Should we restrict erythrocyte transfusion in early goal directed protocols?

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Abstract
Background: Early goal-directed therapy has been endorsed in the guidelines of the Surviving Sepsis Campaign as a key strategy among patients presenting with severe sepsis or septic shock. But more importantly, early goal-directed therapy also became standard care for non-septic critically ill patients and was adopted for high-risk surgical patients.

Discussion: Importantly, transfusion of red blood cells is a central part of many protocols of early goal-directed therapy to indicate the need for use of inotropes and red blood cells, as both central venous saturation and hematocrit are used as transfusion triggers. However, burgeoning data has strongly linked transfusion with worse clinical outcomes. If correct, could these early goal-directed therapy ‘bundles’ have better outcome if a restrictive transfusion practice is adopted?

Summary: Early goal-directed therapy has evolved as standard care for most critically ill patients, and many protocols contain transfusion of red blood cells targeting high hemoglobin level as a key element. As red blood cell transfusions are associated with increased morbidity and mortality, transfusion thresholds need to be more individualized.

Keywords: Allogeneic blood transfusion, Protocol directed therapy

Background
In a single-center study published in 2001 involving patients presenting with severe sepsis and septic shock, mortality was markedly lower among those who were treated according to a 6-hour protocol of early goal-directed therapy (EGDT) than among those receiving usual care [1]. The EGDT protocol included indications for central venous pressure and mean arterial pressure (<65 mm Hg) to guide both fluid and vasopressor administration. Additionally, both central venous saturation (<70%) and hematocrit (<30%) were included to indicate the need for use of inotropes and red blood cell (RBC) transfusion, respectively.

Importantly, burgeoning data has strongly linked transfusion with worse clinical outcomes. If correct, could these EGDT ‘bundles’ have better outcome if a restrictive transfusion practice is adopted?

Discussion
Following these auspicious results [1] EGDT has been endorsed in the guidelines of the Surviving Sepsis Campaign as a key strategy among patients presenting with severe sepsis or septic shock. But more importantly, EGDT also became standard care for non-septic critically ill patients and more recently, EGDT was adopted for high-risk surgical patients [2]. Thus, protocols were implemented at hospitals around the world incorporating all elements of the care bundle, but the impact of the different elements of an EGDT protocol has yet to be individually investigated. Based on current knowledge, it may be conceivable that individual elements may even be harmful (e.g. RBC transfusion and central venous pressure), and thereby reducing the potential of more beneficial effects.

In this respect, we would like to caution the reader: In previous EGDT protocols transfusion of RBC targeting hemoglobin >8 g/dL or hematocrit level >30% is a key element to increase central venous oxygen saturation (Table 1). Importantly, evidence for augmentation of oxygen delivery and thereby increase of central venous oxygen saturation above 70% by RBC transfusion is
of hematocrit < 30% must be < 60%
10 ≤ 12
tics and early adequate volume resuscitation using clin-
in management of sepsis: early administration of antibi-
ception (13.6% vs. 7.0%; P < 0.001) again with very similar
EGDT group compared to usual care received signifi-
in-hospital mortality. Not surprisingly, patients in the
the primary end point was 60-day
poor. In contrast, a rational use of RBC concentrates is
In the recent ProCESS trial [4] 1,341 patients with sepsic
shock were randomly assigned to one of three groups
for 6 hours of resuscitation: protocol-based EGDT in-
cluding RBC transfusion if hematocrit < 30% and central
venous saturation < 70%; protocol-based standard ther-
apy or usual care. The primary end point was 60-day in-hospital mortality. Not surprisingly, patients in the
EGDT group compared to usual care received signifi-
cantly more vasopressors (54.9% vs. 44.1%, P = 0.003),
more dobutamine (8.0% vs. 0.9%; P < 0.001), and more
RBC transfusion (14.4% vs. 7.5%; P = 0.001) without any
clinical benefit but used more resources.

In the more recent ARISE trial [5] 1,600 patients with early septic shock were randomly assigned to receive either EGDT or usual care. The primary outcome was all-cause mortality within 90 days after randomization. Again, patients in the EGDT group were more likely to re-
ceive vasopressor infusions (66.6% vs. 57.8%; P < 0.001),
dobutamine (15.4% vs. 2.6%; P < 0.001), and RBC trans-
fusion (13.6% vs. 7.0%; P < 0.001) again with very similar
outcomes as ProCESS.

Both studies confirmed the most important elements in management of sepsis: early administration of antibi-
etics and early adequate volume resuscitation using clin-
ical parameters ascribed by the protocol. Of note two of
the areas questioned here, the indication for dobutamine
and transfusion “triggers” of hematocrit < 30% must be
reassessed in light of existing evidence.

RBC transfusions are frequently given to patients with
septic shock. Few of these transfusions are given to pa-
tients who are bleeding and most to non-bleeding pa-
tients. However, the use of a high hemoglobin threshold
for transfusion as part of an EGDT protocol should be
questioned. In this respect, Holst et al. [6] compared
two different transfusion strategies and randomized
1,005 patients with septic shock to receive one unit RBC
when the hemoglobin level was ≤7 g/dl (lower threshold)
or when the level was ≤9 g/dl (higher threshold) during
the ICU stay. Primary endpoint was mortality at 90 days
that was similar between both groups. However, the lower-
threshold group received a median of 1 unit of blood (inter-
quartile range, 0 to 3) and the higher-threshold group
received a median of 4 units (interquartile range, 2 to 7).
These authors concluded that RBC transfusion at a hemoglobin threshold of 7 g/dl is safe in septic patients,
and a higher threshold was not beneficial and resulted in a
10–20 times higher transfusion adverse events.

In high-risk cardiac surgical patients, Murphy et al.
[7] recently randomly assigned 2,007 patients post car-
diac surgery (they were either revascularized or replaced
defective valves) to a restrictive transfusion threshold
(hemoglobin level <7.5 g/dl) or a liberal transfusion
threshold (hemoglobin level <9 g/dl) group. The primary
outcome was a serious infection (sepsis or wound infec-
tion) or an ischemic event (permanent stroke, myocard-
ial infarction, infarction of the gut, or acute kidney
injury) within 3 months after surgery. Transfusion rates
were 53.4% (higher than many liberal transfusion hospi-
tals) and 92.2% in the two groups, respectively. The re-
strictive transfusion threshold was not inferior to the
liberal threshold with respect to morbidity or 30 day
dead mortality. Mortality at 90 days was statistically higher in
the restrictive group with 16 more deaths than in the
liberal-threshold group. These finding are perplexing
since the causes of death were not related to anemia and
no plausible mechanism was offered by the authors. In
this respect, this study provides non-inferiority data on
restrictive transfusion and should not result in change of
practice until these findings are either corroborated or
refuted. It is also unclear whether the liberal transfused
group were benefiting from the ‘volume therapy’ which
the restrictive group has not received.

In-line with this discussion, two US health care organiza-
tions (American Medical Association Physician Con-
sortium for Performance Improvement and The Joint Commission)
have previously recommended strategies to minimize over-
use in healthcare, naming blood products as one of the top
five targets. In addition, the Choosing Wisely® campaign
launched by the American Board of Internal Medicine
Foundation both in US and now Canada, repeat the
same message [8]. The World Health Organization has

| Study            | Field of interest                  | RBC transfusion trigger                      |
|------------------|-----------------------------------|---------------------------------------------|
| Meybohm et al. [1] | Severe sepsis and septic shock    | Hct < 30%, if ScvO₂ < 70%                   |
| Lobo et al. [10]  | Major non-cardiac surgery         | Hct < 30%, if PAOP < 16 mm Hg               |
| Donati et al. [11]| Major abdominal surgery           | Hb < 10 g/dl, if CVP < 10 mm Hg             |
| Smetkin et al. [12]| Cardiac surgery                   | Hb < 8 g/dl, if ScvO₂ < 60%                |
| ProMISE Investigators [13]| Severe sepsis and septic shock | Hb < 10 g/dl, if ScvO₂ < 70%                |
| ProCESS Investigators [4]| Septic shock              | Hct < 30%, if ScvO₂ < 70%                   |
| ARISE Investigators [5]| Septic shock              | Hct < 30%, if ScvO₂ < 70%                   |

Hct indicates hematocrit; Hb, hemoglobin; ScvO₂, central venous oxygen saturation; CVP, central venous pressure; PAOP, pulmonary artery occlusion pressure.
adopted resolution 63.12, also adopted by the United States Department of Health and Human Services, recommending all member states to implement a patient blood management (PBM) program employing multiple strategies to minimize unnecessary exposure to blood products as a new standard of care. In detail, PBM is a proactive evidence based approach to identify, diagnose and treat anemia before a transfusion threshold is met. Optimization of hemostasis and minimization of blood loss are additional core principles of PBM to reduce costs and to improve patient outcome [9].

Summary
EGDT has evolved as standard care for most of critically ill patients, and many EGDT protocols contain transfusion of RBC targeting hemoglobin >8 g/dL or hematocrit level >30% as a key element to increase central venous oxygen saturation. In contrast, RBC transfusions are associated with increased morbidity and mortality, and therefore, a PBM program to minimize unnecessary exposure to blood products could be adopted within EGDT protocols. Additionally, transfusion thresholds for RBC transfusion need to be more individualized.

Abbreviations
EGDT: Early goal directed therapy; PBM: Patient blood management; RBC: Red blood cell.

Competing interests
PM and KZ are involved in a multicenter epidemiologic project focusing on implementation of patient blood management.

Authors’ contributions
PM, AS and KZ wrote the manuscript. All authors read and approved the final manuscript.

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