Transfusion and Apheresis Science xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Transfusion and Apheresis Science

journal homepage: www.elsevier.com/locate/transci

Review

# Microcirculation and red cell transfusion in patients with sepsis

Øystein Wendelbo[a,*], Tor Hervig[b,c], Oddbjørn Haugen[d,e], Jerard Seghatchian[f,*], Håkon Reikvam[a,b]

[a] Department of Medicine, Haukeland University Hospital, Norway
[b] Department of Clinical Science, University of Bergen, Bergen, Norway
[c] Department of immunology and Transfusion Medicine, Haukeland University Hospital, Norway
[d] Department of Clinical Medicine, University of Bergen, Norway
[e] Department of Anesthesiology, Haukeland University Hospital, Norway
[f] International Consultancy in Blood Components Quality/Safety Improvement and DDR Strategies, London, United Kingdom

ARTICLE INFO

*Article history:*
Available online xxx

*Keywords:*
Sepsis
Transfusion
Red blood cell concentrates

ABSTRACT

Early identification of sepsis followed by diagnostic blood cultures and prompt administration of appropriate intravenous antibiotics covering all likely pathogen remains the corner stone in the initial management of sepsis. Source control, obtained by harvesting microbiological cultures and removal or drainage of the infected foci, is mandatory. However, optimization of hemodynamically unstable patients including volume support supplemented with vasopressor, inotropic and transfusion of red blood cells (RBCs) in case of persistent hypoperfusion have the potential to reduce morbidity and mortality. Given the imbalance between the ability of the cardiovascular system to deliver enough oxygen to meet the oxygen demand, transfusion of RBCs should theoretically provide the ideal solution to the challenge. However, both changes in the septic patients' RBCs induced by endogenous factors as well as the storage lesion affecting transfused RBCs have negative effects on the microcirculation. RBC morphology, distribution of fatty acids on the membrane surface, RBC deformability needed for capillary circulation and the nitrogen oxide (NO) signaling systems are involved. Although these deteriorating effects develop during storage, transfusion of fresh RBCs has not proven to be beneficial, possibly due to limitations of the studies performed. Until better evidence exists, transfusion guidelines recommend a restrictive strategy of RBC transfusion i.e. transfuse when hemoglobin (Hb) <7 g/dL in septic patients.



**Contents**



* Corresponding author at: Department of Medicine, Haukeland University Hospital, N-5021 Bergen, Norway.
*E-mail addresses:* Oystein.wendelbo@helse-bergen.no (Ø. Wendelbo), jseghatchian@btopenworld.com (J. Seghatchian).

https://doi.org/10.1016/j.transci.2017.11.020
1473-0502/

## 1. Introduction

Sepsis is a common condition with a high mortality [1], and ranks as the leading cause of death among critically ill patients in non-coronary intensive care units (ICU) [2]. The ACCP/SCCM Consensus Conference in 1991 developed initial definitions that focused on the then-prevailing view that sepsis resulted from a host's systemic inflammatory response syndrome (SIRS) to an infection [3]. The recent definitions published in the Journal of the American Medical Association (JAMA) in 2016 [4], redefined sepsis as life-threatening organ dysfunction caused by a dysregulated host response to infection [5].

RBCs transfusion is a common intervention in the ICU to treat non-bleeding patients with anemia, and 40–80% of RBC transfusions in the ICU are given for low hemoglobin (Hb) levels or for alterations in tissue perfusion [6,7]. The physiological rationale for RBCs transfusions is to increase the delivery of oxygen (DO2) to the tissues in the setting of potential delivery-dependent oxygen consumption. However, the effect of RBCs transfusion has been questioned due to alterations in the septic microcirculation and RBCs storage lesions.

The microcirculation is severely hampered in septic shock due to inflammation and massive cytokine release, causing sepsis-induced microvascular dysfunction [8], endothelial and glycocalyx damage [9], and pathological shunting and heterogeneous perfusion [10]. Moreover, changes in the RBCs or inflammatory mediators in blood bags may further compromise microvascular perfusion and tissue oxygen uptake. Alteration in the microcirculation may persist even after correction of systemic hemodynamic parameters and left uncorrected contribute to worsening of prognosis. Mortality is estimated to 30–50% for patients with severe sepsis, and 70% for patients with failure in three or more organ systems [11–16].

Packed RBCs transfusion in early goal directed therapy for severe sepsis and septic shock did not make it into the latest Surviving Sepsis Guidelines as a graded recommendation. Rather, blood transfusion as part of EGDT for severe sepsis/septic shock is considered an "option" [17].

The aim of this review is to highlight some of the controversies regarding changes in the septic patients' red cells and the storage lesion affecting transfused RBCs and the potential negative effects on the microcirculation. Furthermore, we discuss transfusion thresholds in patients with septic shock.

## 2. Microcirculatory changes in patients with septic shock

The microcirculation consists of an integrated vascular network (arterioles, capillaries, venules) with a diameter less than <100 μm [8]. Normally, capillary blood flow is tightly regulated in the microcirculation by driving pressure, arterial tone, hemorheology, capillary patency, plasma components (inflammatory cytokines and plasma proteins) as well as endothelial and blood cells [8].

The arterioles control the flow of blood to the capillaries by contraction and relaxation of smooth muscle of the arterioles, varying their diameter in response to various signals. Increased blood pressure is a strong stimulus distending the vessel, causing contraction. Consequently, microcirculation blood flow remains constant despite of change in systemic blood pressure. The sympathetic nervous system and circulating hormones in the bloodstream e.g. catecholamine, renin-angiotensin, vasopressin can also stimulate the arterioles causing vasodilation or vasoconstriction [18]. During normal function the endothelium plays a central role in regulation of microcirculatory perfusion by sensing flow, metabolic, and other regulating substances to alter arteriolar tone and capillary recruitment [19]. Importantly, this endothelial sensing is capable of detecting hemodynamic conditions e.g., lactate levels, and transmitting information to the arterioles by cell to cell signaling, to adjust the perfusion accordingly [20]

Nitric oxide (NO) is contributes in regulation of the immune system and circulation [21,22]. NO is generated by a family of nitric-oxide synthases (NOS) within cells [23]. There are three tissue-specific isoforms termed endothelial (eNOS), neural (nNOS) and inducible NOS (iNOS). NO is an important regulator of vascular function in septic shock. Endothelial-derived NO dilates blood vessels by relaxing vascular smooth muscle. Excessive production of NO observed in patients with sepsis, may lead to severe hypotension and cause signs of shock. NO is essential in maintaining microvascular function by regulating the supply and distribution of oxygen and nutrients throughout all tissues and organs [24]. However, these regulatory mechanisms are severely disturbed in septic shock. Although the proinflammatory mediators upregulate an increase in systemic NO production, and an increased concentration of inducible nitric oxide synthase (iNOS), iNOS is heterogeneously expressed in different areas of organ beds [25–31]. Areas that lack iNOS have less NO induced vasodilation and become underperfused resulting in pathological shunting of blood flow [26,32]. NO can also be consumed by reactive oxygen species (ROS). Reactive oxygen species (ROS) are chemically reactive chemical species containing oxygen e.g. superoxide ($O^{2-}$) and peroxynitrite ($ONOO^{-}$). Polymorphonuclear neutrophils (PMNs) represent the first line of defense of the innate immune system. Phagocytosis of the microorganisms induces apoptosis in PMNs, which is dependent upon reactive oxygen species (ROS) production and is important for the resolution of infection and inflammation. For most bacterial infections, polymorphonuclear neutrophils (PMNs) represent the first line of defense of the innate immune system. Phagocytosis of the microorganisms induces apoptosis in PMNs, which is dependent upon reactive oxygen species (ROS) production and is important for the resolution of infection and inflammation [33–35]. However, during sepsis, excess production of ROS can be a detriment, including significant cytotoxicity to organs and contributing to multiorgan system failure [36], cumulatively known as oxidative stress.

Glycolax, another pivotal component of the microcirculation is also hampered in septic shock. The glycolax layer consists of glucosaminoglycans that covers the luminal endothelial surface. Normally, it facilitates the flow of RBCs, and prevents adhesion of white blood cells and platelets to the endothelium. During sepsis the size of the glycolax is markedly decreased [9,37,38], and it is more permeable promoting leukocyte rolling and adhesion to the endothelium [37]. Microcirculatory changes in septic shock results in decrease of capillary density and presence of capillaries of stopped or intermittent flow. These alterations observed during sepsis are associated with arteriovenous shunting of oxygen contributing to explain reduced oxygen extraction rate and increased diffusion distance for oxygen [10,39–41].

Coagulation abnormalities occurs frequently during severe sepsis [42], contributing to dysregulation of hemostatic system that ultimately may lead to disseminated intravascular coagulation (DIC) and result in microvascular thrombosis and hypoperfusion

Please cite this article in press as: Wendelbo Ø, et al. Microcirculation and red cell transfusion in patients with sepsis. Transfus Apheresis Sci (2017), https://doi.org/10.1016/j.transci.2017.11.020