbiology department in accordance with hospital protocol

In the case of grade 3 and 4 reactions:

- Take blood samples for serum histamine and tryptase measurement at 3 time points as detailed below:

| Time of sampling   | <30 min   | 30 min to 2 h | >24 h               |
|--------------------|-----------|---------------|---------------------|
| Substance measured | Histamine | Tryptase      | Tryptase (baseline) |
| Type of tube       | EDTA      | EDTA or plain | EDTA or plain       |

- Take blood samples to measure IgA and anti-IgA antibodies in case of IgA deficiency.
- The supplementary form should be completed (Annex 1).

#### *Nonimmediate Procedures (Secondary Prevention)*

- Previous reactions to a BC should be detailed in the patient file.
- The strategy relating to transfusion is determined by the attending physician and those responsible for the administration of the transfusion, in consultation with the transfusion center physician and hemovigilance specialists.
- The strategy should be selected on a case-by-case basis, taking into account previous allergic reactions. Remember that later expressions of the condition may be much more serious than previously insignificant episodes.
- Detailed instructions on close monitoring during further transfusions should be given and should include at least monitoring of blood pressure and heart and respiratory rates every 15 minutes.
- Even though prophylactic premedication is frequently prescribed, its benefit has not been scientifically demonstrated.
- Prior removal of plasma from the BC should be discussed with a senior hematologist (eg, in the case of patients with a deficit of IgA, plasma removal is mandatory).
- The same patient should not undergo transfusion with BCs from the batch where the culprit BC originated. Similarly, avoid transfusing units from donors who donated to that same batch
- Where an allergic reaction occurs in association with transfusion of a product containing MB-plasma, no further transfusion should be undertaken pending a full investigation to rule out sensitivity to any components of this complex, in particular methylene blue.
- These investigations are carried out regardless of histamine and tryptase levels (and even if these are not measured). The investigations consist of skin tests (prick and intradermal) and in vitro tests (Annex 1).

### Approach to the BC

There is no available scientific evidence to justify the recommendation to destroy all BCs issued from the batch in which the sensitizing BC originated.

Because of the absence of scientific evidence, we recommend the following steps:

- In the case of transfusion from a common donor pool, an investigation of hypersensitivity reactions should be undertaken and should involve any recipients of BC from this pool.
- A note is made in the donor(s) file, except if the BC concerned is a pooled platelet concentrate or solvent detergent plasma.

### Approach to the Donor

A definitive approach to the donor has not yet been established or validated in the medical literature, although the group of experts proposes the following suggestions:

- Trace the donor sources associated with a severe reaction.
- Exclude donors previously suspected or known to have caused several severe reactions (this blood should now be sent for fractionation and further analysis).
- In the light of current knowledge, no additional measures are recommended for the donor, with the exception of severe reactions involving MB pathogen-attenuated frozen plasma (MB-plasma).
- The suggestions of the group of experts are set out below.

### How Should the Resulting Information Be Processed and Applied?

After gathering all the information relating to the reaction, transfusion can be identified as the cause with greater certainty, especially after taking into account the following factors:

- Administration of other substances (drugs, solutions, antiseptics, radiocontrast media)
- Chronology of symptom onset; after the beginning of the transfusion or after the administration of other substances and treatments
- Type of BC
- Previous history of allergy (other than that due to transfusion)

Causality assessment guides are proposed in Table 3.

Table 3. Causality Assessment Guides

| Clinical Characteristics   | Probability That the Blood Component Caused the Reaction |
|--|--|
| Presence of another possible triggering factor and a prior hypersensitivity reaction to this factor      | Excluded or not doubtful according to the chronology     |
| Clinical symptoms occurring more than 4 h before the transfusion   | Excluded or not doubtful                                 |
| Presence of another possible triggering factor without evidence of prior hypersensitivity to this factor | Possible   |
| Absence of another triggering factor and absence of laboratory confirmation of the role of the BC        | Likely   |
| Absence of another triggering factor and presence of laboratory confirmation of the role of the BC       | Certain  |

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### ■ PM Mertes

Service d'Anesthésie-Réanimation  
CHU de Nancy, Hôpital Central  
29 Avenue de Lattre de Tassigny  
54035 Nancy Cedex, France  
E-mail: [pm.mertes@chu-nancy.fr](mailto:pm.mertes@chu-nancy.fr)

## Annex 1. Supplementary information file in case of an allergic reaction of severity grade $\geq 3$

File number:

Completion date:

– Age /\_/\_/\_/\_/

Sex /\_/\_/

– Previous history of allergy YES  NO  UNSURE

*If yes, indicate (urticaria, rhinitis, asthma, anaphylactic shock, other):*

If allergen identified, specify:

– Previous adverse reactions to a BC YES  NO  UNSURE

*If yes, indicate date, diagnosis, severity and the BC received for each event:*

*No. of the adverse reaction files: .....*

– Previous transfusion with MB-plasma YES  NO  UNSURE

*If yes, indicate the quantity and dates:*

– Previous exposure to methylene blue YES  NO  UNSURE

*If yes, indicate the nature of the exposure:*

– Premedication YES  NO  UNSURE

*If yes, indicate the timing and type:*

– Start time of the transfusion: /\_/\_/\_/ : /\_/\_/\_/

– End time of the transfusion: /\_/\_/\_/ : /\_/\_/\_/

– Time of onset of symptoms: /\_/\_/\_/ : /\_/\_/\_/

– Indicate the chronology of the BC(s) administered and the medications administered during the 6 hours before and 6 hours after the onset of signs. (Indicate precisely the timing of blood administration and the time when an adverse reaction was evident.):

.....  
 .....  
 .....

### 1. Symptoms

#### • General symptoms

– Temperature before transfusion: /\_/\_/ /\_/\_/ /\_/\_/ °C

– Temperature at the moment of the adverse reaction: /\_/\_/ /\_/\_/ /\_/\_/ °C

– Shivering YES  NO  UNSURE

#### • Mucocutaneous symptoms

– Localized urticaria YES  NO  UNSURE

– Generalized urticaria YES  NO  UNSURE

– Pruritus YES  NO  UNSURE

– Other exanthems YES  NO  UNSURE

*If yes, specify:*

– Angioedema (face, mucous membranes) YES  NO  UNSURE

(Quincke edema)

*If yes, specify:*

– Others YES  NO  UNSURE

*If yes, specify:*

#### • Cardiovascular and hemodynamic symptoms

– Blood pressure (BP) before transfusion: /\_/\_/ /\_/\_/ /\_/\_/ /\_/\_/ mm Hg

– BP at the time of the adverse reaction: /\_/\_/ /\_/\_/ /\_/\_/ /\_/\_/ mm Hg

– Heart rate (HR) before transfusion: /\_/\_/ /\_/\_/ /\_/\_/ beats/min

– HR at the time of the adverse reaction: /\_/\_/ /\_/\_/ /\_/\_/ beats/min

– Shock YES  NO  UNSURE

– Arrhythmia YES  NO  UNSURE

- Respiratory symptoms
    - Cough YES  NO  UNSURE
    - Dyspnea YES  NO  UNSURE
    - Bronchospasm YES  NO  UNSURE
    - Cyanosis YES  NO  UNSURE
    - Desaturation YES  NO  UNSURE
- If yes, specify:* SpO<sub>2</sub>: PaO<sub>2</sub>:

- Gastrointestinal symptoms
  - Nausea YES  NO  UNSURE
  - Vomiting YES  NO  UNSURE
  - Diarrhea YES  NO  UNSURE
  - Abdominal pain YES  NO  UNSURE

• Other signs  
 .....  
 .....

2. Laboratory results (initial report)

- ↳ Tryptase after adverse event: /\_/\_/\_/ μg/L. Indicate time sample taken /\_/\_/ h /\_/\_/
  - ↳ Tryptase at ≥24 h /\_/\_/\_/ μg/L
  - ↳ Histamine after adverse event: /\_/\_/\_/ nmol/L. Indicate time sample taken /\_/\_/ h /\_/\_/
  - ↳ IgA level: /\_/\_/\_/ g/L
  - ↳ If low, investigate anti-IgA:
  - ↳ Other investigations related to the adverse event:
- .....

3. Treatment administered

.....  
 .....

4. Outcome

.....  
 .....

5. Results of allergy tests

(performed 4-6 weeks after the event, particularly when MB-plasma is implicated)

- Skin tests Date:
  - to MB-plasma from the donor POSITIVE  NEGATIVE
  - to MB POSITIVE  NEGATIVE
  - Other (specify) POSITIVE  NEGATIVE
  
- Basophil activation test Date:
  - to MB-plasma from the donor POSITIVE  NEGATIVE
  - to donor-derived plasma POSITIVE  NEGATIVE
  - to MB POSITIVE  NEGATIVE
  - others (specify): POSITIVE  NEGATIVE