Pulmonary Transfusion Reactions

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Key Words

Acute lung injury · Transfusion reaction ·
Transfusion risks

Summary

Background: In recent years, pulmonary transfusion reactions have gained increasing importance as serious adverse transfusion events. **Methods:** Review of the literature. **Results:** Pulmonary transfusion reactions are not extremely rare and, according to hemovigilance data, important causes of transfusion-induced major morbidity and death. They can be classified as primary with predominant pulmonary injury and secondary as part of another transfusion reaction. Primary reactions include transfusion-related acute lung injury (TRALI), transfusion-associated circulatory overload (TACO) and transfusion-associated dyspnea (TAD). Secondary pulmonary reactions are often observed in the wake of hemolytic transfusion reactions, hypotensive/anaphylactic reactions, and transfusion-transmitted bacterial infections. **Conclusion:** Knowledge and careful management of cases of pulmonary transfusion reactions are essential for correct reporting to blood services and hemovigilance systems. Careful differentiation between TRALI and TACO is important for taking adequate preventive measures.

Schlüsselwörter

Akute Lungeninsuffizienz · Transfusionsreaktion ·
Transfusionsrisiken

Zusammenfassung

Hintergrund: Pulmonale Transfusionsreaktionen haben in den letzten Jahren zunehmend als Auslöser von schweren Transfusionsreaktionen an Bedeutung gewonnen. **Methodik:** Auswertung der Literatur. **Ergebnisse:** Pulmonale Transfusionsreaktionen sind nicht extrem selten und stellen heute nach Hämovigilanzdaten wichtige Ursachen von transfusionsbedingten schweren Erkrankungen und Todesfällen dar. Man kann pulmonale Transfusionsreaktionen als primär oder sekundär klassifizieren, abhängig davon, ob die Lungenschädigung im Vordergrund steht oder eine andere Transfusionsreaktion, in deren Gefolge die Atemnot auftritt. Zu den primären pulmonalen Transfusionsreaktionen werden die transfusionsassoziierte akute Lungeninsuffizienz (TRALI), die transfusionsbedingte Volumenüberladung und die transfusionsassoziierte Dyspnoe gezählt. Sekundäre pulmonale Transfusionsreaktionen können im Gefolge von hämolytischen, anaphylaktischen und septischen Transfusionsreaktionen auftreten. **Schlussfolgerung:** Die Kenntnis der verschiedenen Formen pulmonaler Transfusionsreaktionen ist Voraussetzung für deren korrekte Meldung im Rahmen der Hämovigilanz. Insbesondere die Unterscheidung von TRALI und Volumenüberladung ist wichtig für das Ergreifen adäquater Vorsorgemaßnahmen.

Introduction

Pulmonary transfusion reactions have been observed since the very early beginning of blood transfusion. Manifestations of

transfusion-induced pulmonary reactions can be classified as primary and secondary reactions. Reactions with predominant pulmonary injury and respiratory distress are considered as primary pulmonary transfusion reactions, including transfu-

sion-associated circulatory overload (TACO), transfusion-related acute lung injury (TRALI), and transfusion-associated dyspnea (TAD) (table 1). Secondary pulmonary transfusion reactions occur in the wake of another transfusion reaction in which the lung is not the mainly affected tissue. These include hypotensive/anaphylactic reactions, hemolytic transfusion reactions and transfusion-transmitted bacterial infections.

Transfusion-Related Acute Lung Injury

TRALI is a serious, often life-threatening pulmonary transfusion reaction characterized by non-cardiogenic lung edema, hypoxemia and respiratory distress in temporal association with blood transfusion. Since Barnard's initial description in 1951 [1], non-cardiogenic lung edema related to transfusion has been widely reported using various designations until, in 1983, Popovsky et al. [2] coined the term 'transfusion-related acute lung injury' (TRALI) to emphasize the similarity in pathophysiology with the syndrome of acute lung injury (ALI) seen in critically ill patients. With the first analysis of a large series of 36 patients reported in 1985 by Popovsky and Moore [3], TRALI was recognized as a distinct clinical entity. The relevance of TRALI for blood transfusion became more evident in 1990 when Sazama [4] published that 15% of 355 transfusion-associated fatalities reported to the United States Food and Drug Administration in the period from 1976 through 1985 were caused by acute pulmonary injury, representing the second most common cause of transfusion-associated death in the USA. Later, this finding was confirmed by another analysis [5]. However, a broader recognition of TRALI was gained only after publication of the results of the British 'Serious Hazards of Transfusion' (SHOT) initiative which consistently demonstrated since 1996 that TRALI is one of the most common causes of transfusion-associated major morbidity and death [6].

Clinical Features, Diagnostic Criteria, Incidence, Treatment and Prognosis

TRALI is typically characterized by respiratory distress, hypotension, fever and cyanosis appearing within minutes to just a few hours from the initiation of the relevant blood transfusion (table 2). In rare, atypical cases, TRALI has been reported to occur later [7]. In artificially ventilated patients TRALI presents with hypoxemia, i.e. a sudden drop of the arterial oxygen tension, and sometimes copious frothy edema can ooze from the endotracheal tube. The anesthesiologist often comments that the lungs 'feel heavy' and are difficult to ventilate as the systemic blood pressure simultaneously begins to decrease, occasionally quite precipitously. These initial symptoms are caused by the onset of pulmonary edema. The subsequently performed chest radiograph shows bilateral general-

Table 1. Pulmonary transfusion reactions

Primary pulmonary transfusion reactions	Secondary pulmonary transfusion reactions
TACO	allergic/anaphylactic transfusion reactions
TRALI	transfusion-transmitted bacterial infections
TAD	hemolytic transfusion reactions

Table 2. Characteristics of TRALI

Features	Frequency
Respiratory distress	virtually all
Hypoxemia	virtually all
Bilateral lung infiltrations in chest radiograph	virtually all
Cyanosis	very common
Hypotension	very common
Fever	common
Hypertension	unusual
Occurrence > 6 h after initiation of transfusion	unusual

ized lung infiltrations. The florid radiologic picture is often described as 'white lung'. There is sometimes a remarkable dichotomy between the florid radiologic picture accompanying significant oxygen desaturation and the paucity of auscultatory findings.

Discrepancies in hemovigilance reports resulted in the development of a consensus view based on which symptoms should be considered to be a sine qua non for a diagnosis of TRALI. The European Haemovigilance Network (EHN) suggested i) the occurrence of respiratory distress within 6 h of initiation of transfusion, ii) the absence of signs of circulatory overload, and iii) the radiographic evidence of new bilateral pulmonary infiltrates. These are basically the criteria that Popovsky and Moore proposed in 1985 [3]. The Canadian Consensus Conference in Toronto in 2004 added the criteria iv) hypoxemia ($\text{PaO}_2/\text{FIO}_2 < 300$ mm Hg or pulse oximetry $< 90\%$ or other clinical evidence) and v) no presence of other risk factors for ALI [8]. If there is another ALI risk factor present, 'possible TRALI' should be diagnosed. For the clinician faced with a patient who might have TRALI, several other conditions need to be considered in the differential diagnosis: i) underlying pulmonary diseases, ii) underlying heart disease such as congestive heart failure, iii) TACO, iv) allergic or anaphylactic reactions, and v) all the risk factors for ALI.

The incidence per unit transfused has been reported as 1:5,000 for antibody-mediated TRALI [3] and 1:1,120 for non-immunogenic TRALI [9]. The SHOT committee recently calculated an incidence for plasma and platelets of 1:75,000 to 1:88,000 and for red cells of 1:557,000 [10]. However, due to underreporting, misdiagnosis, different quality of blood components, and varying criteria used for the diagnosis of TRALI in hemovigilance schemes, the real incidence of TRALI is not established.

To date no formally structured, prospective trials of different treatments have been reported. In mild TRALI reactions oxygen support is sufficient whereas in severe TRALI artificial ventilation is required. Lung protective small tidal volume settings should be used for optimum ventilatory care. The frequently present arterial hypotension can often be managed with intravenous fluid alone. Although vigorous diuretic treatment is used in ALI, their use is not recommended in TRALI as patients who are significantly hypotensive and need fluid support can experience worsening of their condition [11]. Concerning corticosteroid therapy, there are no convincing data to support or to refute it.

Typical episodes of TRALI improve within 48 h, although in a minority hypoxemia and pulmonary infiltrates can persist at least for 7 days [3]. There seems to be no sustained pulmonary injury [3]. Compared to ALI, the reported mortality rates of 1–10% in cases of TRALI are much lower [3, 6, 10].

Pathogenesis and Prevention

Currently the induction of TRALI is attributed to the passive transfusion of either leukocyte antibodies or neutrophil-priming substances accumulated in stored cellular blood components.

Since the description of leukoagglutinins in TRALI cases in the serum of one recipient and two donors by Ward in 1970 [12], the association of TRALI with leukocyte antibodies has been reported by a variety of authors. In their basic study, Popovsky and Moore [3] analyzed a series of 36 well-defined TRALI cases and 89% of them presented leukocyte antibodies. In *ex vivo* rat lung models, antibody-mediated TRALI could be reproduced [13, 14]; in addition, transfusion of plasma with leukocyte antibodies caused dyspnea and lung infiltration in healthy volunteers [15]. The implicated leukocyte antibodies are directed against human neutrophil alloantigens (HNA) and human leukocyte antigens (HLA) [16, 17]. These antibodies are mainly detected in blood components donated by (multi-)parous women. Neutrophil-agglutinating/aggregating antibodies such as anti-HNA-3a were frequently associated with severe or fatal cases of TRALI [16, 17]. Leukocyte antibodies that bind to, but do not agglutinate, neutrophils are thought to prime neutrophils so that they become rigid, owing to the polymerization of actin fibers in the cytoskeleton, and hyperreactive [17]. Since the diameter of 50% of the lung capillary segments is smaller than the diameter of a spherical neutrophil, neutrophils, even under physiologic conditions, have to change shape and squeeze through the narrow pulmonary capillaries. Therefore, neutrophil agglutinates and stiff neutrophils are thought to become mechanically entrapped in the lung capillaries. Mechanical sequestration of neutrophils has been shown to play a major role in the non-transfusion-related acute respiratory distress syndrome (ARDS). The trapped hyperreactive neutrophils release their cytotoxic microbicidal ar-

Fig. 1. In the threshold model, the occurrence of TRALI and its severity depends on the degree of neutrophil activation by the transfused TRALI mediators and the patient's individual susceptibility to TRALI. Accordingly, where the external stimulus to neutrophil activation is sufficient, lung damage can occur in otherwise healthy individuals with no other likely cause of lung injury. However, these cases are the minority because most patients receiving transfusions have significant co-morbidities, which may also affect the lung tissues. Early reports noted that most patients with TRALI had recently undergone surgery. The proposed threshold model of TRALI summarizes these factors as the strength of transfusion-related mediators (antibodies, lipids, etc.) on the one hand and as the individual predisposition of the transfusion recipient on the other hand, covering both constitutive (genetic) and co-morbidity-related factors (infection, disseminated intravascular coagulation, aspiration, shock, etc.). Depending on the magnitude of the neutrophil response, lung injury can be mild or severe, with corresponding clinical effects.

senal consisting of reactive oxygen species (ROS) and toxic enzymes. ROS and enzymes injure the pulmonary endothelium, resulting in an increased leakage of protein-rich fluid and neutrophil emigration. At first glance, the implication of antibodies to HLA class II antigens is surprising as these antigens are not expressed on resting neutrophils. However, there is increasing evidence that HLA class II antibodies first bind to monocytes with subsequent release of pro-inflammatory mediators and activation of neutrophils accumulated or sequestered in the alveolar capillary bed [18, 19]. Antibody-mediated TRALI occurs mainly after transfusion of fresh frozen plasma, frequently requires (~70%) mechanical ventilation (severe TRALI) and is not uncommonly fatal (6–10% of cases) [3, 6].

Non-immune TRALI occurs after transfusion of stored platelet and erythrocyte concentrates [9]. The neutrophil-priming substances include CD40 ligand, neutrophil-priming lipids such as the platelet-activating factor (PAF) and a number of other less well characterized agents [9, 20]. Non-immune TRALI requires the initial adherence of the patient's neutrophils to activated endothelial cells of the alveolar capillaries as a result of the patient's underlying disease. Transfusion of stored cellular blood components containing neutrophil-priming substances then activates the adherent and hyperreactive neutrophil, with subsequent release of the microbicidal arsenal and endothelial injury. Non-immune TRALI is characterized by a more benign clinical course, with oxygen support being sufficient in most cases. A mortality rate of about 1% was found in one study [9].

Table 3. Incidence of TACO

Reference	Study period	Type of blood components studied	Number of transfusion recipients studied	Type of patients studied	Calculated risk per 100,000 recipients
<i>Original data</i>					
Popovsky and Tuswell, 1985 [26]	1975–1982	RBC	not reported		31.6
Popovsky and Tuswell, 1985 [26]	1983–1984	RBC	2,832		141
Popovsky et al., 1996 [27]	1992–1993	RBC	382	orthopedic surgery	1047
Bierbaum et al., 1999 [28]	1996–1997	RBC	4,409	orthopedic surgery	6220
Rosencher et al., 2003 [29]	1999	RBC	2,762	orthopedic surgery	3000–4000
Rana et al., 2006 [30]	2003	all	1,352	medical and surgical ICU patients	1849
Gajic et al., 2006 [45]		all	916	medical ICU patients	7353
<i>Hemovigilance data</i>					
France	2000	cellular components			33.4
Québec	2000	RBC			42.2
Québec	2000	platelet pools			16.8

Neither transfusion of leukocyte antibodies nor non-immune neutrophil-priming substances will necessarily cause TRALI in the recipient. It is well known that the development of ALI also depends on the individual predisposition of the patient, which has recently been compiled in the threshold model of TRALI [17]. In this model the occurrence of TRALI and its severity depends on the degree of neutrophil activation by the transfused TRALI mediators and the patient's individual susceptibility to TRALI (fig. 1).

The use of leukocyte-reduced cellular blood products has diminished the number of immune TRALI reactions due to leukocyte antibodies in the recipient. Since in donor antibody-mediated TRALI the implicated blood component was usually donated by a multiparous woman, Thompson et al. [21] raised concern about the use of blood from multiparous donors as early as 1971. The adverse clinical effects of plasma from multiparous donors have been confirmed by Palfi et al. [22] in a prospective randomized controlled trial in which 105 intensive care patients, judged to need at least 2 units of plasma, were randomly assigned to receive 1 unit of control plasma and, 4 h later, a plasma unit from a multiparous donor, i.e. three or more live births, or to receive the plasma in opposite order. Transfusion of plasma from multiparous donors was associated with significantly lower oxygen saturation and higher tumor necrosis factor- α concentrations than transfusion of control plasma. One patient presented typical signs of TRALI immediately after transfusion of the first plasma unit which was from a multiparous donor who had formed granulocyte-specific antibodies. In 2003, the English National Blood Service therefore introduced a 'plasma from male donors only' policy. Although female plasma in stock was not withdrawn, the number of possible/likely TRALI reports dropped in 2004 and 2005 [23], indicating that this approach is able to reduce the number of severe leukocyte antibody-mediated TRALI reactions. In order to avoid shortages of plateletpheresis con-

centrates and blood group AB plasma, screening of parous female apheresis donors for leukocyte antibodies can reduce their deferral [24].

For non-immune TRALI, careful selection of fresh blood components for transfusion of patients at risk has been suggested, including the use of washed or fresh components. However, this raises a number of questions including potential adverse consequences which have to be addressed before preventive measures are established – especially in view of the usually mild clinical course of non-immune TRALI.

Transfusion-Associated Circulatory Overload

TACO has long been known as a complication of massive plasma transfusion as required in the treatment of patients with thrombotic thrombocytopenic purpura (TTP). In a study by Novitzky et al. [25], 5 of 10 patients treated with plasma infusion, but none of 9 patients treated with plasma exchange, experienced TACO. Although there is growing evidence that TACO is not an infrequent adverse event of blood transfusion and not restricted to TTP patients, only few studies have been conducted so far (table 3). The first retrospective study performed in 1985 at the Mayo Clinic by Popovsky and Tuswell [26] found an incidence of 1 in 3168 patients receiving red blood cell (RBC) transfusions; after installing a consultation service, the incidence was 1 in 708 patients during a 2-year period. The reported increase was undoubtedly related to increased awareness. The mean age of patients with volume overload was 60, and in 20% of patients, a single unit of RBCs was sufficient to precipitate TACO. A retrospective multi-institutional study of elderly patients undergoing total hip or knee replacement identified 4 of 382 patients with volume overload, even though the intra-operative blood loss was small with transfusion requirements of 1–2 units only. The mean age

in the study was 77 years, but 87 years for the patients who developed TACO [27]. Bierbaum and coworkers [28] analyzed data obtained from 9,482 patients with total hip or knee replacement, of whom 4,409 had a blood transfusion. Fluid overload necessitating the use of a diuretic occurred in 6.2% of patients receiving a transfusion, and in 4% of patients not receiving a transfusion. The mean age in the study was 67 years. Finally, the European OSTHEO study on blood management in elective knee and hip arthroplasty collected data on 3,996 patients with a mean age of 69 years, of whom 2,762 received blood transfusions. Volume overload was reported in 3 to 4% of these patients [29]. Only recently, Rana and coworkers [30] presented data on a retrospective analysis of 1,351 transfused patients on intensive care units (ICUs) at the Mayo Clinic in Rochester. Of these, 49 developed lung edema within 6 h after transfusion, of whom 7 had suspected TRALI, 17 possible TRALI, and 25 TACO (1.8%).

From these studies, it appears that the incidence of TACO can be expected to be in the range of 1,000–6,000 cases per 100,000 transfused patients, depending on age and co-morbidity. This seems to be in contrast to hemovigilance data reported so far. The French hemovigilance system reported 742 cases in 6 years of reporting [31]; for the year 2000, the calculated incidence rate was 33.4 per 100,000 recipients of cellular components. A comparable incidence is reported by HemaQuébec for the year 2000: 42.2 per 100,000 for recipients of RBCs and 16.8 per 100,000 for platelet pool recipients [31]. This may indicate that in hemovigilance schemes, TACO is currently under-appreciated and under-reported. The excellent British hemovigilance system (SHOT) has not yet introduced TACO as a separate category; accordingly, in the 2006 SHOT report, only 3 cases were identified. As a consequence, beginning 2008, TACO will be requested as a separate category and more reliable data on the incidence of TACO can be expected from this. However, it must be kept in mind that it will remain difficult to differentiate whether suspected TACO cases were indeed caused by excessive transfusion or whether worsening of cardiac function or coincident disruption of the underlying fluid balance did precipitate lung edema.

Pathophysiology

In the normal lung, fluid leakage occurs primarily through small gaps between capillary endothelial cells. The filtered fluid enters the alveolar interstitial space from where the fluid moves into the peribronchovascular system. It is removed by the lymphatics and returned to the systemic circulation [32]. Intravenous administration of blood, like any fluid, can cause circulatory overload resulting in a rise of the central venous pressure and, under some circumstances, heart failure. The amount of blood in the pulmonary vessels is increased, which results in elevated transvascular fluid filtration and, finally, lung edema. It has long been known that large volumes of

both crystalloid solutions and blood components are well tolerated by healthy individuals; however, even if arterial blood gases are still unchanged, alterations in the lung fluid balance may already be present [33]. There is evidence that many asymptomatic patients who develop TACO after transfusion had excess fluid before; transfusion may cause these patients to become symptomatic [34]. In addition, many patients who develop TACO are either advanced in years or very young, and a considerable number suffers from congestive cardiac or renal failure, all of which reduces the volume tolerance. These patients are especially at risk to develop TACO [35].

Clinical Presentation and Diagnosis

Most patients with TACO develop respiratory distress within 1–2 h of transfusion [35]. In addition, they frequently complain about chest tightness and headache; a dry cough is common. Clinical signs of TACO include tachypnea, tachycardia, cyanosis, and an elevated blood pressure. Because of the increased central venous pressure, an engorgement of neck veins can be seen. An S3 may be heard on cardiac auscultation as a correlate of fluid overload, and moist sounds on lung auscultation may indicate the presence of lung edema. The SHOT schema suggests that TACO should be taken into account if any 4 of the following 5 criteria occur within 6 h of transfusions [6]: acute respiratory distress, tachycardia, increased blood pressure, acute or worsening pulmonary edema, and evidence of positive fluid balance. The likelihood of the diagnosis increases if the patient is less than 3 years old or of advanced age and/or has a history of renal and/or cardiac failure. Clinically, monitoring of the central venous pressure, either frequently or continuously, provides a reliable guide for the diagnosis; arterial blood pressure and heart rate may add supplementary information.

Chest Radiography

The general appearance of a chest radiograph does not identify whether pulmonary edema is primarily hydrostatic or caused by disturbed permeability [36]. There have been studies demonstrating a correlation between the vascular pedicle width and the cardiothoracic ratio with an increase of the pulmonary artery occlusion pressure [37], but the sensitivity was low (<50%) and the use of this method in clinical routine must be questioned. Cardiomegaly may be seen on the chest radiograph but does not exclude any of the differential diagnoses.

Echocardiography

The left ventricular ejection fraction has a high sensitivity and specificity for the systolic function and can thus be helpful in identifying volume overload; diastolic dysfunction, which may lead to hydrostatic edema as well, cannot be ruled out by echocardiography [38].

Table 4. Parameters in the differential diagnosis between TRALI and TACO

Parameter	TRALI	TACO
<i>Clinical findings</i>		
Body temperature	fever may be present	unchanged
Blood pressure	hypotension	hypertension, posttransfusion systolic blood pressure elevation > 30 mm Hg
Pulse	+/-	tachycardia
Respiration	acute dyspnea	acute dyspnea
Neck veins	unchanged	distension may be present
Auscultation of the lung (heart)	crackles, paucity of findings	crackles, rales (S3 gallop may be present)
Fluid balance	+/-	positive
Response to diuretic	minimal, sometimes deterioration	significant
<i>Additional findings</i>		
Chest radiograph	new bilateral infiltrates	new bilateral (central) infiltrates, enlarged cardiac silhouette, Kerley's B lines
Echocardiography	normal or decreased ejection fraction	decreased ejection fraction
Pulmonary artery occlusion pressure	< 18 mm Hg	> 18 mm Hg
Central venous pressure	normal/unchanged	increased
Edema fluid	exudate	transudate
<i>Laboratory findings</i>		
WBC	transient leukopenia may be present	unchanged
BNP	< 100–200 pg/ml	> 500–1,200 pg/ml

Measurement of Pulmonary Artery Occlusion Pressure

Pulmonary artery occlusion pressure (PAOP) is an invasive procedure but, in expert hands, represents an excellent surrogate marker for the left atrial pressure. It has been introduced in clinical routine use for the diagnosis of ARDS [39]. In cardiogenic edema, PAOP is usually greater than 18 mm Hg, whereas it is less than 18 mm Hg in noncardiogenic edema. This PAOP limit is of course not 100% specific, and the PAOP may sometimes be greater than 18 mm Hg in patients with noncardiogenic edema [40]. However, there seems to be no significant benefit of PAOP over measurement of the central venous pressure [41].

Pulmonary Edema Fluid Protein Concentration

Pulmonary edema fluid protein concentration is more of an experimental parameter for the differential diagnosis between transudate and exudate. The pulmonary vascular barrier integrity can be tested by the pulmonary edema fluid protein concentration to plasma protein concentration ratio [42]. To obtain edema fluid, a catheter is inserted blindly into a distal airway, and fluid is sampled by suction. A ratio below 0.65 indicates the presence of a transudate (a hydrostatic edema). In two pediatric TRALI cases, a ratio above 0.75 was felt to be helpful in identifying noncardiogenic pulmonary edema [43]. However, the utility of this metric for distinguishing TRALI from TACO has not been evaluated in formal experiments [44].

Leukopenia

Leukopenia for TRALI has been demonstrated by different authors. It has not been reported for TACO. Church et al. [43] report transient, profound leukopenia in two children with TRALI.

An algorithm for the differential diagnosis of posttransfusion acute pulmonary edema has recently been suggested by Gajic and coworkers [45].

Differential Diagnosis

The differential diagnosis includes TRALI and ALI due to other causes, hemolytic and anaphylactic transfusion reactions, transfusion of bacteria-contaminated blood components, and cardiogenic failure. The latter four are normally associated with a decreased blood pressure, in contrast to TACO which is associated with an elevated blood pressure. Fever and transient leukopenia may be associated with TRALI, whereas an S3, heard on cardiac auscultation, and jugular venous distension are not to be expected in TRALI, but may occur with TACO or cardiogenic failure [44] (table 4). Patients with a known congestive heart failure are at risk for TACO as are patients with a positive fluid balance; however, TRALI is not ruled out by these findings [46].

Additional diagnostic procedures as outlined in 'diagnosis' may be necessary, especially in order to differentiate between TRALI and TACO. With regard to the latter, analysis of B-type natriuretic peptide (BNP) may be of interest. BNP is secreted from the ventricles in response to volume expansion and pressure overload [47]. In an emergency setting, BNP is a specific indicator of dyspnea from cardiac causes [48]. It is also an established marker for congestive heart failure [49]. BNP levels can be used to differentiate between cardiogenic and noncardiogenic pulmonary edema in patients with acute respiratory failure [50]: BNP levels below 100–200 pg/ml and above 500–1,200 pg/ml have an approximately 90% specificity.

ty for ALI and cardiogenic pulmonary edema, respectively [33, 50].

Two case reports demonstrated the possible utility of BNP to distinguish TRALI from TACO [51, 52]. Zhou et al. [53] demonstrated that a 0.5 increase in BNP following transfusion has a sensitivity of 81% and a specificity of 89% for the diagnosis of TACO; however, in this study, the authors were not able to compare their data to BNP levels in patients with TRALI. A variant of BNP, N-terminal pro-brain natriuretic peptide (NT-proBNP), has a longer half-life in circulation and is also more stable in laboratory samples. Tobian et al. [34] studied its usefulness as a diagnostic marker for TACO. Elevated posttransfusion NT-proBNP (>1,000 pg/ml) had a sensitivity of 93.8% and a specificity of 83.3% for the diagnosis of TACO. Again, a TRALI control group was not included. Two things should thus be kept in mind: i) BNP levels have not yet been investigated systematically in TRALI patients, and ii) in critically ill patients, a convincing association between PAOP as an indicator of volume overload and BNP levels was not found in all studies [54, 55].

Treatment, Outcome, and Prevention

Upright positioning of the patient and supplemental oxygen are the first steps in the treatment. If symptoms persist, a prompt reduction in plasma volume, usually by using a diuretic, is required. A certain percentage of patients will require intubation and positive pressure ventilation.

TACO is not a benign condition. Clinical consequences include hospitalization, greater intensity of care, and death [56]. The reported fatality rate is between 3.6 [31] and 20% [57]. As an occasional consequence, hypertensive encephalopathy has been reported in patients with circulatory overload [58].

Volume overload, be it by crystalloids or by blood, is best prevented by close attention to the state of the patient's circulation. Slow transfusion and, if necessary, administration of a diuretic may minimize the risk of heart failure and overloading the circulation. However, blood volume is greatly increased in patients with renal failure, who may not respond to diuretics.

Transfusion-Associated Dyspnea

Hemovigilance systems have occasionally received reports of cases with – usually mild – respiratory distress in timely association with transfusion, which they could not assign to the known pulmonary transfusion reactions. Therefore, the EHN suggested to introduce the term ‘transfusion-associated dyspnea (TAD)’ for these pulmonary transfusion complications [59], which will allow hemovigilance systems to classify all reported pulmonary transfusion reactions without the need for exceptions or the risk of inappropriate assignment.

Secondary Pulmonary Transfusion Reactions

Allergic/Anaphylactic Transfusion Reaction

Anaphylactic reactions are rapid and potentially dangerous reactions to an immunologically foreign substance in a sensitized person. Besides facial, laryngeal, and pharyngeal edematous swelling, skin rash, urticaria, fever, hypotension, gastrointestinal symptoms, and anaphylactic reactions frequently affect the respiratory system, mostly with bronchospasm. In a study of 273 consecutive allergic transfusion reactions, platelets caused the highest rate of allergic reactions, followed by fresh frozen plasma [60]. Of the 21 patients with severe allergic reactions, 13 (62%) had pulmonary symptoms, of whom 6 had documented hypoxia and 2 required intubation. In a series of 7 Japanese patients with anti-haptoglobin antibodies who developed an anaphylactic shock under transfusion, 6 patients (86%) had respiratory distress or arrest [61].

For the majority of these reactions, the underlying pathomechanism is unclear. Although anti-Chido/Rodgers [62, 63], anti-IgA [31] and anti-haptoglobin antibodies [61] in the recipient have been associated with allergic/anaphylactic reactions, it appears that the vast majority of reactions is not related to these antibody entities [64, 65]. Numerous substances released from white blood cells, including bioactive lipids and cytokines, may account for allergic/anaphylactic reactions [65], although a comparison of leukocyte depletion did not find differences with respect to allergic reactions [66, 67].

Bacterial Contamination

The transfusion of blood components contaminated with bacteria has been reported to be associated with fever, sepsis, septic shock, dyspnea, and ARDS. Bacterial contamination is critical for platelet components because they are stored at room temperature for up to 5 days, which does substantially support bacterial growth. However, severe reactions have also been reported after the transfusion of packed RBCs, in which psychrophilic bacteria may be enriched because they are stored at 4 °C.

Hemolysis

Intravascular hemolysis due to the transfusion of incompatible RBCs may present with dyspnea. In addition to dyspnea, patients with acute hemolysis usually experience nausea, back pain and skin flushing. Hemoglobinuria, fever, disseminated intravascular coagulation, and renal failure may be present. Dyspnea has been attributed to the activation of the complement cascade by antigen-antibody complexes [68].

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