INTRODUCTION: TRALI (transfusion-related acute lung injury) and TACO (transfusion-associated circulatory overload) are severe post-transfusion reactions with high hospital mortality, uncertainty in pathophysiologic mechanisms and a blurred clinical presentation often lead to these conditions being underdiagnosed or missed by clinicians. OBJECTIVE: To analyze and summarize the current understanding of the pathophysiology, differential diagnosis and treatment of TRALI and TACO syndrome. To highlight the best approaches and current practices to improve treatment efficacy and awareness among specialists. MATERIALS AND METHODS: Articles in the following databases were analyzed: PubMed, eLibrary. The main inclusion criteria were: free access to the full content of the publications, compliance with the review topics concerning pathophysiology, diagnosis and treatment of TRALI- and TACO-syndrome. Exclusion criteria: abstracts, conference proceedings and editorial letters, as well as publications not indexed in specialized abstract databases. RESULTS: This article presents the main reference points, thanks to which clinicians can make a differential diagnosis among posttransfusion complications and select the optimal treatment. Since TACO is a simulated cardiogenic pulmonary edema as a result of altered cytokine profile, and TRALI-syndrome is a consequence of specific immunologic conflict between donor and recipient after hemotransfusion, these conditions should be differentiated in the inpatient setting, and specialists should use the full range of modern laboratory and instrumental methods. CONCLUSIONS: Despite a large number of studies, the pathophysiologic mechanisms of TRALI and TACO remain somewhat unclear, and current approaches to diagnosis and treatment are not effective. Therefore, the existing gaps in the diagnostics of posttransfusion reactions should be clarified in further studies, and clinicians should be extra vigilant in their choice of diagnosis.
KEYWORDS: TACO, TRALI, post-transfusion complications, transfusion reaction, pathophysiology, diagnosis, circulatory overload

* For correspondence: Andrey I. Yaroshetskiy — MD, Ph.D., Sc.D, Professor, Pulmonology Department, Sechenov First Moscow State Medical University (Sechenov University), Moscow, Russia; e-mail: yaroshetskiy_a_i@staff.sechenov.ru

Introduction

To date, one of the leading causes of mortality associated with blood transfusion are transfusion-related acute lung injury (TRALI) and transfusion-associated circulatory overload (TACO) syndromes [1]. Historically, post-transfusion complications first attracted the attention of clinicians since 1930s, which were mainly explained in this category of patients by the presence of chronic diseases [2, 3]. However, in 1966 three cases of pulmonary edema were described in patients after blood transfusion without signs of left ventricular failure, and pulmonary edema was interpreted as a manifestation of an allergic reaction [4, 5]. Currently, it is customary to distinguish the classification of post-transfusion complications depending on the aetiology: infectious and non-infectious [6], as well as depending on the clinical manifestations: acute and delayed [7].

Objective

The aim of our study is to analyze and summarize current understanding of the pathophysiology, differential diagnosis and treatment of TRALI and TACO syndrome. To highlight the best approaches and current global practices to improve the effectiveness of treatment, diagnosis and specialist awareness of the pathophysiological processes involved in TRALI and TACO syndrome.

Materials and methods

Articles were analyzed by keywords (TRALI syndrome, TACO syndrome, circulatory overload) in the following databases: PubMed, elibrary. The main inclusion criteria were: free access to the full content of publications, relevance to the topic of the review regarding pathophysiology, diagnosis and treatment of TRALI and TACO syndrome. Exclusion criteria: abstracts, conference proceedings and editorial letters, as well as publications not indexed in specialized abstract databases. With the exception of the history of the description of the analyzed syndromes, the depth of the search was 40 years. In all the studies found, the bibliography was examined in order to identify additional, previously undiscovered publications. The date of the last search query was March 16, 2023. The recommen-
A state-of-the-art of the problem

TRALI-syndrome is an acute lung injury associated with transfusion of donor blood components, accompanied by pulmonary edema, hypoxia, fever and arterial hypotension within 6 hours after transfusion [8]. Vlaar A.P.J. et al. in 2019 also proposed to further divide TRALI-syndrome into two categories: TRALI-syndrome type I (without a risk factor for acute respiratory distress syndrome — ARDS) and TRALI-syndrome type II (with risk factors for ARDS). The range of reported cases had considerable variation due to different diagnostic criteria and a few studies [9, 10]. A decrease in the incidence of TRALI-syndrome was achieved after the implementation of a strategy to use predominantly male plasma for transfusion, as donation of plasma from multiparous women resulted in a higher mortality rate among recipients [11]. In contrast to European and North American countries, where transfusion policy is more liberal, which provokes a higher incidence of TRALI syndrome, Russia has more stringent indications for transfusion of fresh frozen plasma (FFP), which are mainly performed in surgical departments [12, 13]. Nevertheless, this does not exclude TRALI from the list of complications at all, and TRALI syndrome has to have a significant prevalence in Russia [14, 15].

TACO-syndrome, or transfusion-associated circulatory overload, is also one of the leading pulmonary complications of haemotransfusion, characterised by acute respiratory distress syndrome with signs of congestive heart failure, tachycardia, increased blood pressure and signs of positive fluid balance [16]. TACO-syndrome remains an undiagnosed complication to a greater extent than TRALI-syndrome [17]. In Russia, the counting of clinical cases of TACO-syndrome is not indicative, because there are no data in the Russian-language literature corresponding to diagnostic criteria, and differential diagnosis of TRALI and TACO-syndrome is difficult due to the lack of pathognomonic symptoms [18].

Pathophysiology

The pathogenesis of acute posttransfusion lung injury TRALI and TACO-syndrome is based on fundamentally different mechanisms. TRALI syndrome is characterized by donor-recipient immunological conflict during which antibodies to leukocyte antigens (HLA — Human Leukocyte Antigens) are produced or the presence of antileukocyte antibodies in transfused preparations [19]. This mediates...
the interaction of polymorphonuclear leukocytes (PNN — Polymorphonuclear Neutrophils) with endothelial cells of the vascular network against the background of an altered cytokine profile, including increased affinity of membrane proteins of beta-2 integrins (CD18), which allows neutrophils to adhere to the wall of pulmonary capillaries [20], leading to the release of intracellular proteases and edema [21]. In favor of this theory and the influence of the inflammatory genesis of the disease are the recorded increased post-transfusion levels of soluble CD40 ligand (sCD40L), an inflammatory mediator that can induce priming of PMN-oxidase, causing PMN-mediated endothelial damage [22].

Nonimmune genesis of TRALI syndrome is also possible, mediated by transfusion of preserved blood components containing lipids and/or cytokines, which cause granulocyte activation [23, 24]. In addition, the role of platelets in inducing the formation of neutrophil extracellular traps (NET — Neutrophil Extracellular Traps), consisting of modified chromatin and cytoplasmic hydrolases leading to direct pulmonary endothelial cytotoxicity and TRALI syndrome, respectively, has recently been widely discussed [25]. Also, it has been shown that concentrates of transfused platelets, including CD40-positive platelets, can alter the expression of nuclear factor κB (NF-κB), activating the production of interleukin-8 (IL-8) and monocyte chemotactic protein 1 (MCP-1), causing leukocyte recruitment to the inflammatory zone [26]. In this regard, the inflammatory mechanism in the pathophysiology of TRALI syndrome is a key.

TACO-syndrome, on the contrary, has no immunological component, and the pathophysiology of this condition is caused by increased hydrostatic pressure in the pulmonary circulation, which leads to fluid leakage into the alveolar space, mimicking the clinic of acute left-sided heart failure [27]. Nevertheless, TACO-syndrome cannot be named cardiogenic pulmonary edema, exclusively because it has been shown that patients with TACO-syndrome have an altered cytokine profile: for example, increased levels of IL-10 in recipients before transfusion have been described [28]. The same study reported previous elevated plasma levels of IL-6 and IL-8 in TRALI-syndrome patients compared to controls, and similar data have been found in other prospective studies [29, 30]. There are also observations that the pathogenesis of TACO syndrome involves inflammatory mechanisms that increase the negative impact on the cardiovascular system, due to which even a minor transfusion load leads to pulmonary edema [31, 32]. The hemolysis of erythrocytes increases proportionally with the storage time of erythrocyte mass, which increases cell-free encapsulated plasma hemoglobin [33]. Hemoglobin absorbs NO (nitric oxide) via a deoxygenation reaction, and NO reacts with oxyhemoglobin to form methemoglobin, reducing NO bioavailability, inducing cardiovascular dysfunction even without the effects of circulatory overload [34]. However, this hypothesis finds its opponents, so it is subject to clarification in the future [35].

Clinical presentation

In the literature, there are several algorithms for the diagnosis of TACO syndrome proposed by ISBT (International Society for Blood Transfusion) (Table 1) and NHSN (National Hemovigilance Safety Network) (Table 2) [36, 37].

Table 1. Definition of TACO syndrome according to the International Society for Blood Transfusion (ISBT-IHN-AABB 2018-International Society for Blood Transfusion-International Hemovigilance Network-Association for the Advancement of Blood & Biotherapies) [37]

<table>
<thead>
<tr>
<th>Patients with suspected TACO syndrome must demonstrate at least one mandatory criterion from onset or up to 12 hours after transfusion, and &gt; 3 criteria (mandatory* and/or optional)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute or worsening respiratory failure* or evidence of acute or progressive pulmonary edema* based on clinical examination, radiography</td>
</tr>
<tr>
<td>Cardiovascular changes not explained by the underlying disease, including the appearance of tachycardia, hypertension, distension of the jugular vein, cardiac shadow enlargement, peripheral oedema, or a combination of these</td>
</tr>
<tr>
<td>Signs of fluid overload and/or clinical improvement after administration of diuretics</td>
</tr>
<tr>
<td>Elevation of brain natriuretic peptide or N-terminal brain natriuretic peptide above the age standard and more than 1.5 times the pre-transfusion value</td>
</tr>
</tbody>
</table>

Table 2. Definition of TACO syndrome. National Haemodialysis Safety Network (NHSN 2016 — National Hemovigilance Safety Network Definition) [37]

<table>
<thead>
<tr>
<th>Occurrence or exacerbation of ≥ 3 of the following criteria within 6 hours of transfusion:</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARDS</td>
</tr>
<tr>
<td>Positive fluid balance</td>
</tr>
<tr>
<td>Elevated levels of brain natriuretic peptide (BNP)</td>
</tr>
<tr>
<td>Radiographic signs of pulmonary edema</td>
</tr>
<tr>
<td>Signs of left heart failure</td>
</tr>
<tr>
<td>Increased central venous pressure</td>
</tr>
</tbody>
</table>

In Russia, the diagnosis of TACO-syndrome is usually established by a combination of clinical manifestations during or after transfusion: peripheral oxygen saturation (SpO2) < 90% or partial pressure of oxygen (PaO2) / fraction of oxygen (FiO2) < 300 mm Hg, crepitation rales in the upper lung regions, increased filling and tension of the jugular veins, an intractable dry cough, dyspnea, forced body position-orthopneia, accessory respiratory muscles work during respiration, cyanosis, increased blood pressure (BP), headache [38],
TRALI syndrome is clinically characterized by acute respiratory failure, a PaO₂/FiO₂ less than 300 mm Hg or (SpO₂ less than 90 %), dyspnea, tachypnea, tachycardia, cyanosis, pulmonary rales, fever, hypotension or hypertension [39]. The diagnostic criteria for TRALI syndrome (Table 3) are better defined than for TACO syndrome; however, as can be seen, TRALI syndrome is sometimes almost impossible to distinguish clinically from TACO syndrome (Table 4).

### Instrumental diagnostics

The gold standard for the diagnosis of TACO syndrome used to be the measurement of pulmonary artery occlusion pressure. If this value is greater than 18 mm Hg, cardiogenic edema and TACO-syndrome, respectively, are more likely. However, the use of pulmonary artery catheterization as a method is rather niche, as it is non-specific and not associated with a positive outcome trend in these patients [40]. PAOP in patients with TRALI syndrome is usually within normal limits [41]. Computed tomography and standard radiography are also widely used: it allows you to assess the presence of pulmonary edema, which can be a characteristic of both TACO and TRALI, so it is a non-specific criterion in differential diagnosis. Aggravated history, increased pressure in the jugular vein and in the pulmonary circulation, as well as the presence of pleural effusions are more likely to confirm the diagnosis of TACO-syndrome [42]. In TACO syndrome, changes in the width of the vascular pedicle and cardiothoracic index (the percentage of the cross-sectional area of the cardiac shadow in relation

<table>
<thead>
<tr>
<th>Table 3. Revised diagnostic criteria Vlaar A.P.J., Toy P., Fung M., et al. [8]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TRALI syndrome type I patients who do not have risk factors for ARDS and fulfil the following criteria:</strong></td>
</tr>
</tbody>
</table>
| a. 1. Acute onset  
2. Hypoxemia (PaO₂/FiO₂ ≤ 300 mm Hg or SpO₂ < 90 %)  
3. Evidence of bilateral pulmonary edema on plain radiograph, computed tomography or ultrasonography  
4. No evidence of pulmonary arterial hypertension (PAH): mean pulmonary artery pressure greater than 25 mm Hg, pulmonary artery occlusion pressure (PAOP) ≤ 15 mm Hg, pulmonary vascular resistance > 3 WU; or if PAH is present but is not a major factor in hypoxaemia |
| b. Development within 6 hours of transfusion |
| c. No alternative source of risk for ARDS |

**TRALI syndrome type II — patients who have risk factors for ARDS or who already have mild ARDS (PaO₂/FiO₂ 200–300 mm Hg); worsening respiratory status associated with blood transfusion:**

a. The features described in categories a and b for TRALI syndrome type I, and  
b. Stable respiratory status 12 hours before transfusion

<table>
<thead>
<tr>
<th>Table 4. Comparison of clinical characteristics of TRALI and TACO</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Similar characteristics</strong></td>
</tr>
<tr>
<td>Indicator</td>
</tr>
<tr>
<td>Chest X-ray</td>
</tr>
<tr>
<td>Respiratory syndrome</td>
</tr>
<tr>
<td>Auscultation</td>
</tr>
</tbody>
</table>

| **Different characteristics** |
|-----------------------------|----------------|----------------|
| Body temperature | Often elevated | Often unchanged |
| Blood pressure | Hypotension | Hypertension |
| Pulmonary artery occlusion pressure | ≤ 18 mm Hg | > 18 mm Hg |
| Response to diuretics | Minimal | Significant |
| Pulmonary edema | Exudative | Transudative |
| White blood cell count in peripheral blood | Possible transient leucopenia | No change |
| Fluid balance | Normal, positive, negative | Positive |
to the internal cross-section of the chest) may be observed on radiographs: a vascular pedicle width of more than 70 mm together with a cardiothoracic ratio above 0.55 may predict a PAOP above 18 mm Hg [43]. Echocardiography is a useful method to confirm TACO syndrome: systolic ejection fraction < 45 %, as well as signs of hypertension in the small circulation [44]. Analysis of the ratio of protein concentration in alveolar fluid/plasma can theoretically indicate the presence of circulatory overload. A ratio below 0.65 indicates hydrostatic edema. At the same time, in TRALI syndrome, a ratio above 0.75 was considered specific for determining non-cardiogenic pulmonary edema [45].

Laboratory diagnostics

Transient leukopenia and thrombocytopenia are common laboratory symptoms in TRALI syndrome [46, 47]. Other changes in the peripheral blood are nonspecific. An important confirmation of TRALI syndrome is the presence of HLA class I antibodies, HLA class II antibodies, and anti-HNA antibodies [48]. The absence of antibodies does not categorically exclude the diagnosis of TRALI syndrome, although the presence of antibodies in plasma is almost certainly in favour of TRALI syndrome. B-type natriuretic peptide > 250 or BNP pre- / post-transfusion ratio > 1.5 or N-terminal pro-BNP > 1000 pg/ml has shown the greatest specificity and accuracy for the diagnosis of TACO syndrome [49, 50]. Klanderman R.B. et al. proposed to consider conversely a lower cut-off limit below which TACO for BNP less than 300 pg/ml or NT-proBNP less than 2000 pg/ml can be excluded [51].

When using BNP as a marker for differential diagnosis of TACO and TRALI, the situation is less clear: a study by Li G. et al. from 2009 showed that BNP levels are higher after transfusion in patients with TACO-syndrome (559 pg/ml) compared to patients with TRALI (375 pg/ml) and probable TACO (pTACO), but the authors, referring to the low AUC = 0.63 for BNP, concluded that the diagnostic accuracy of brain natriuretic peptide is low and cannot unequivocally exclude the diagnosis. The situation is the same with NT-pro-BNP, where the AUC was 0.70, despite the large difference between NT-pro-BNP in TACO and TRALI (5197 pg/ml vs 1558.5 pg/ml, respectively) [52]. This is in agreement with other studies that emphasized the usefulness of BNP, but warned clinicians to rely solely on BNP levels at the diagnostic stage [53]. Also, it is worth noting that BNP values may be elevated by other mechanisms associated with chronic heart failure decompensation [54]. It is also noteworthy that determination of type A natriuretic peptide (ANP) is rarely part of the diagnostic plan in TACO syndrome. It may potentially be of high value in the differential diagnosis because of its shorter half-life than BNP [50].

The role of inflammatory biomarkers is still a controversial issue: IL-10 elevation has shown the greatest effectiveness in the diagnosis of TACO-syndrome, and the serological profile of IL-6 and IL-8, according to some experts, can be used to differentiate other posttransfusion complications [28, 29]. A study by Roubinian N. H. et al. showed that five cytokines (IL-6, IL-8, IL-10, granulocyte-macrophage colony-stimulating factor — GM-CSF, and tumor necrosis factor-alpha — TNF-α) showed good discrimination of TRALI compared to TACO before and after transfusion (AUC = 0.88; 95% CI = 0.80; and AUC = 0.81; 95% CI = 0.71–0.91, respectively). Patients with TACO syndrome also have an altered cytokine profile, with elevated post-transfusion levels of IL-6 and pre-transfusion levels of IL-10. TRALI, on the other hand, is preceded by elevated plasma levels of TNF-α, IL-6, IL-8 and pre-transfusion levels of IL-8 [28].

A number of studies also mentioned other serological markers that may be useful in assessing the probability of TACO: plasminogen activator inhibitor, cystatin C [55], galectin-3 [56], but their diagnostic significance remain unclear. Elevated troponin C level may indirectly indicate volume overload, but troponin as biomarker may be elevated in acute heart failure, so they are supposed to be considered as a risk factor rather than a diagnostic marker [49]. A promising biomarker of cardiac dysfunction associated with TACO syndrome is the soluble isoform of ST2 (sST2), but the data to date are insufficient to unambiguously assess its applicability [57, 58].

Treatment

If TACO or TRALI syndrome is suspected, the transfusion should be stopped immediately, the blood service should be notified, the remaining blood components used in the transfusion should be stored for analysis, and the correct prescription of blood product should be rechecked on the basis of blood component labeling and patient identification to exclude blood incompatibility [59]. If SpO₂ < 90 % or PaO₂ < 60 mm Hg, oxygen therapy, non-invasive or invasive ventilation should be used, according to patient’s physiological data [60–62]. Currently, insufficient studies have been performed to provide definitive guidelines for optimal positive end-expiratory pressure (PEEP) in patients with TACO or TRALI. The benefits of higher PEEP values in these syndromes remain unclear, and anecdotal evidence suggests that a PEEP of 10 is not effective [63]. In TACO syndrome, diuretics may be effective in controlling symptoms by reducing pulmonary interstitial volume and reducing pulmonary congestion through venodilation [64]. Prophylactic administration of diuretics has no apparent efficacy despite safety in the absence of comorbidities [65–67]. Other options for pharmacotherapy in TACO syndrome have not been described.

The treatment of TRALI syndrome is symptomatic and often sufficient to resolve itself. However, in severe cases,
extracorporeal membrane oxygenation (ECMO) may be considered [68]. Many guidelines for the treatment of TRALI syndrome include information on the necessary administration of corticosteroids based on the immune-mediated genesis of the disease, but some studies have questioned such conclusions [69, 70]. Nevertheless, successful experience with high-dose steroids has been described elsewhere [71, 72]. The use of diuretics in the absence of signs of volume overload is contraindicated because TRALI syndrome is more often characterized by hypovolemia [73]. Some studies have reported successful symptom control with albumin administration [74]. A few successful cases of plasmapheresis in the treatment of TRALI syndrome has been reported [71, 75], but the method has not been validated in routine practice. Among the experimental methods for treatment of TRALI, one can highlight the study of Kapur R. et al. that showed association of the IL-10 deficiency in dendritic and T cells in vivo with worsening antibody-mediated acute lung injury in mice [76]. IL-10 administration prevented TRALI syndrome in mice and may potentially prove to be a promising new therapeutic approach [76].

Nevertheless, it is now better to focus on methods to prevent such conditions: to stratify risk factors before transfusion, to use leukoreduction techniques to reduce alloimmunisation, and, if possible, to avoid the use of fresh frozen plasma, platelets, packed red blood cells, and cryoprecipitate from female donors [77, 78].

**Conclusion**

This publication aims to highlight the strengths and weaknesses of current methods of treatment and diagnosis of TACO and TRALI syndrome. This review has shown that despite many studies, the pathophysiological mechanisms of TRALI and TACO syndrome remain somewhat unclear, and current approaches to diagnosis and treatment are not adequately effective. Therefore, clinicians should be extra vigilant in making the diagnosis. Future studies should focus on the immunological component of both conditions, as this may help to identify pathogenetic treatment for post-transfusion complications.

**Disclosure.** The authors declare that they have no competing interests.

**Author contribution.** All authors according to the criteria participated in the development of the concept of the article, obtaining and analyzing data, writing and editing the text of the article, checking and approving the text of the article.

**Ethics approval.** Not required.

**Funding source.** This study was not supported by any external sources of funding.

**Data Availability Statement.** Data sharing not applicable — no new data generated.

**Author's ORCID:**

Yaroshetskiy A.I. — 0000-0002-1484-092X

Savko S.A. — 0000-0001-9642-5377

Zhigulin G.M. — 0000-0001-8074-4461

**References**


[10] van Wonderen S.F., Klanderman R.B., Vlaar A.P.J. Understanding transfusion-related acute lung injury (TRALI) and its com-


Roubinian N.H., Hendrickson J.E., Triulzi D.J., et al. Incidence and clinical characteristics of transfusion-associated circulatory overload us-
Predicting the success of pulmonary edema
Transfusion-related circulatory overload — «new» adverse effect of blood transfusion.

Diagnostic approaches to acute transfusion reactions
Noninvasive Positive Pressure Ventilation

B-Type Natriuretic Peptide

Use of B-natriuretic peptide in risk stratification in acute heart failure

Acute cardiogenic pulmonary edema

The accuracy of natriuretic peptides (brain natriuretic peptide and N-terminal pro-brain natriuretic) in the differentiation between transfusion-related acute lung injury and transfusion-related circulatory overload in the critically ill

Association of cystatin C as a diagnostic marker in the differential diagnosis of transfusion-associated circulatory overload

Acute Lung Injury and Transfusion-Associated Circulatory Overload: Mutual

Transfusion-Related Acute Lung Injury (TRALI): Current Concepts

Acute Lung Injured (TRALI): Pathophysiology, Diagnosis and Treatment: A Review


Piccin A., Cronin M., Brady R., et al. Transfusion-associated circulatory overload in Ireland: a review of cases reported to the National


