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Transfusion-related Acute Lung Injury in Critically ill Patient

An essay

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List of Abbreviations

2,3-DPG	:	2,3 diphosphoglycerate
ABLE	:	Age of Blood Evaluation
ACEIs	:	Angiotensin converting enzyme
ALI	:	Acute lung injury
Anti-HLA	:	Human leukocyte antigen
Anti-HNA	:	Antibodies against human neutrophil antigen
APACHE II	:	Acute Physiology and Chronic Health Evaluation II
APRV	:	Airway pressure release ventilation
ARBs	:	Angiotensin receptor blockers
ARDS	:	Acute respiratory distress syndrome
BiPAP	:	Biphasic positive airway pressure
BNP	:	Brain natriuretic peptide
cGMP	:	Cyclicguanosine monophosphate
CINM	:	Critical illness neuromyophathy
CPAP	:	Continuous positive airway pressure
DNase 1	:	Deoxyribonuclease 1
EA	:	Elastase-L1-antitrypsin
ECLS	:	Extracorporeal lung support
ECMO	:	Extracorporeal membrane oxygenation
FACTT	:	Fluids and Catheters Treatment Trial
FFP	:	Fresh frozen plasma
FNHTR	:	Febrile nonhemolytic transfusion reactions
GAT	:	Granulocyte agglutination test
GIFT	:	Granulocyte immunofluorescence test
HETE	:	Hydroxeicosatetranoic acid
HFOV	:	High frequency oscillatory ventilation
HLA	:	Human leukocyte antibodies
HMVEC	:	Human microvascular endothelial cells
HNA	:	Human neutrophil antibodies
HTR	:	Hemolytic transfusion reaction
HUVECs	:	Human umbilical vein endothelial cells
ICAM	:	Intracellular adhesion molecules

List of Abbreviations (Cont.)

IL	:	Interleukin
LCT	:	Lymphocytotoxicity test
LPS	:	Lipopolysaccharide
LysoPCs	:	Lysophosphatidylcholines
MAIGA	:	Monoclonal antibody immobilization of granulocyte antigens
MHC-I	:	Major histocompatability complex-I
MPs	:	Microparticles
MT	:	Massive transfusion
NETs	:	Neutrophil extracellular traps
NIV	:	Non-invasive mechanical ventilation
NMBA	:	Neuromuscular blocking agent
NTBI	:	Non-transferrin bound iron
OR	:	Odds ratio
PAF	:	Platelet-activating factor
PAL-1	:	Plasminogen activator inhibitor-1
PC	:	Pressure control ventilation
PCs	:	Platelet concentrates
PEEP	:	Positive end-expiratory pressure
PKC	:	Protein kinase C
PLTs	:	Platelets
PMNs	:	Polymorph nuclear leukocytes
PRBCs	:	Packed red blood cells
PROWESS II:		Protein C Worldwide Evaluation in Severe Sepsis
PS	:	Phosphatidylserine
PTP	:	Post-transfusion purpura
RBCs	:	Red blood cells
RCT	:	Randomized controlled trial
RECESS	:	Red Cell Storage Study
ROS	:	Reactive oxygen species
TACO	:	Transfusion-associated circulatory overload

List of Abbreviations (Cont.)

TA-GVHD	:	Transfusion associated-graft versus host disease
TF	:	Tissue factor
TNF	:	Tumor necrosis factor
TRALI	:	Transfusion-related acute lung injury
TTBI	:	Transfusion Transmitted Bacterial Infections
UV-B	:	Ultraviolet-B

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Introduction

Transfusion-related acute lung injury (TRALI) is defined as acute-lung injury that is temporally related to blood and blood products transfusion, especially, it occurs in the first six hours following transfusion. TRALI is characterized by non-cardiogenic pulmonary edema, hypoxemia and respiratory distress in temporal association with blood transfusion. It is typically associated with plasma component such as platelets and fresh frozen plasma, though cases have been reported with packed red blood cells since there is some residual plasma in the packed cells ***(Toy et al., 2005).***

TRALI is the leading cause of mortality among all transfusion reactions reported to the US Food and Drug Administration with mortality rates estimated between 6 and 10%. Due to a lack of awareness, nonspecific clinical presentations and the absence of rapid and accurate diagnostic tests, TRALI is thought to be under-diagnosed and under-reported. The incidence of TRALI is estimated to be 1 in 7900 fresh-frozen plasma units, but varies between individual studies ranging between 1 in 2000 and 1 in 8000 ***(Murad et al., 2010).***

Transfusion factors can be divided into immune and non-immune-mediated TRALI. Immune-mediated TRALI is caused by the passive transfer of human neutrophil antibodies (HNA) or human leukocyte antibodies (HLA) present in the blood product, reacting with a matching antigen in the recipient. Non-immune mediated TRALI is caused by transfusion of stored cells-containing blood products ***(Carrick et al., 2011).***

The initial diagnosis is usually made clinically, yet time -consuming serological tests can help confirming the diagnosis respectively. Before establishing the diagnosis of TRALI, over-transfusion, volume overload and congestive heart failure

must be ruled out whenever possible. Treatment is supportive and often requires mechanical ventilation and cardiovascular support ***(Kleinman et al., 2011).***

Aim of the Work

The aim of this work is to discuss new update of transfusion-related acute lung injury in pathophysiology and management to decrease its prevalence and to make transfusion safer.

Pathophysiology of TRALI

The current understanding of the pathogenesis of non-antibody mediated TRALI suggests it is caused by transfusion of a stored cellular blood product in the presence of a "first hit". A second hit then induces lung injury ***(Vlaar, 2012).***

This is in contrast with antibody mediated TRALI in which majority of TRALI cases are related to cognate antibodies in plasma containing transfusion products. In short, TRALI is thought to be mediated by neutrophils ***(Kelher et al., 2009).***

Pulmonary endothelium release cytokines and chemokines which facilitate neutrophil migration to the lung. There, L-selectin mediates loose binding of the neutrophil on the epithelium after which firm adhesion is mediated by E-selectin, platelet-derived P-selectin and intracellular adhesion molecules (ICAM-1). The transfusion product activates these neutrophils and lung injury develops. The neutrophils adhere to the injured capillary endothelium and migrate into the air space where they release oxidants, proteases, platelet-activating factor (PAF) and neutrophil extracellular traps (NETs). The air space is filled with protein-rich edema and cytokines interleukin-1, -6, and -8, (IL-1, IL-6, and IL-8, respectively). These stimulate chemotaxis and stimulate neutrophils to form elastase-L1-antitrypsin (EA) complex. The clinical symptoms of acute respiratory distress is caused by influx of protein-rich edema into the alveolus which leads to the inactivation of surfactant ***(Silliman, 2006).***

Possibly symptoms of acute lung injury are not only caused by release of proteases by activated neutrophils, but also by ischemic lung damage as an effect of platelet aggregation in the pulmonary capillaries. Of interest neutrophil

deficient patients also have been described to develop TRALI and histochemical coloring of lung sections of patients who died of TRALI do not always show neutrophil influx in the alveolar space ***(Danielson et al., 2008).***

The past years research has focused on pro-inflammatory mediators which accumulate in stored cell containing blood that serve as a "second hit". More recently the transfused aged red blood cell (RBC) and platelet (PLT) themselves have been implicated as well in the onset of TRALI ***(Middelburg et al., 2012).***

Recent insights in TRALI pathogenesis:

The role of hemin and NETs has recently been related to TRALI pathogenesis. Hemin is iron-containing protoporphyrin. It is essential for the formation of heme-containing proteins including hemoglobin, myoglobin, nitric oxide synthases and cytochromes. Hemin can be released under various pathological conditions as β-thalassemia, glucose-6-phosphate dehydrogenase deficiency, hemorrhage, hemolysis and muscle injury. An excess of free circulating hemin can result in formation of reactive oxygen species (ROS) and cellular injury ***(Li et al., 2009).***

NETs can be released by activated neutrophils to trap pathogens and thus prevent pathogen spreading. They are composed of DNA fibers decorated with histones and antimicrobial proteins. Their formation follows a specific pattern of histone hypercitrullination, chromatin decondensation, dissolution of granular and nuclear membranes and cytolysis. Although NETs have been associated with beneficial antimicrobial function by trapping gram-negative and gram- positive bacteria, they also have been

related to amongst others colitis ulcerosa, small-vessel vasculitis and preeclampsia ***(Savchenko et al., 2011).***

Recently NETs have been detected in the circulation of patients with TRALI. To determine whether these were causative or consequence in TRALI the effect of NETs have been studied in vitro. In vitro NETs induce enhanced permeability in primed human umbilical vein endothelial cells (HUVECs) and NETs were found in two TRALI mouse models. In these in vivo models mice were primed with lipopolysaccharide (LPS) after which infusion of major histocompatability complex-I(MHC-I) antibody functioned as "secondhit". Mice developed TRALI have extensive NETs release ***(Thomas et al., 2012; Caudrillier et al., 2012).*** In a TRALI mouse model, depletion of either neutrophils or platelets was protective. Comparably, the use of either aspirin or a glycoprotein IIb/IIIa inhibitor to target platelet activation effectively decreased NET formation and lung injury ***(Looney et al., 2009).***

TRALI symptoms could be prevented by deoxyribonuclease 1 (DNase 1) (is a nuclease that cleaves DNA preferentially at phasphodiester linkages adjacent to a pyrimidine nucleotide) which prevents NETs formation by neutrophils. No in vivo TRALI model has to this date focused on the role of NETs in non-antibody mediated TRALI. Of interest, in vitro models support the hypothesis that NETs also have a function in non-antibody mediated TRALI as hemin has been shown to activate neutrophils in vitro and induce NETs formation ***(Kono et al., 2014).***

Contributing factors

1. Aging blood products:

During storage, blood products undergo changes referred to as the "storage lesion". The RBC changes and