

# The majority of patients in septic shock are transfused with fresh-frozen plasma

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## ABSTRACT

**INTRODUCTION:** Fresh-frozen plasma (FFP) transfusion may be widely used in patients in septic shock, but the use is not well-described. Our aim was to describe the current use of FFP transfusion in medical patients with septic shock.

**MATERIAL AND METHODS:** This was a prospective cohort study of medical patients with septic shock (n = 60) admitted to two general intensive care units (ICUs) during a three-month period. Patients were divided into two groups, one received FFP transfusion, the other did not. Baseline characteristics, transfusions and outcome were compared between the groups. Episodes of bleeding, procedures and coagulation parameters were compared between days with and without FFP transfusion.

**RESULTS:** 57% of the patients received a median of six (interquartile range: 3-10) units of FFP during their ICU stay. The FFP-transfused patients had higher sequential organ failure assessment scores at admission (13 (9-15) versus 10 (7-11), p = 0.02) than the untransfused patients, but there were no differences in simplified acute physiology score II or mortality. On days of FFP transfusion, international normalized ratio levels (1.8 (1.4-2.3) versus 1.3 (1.2-1.6), p < 0.0001) were higher, and invasive procedures (p < 0.0001), episodes of bleeding (p < 0.0001), transfusion of red blood cells (p < 0.0001) and platelets (p < 0.0001) more frequent than on days without transfusion. Two thirds of FFP transfusions were given to patients with clinical evidence of bleeding and/or as prophylaxis before invasive procedures.

**CONCLUSION:** The majority of medical ICU patients with septic shock received FFP transfusion. One third of the FFPs were given unrelated to invasive procedures or bleeding.

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Patients with septic shock are characterised by extensive cardiovascular derangement due to stimulation of a series of inflammatory cascades leading to hypotension due to vasoplegia and relative hypovolaemia and widespread dysfunction of the microvasculature ("capillary leak") [1]. Activation of the coagulation cascades, which happens simultaneously, leads to the formation of intravascular thrombus, subsequent tissue injury and ultimately multiorgan dysfunction. In addition to the primary resuscitation according to the ABC (airway, breathing, circulation) principles, the recommended

treatment includes fluids and vasoactive drugs to restore circulation, antibiotics and deep venous thrombosis prophylaxis, whereas transfusion of plasma should only be done in case of bleeding or before invasive procedures in case of coagulopathy [2].

The current use of fresh-frozen plasma (FFP) transfusion in patients in septic shock is unknown, but FFP transfusion can have unpredictable adverse effects. Thus, FFP is likely to be the blood product with the higher adverse event rate and its indications may be limited in these patients [2, 3].

Our aim was to describe the current use of FFP in patients with septic shock in the intensive care unit (ICU) including the characteristics and outcomes of the patients transfused.

## MATERIAL AND METHODS

This was a prospective cohort study of treatment and monitoring of septic shock patients in the first seven days after their diagnosis in the ICU. The patients were included from the general ICUs at Rigshospitalet and Hillerød Hospital; the former is a university hospital, the latter a teaching hospital. Patients were included during a three-month study period at Rigshospitalet from 2007-09-01 to 2007-12-01 and at Hillerød Hospital from 1 January 2008 to 1 March 2008.

All patients diagnosed with septic shock according to consensus criteria were included: 1) Documented or suspected infection. 2) Two of the following systemic inflammatory response syndrome criteria: temperature < 36 or > 38 °C, leukocyte count < 4 or > 12 × 10<sup>9</sup>/l, respiratory frequency > 20 breaths/min. or mechanical ventilation or heart rate > 90 beats/min. 3) Signs of organ failure (cerebral, kidney, liver, lungs or coagulation) or plasma lactate > 2 mmol/l. 4) Systolic blood pressure < 90 mmHg or need for vasopressor infusion despite fluid therapy) [4]. Exclusion criteria were age < 15 years, bleeding due to surgery prior to ICU admission, withdrawal or limitation of treatment, and patient refusal of blood transfusion.

Both patients who developed septic shock prior to ICU admission and patients who developed septic shock in the ICU were included in the study.

The Ethics Committee of Copenhagen and the Danish Data Protection Agency approved the study.

## ORIGINAL ARTICLE

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TABLE 1

Baseline characteristics, transfusion of platelets and red blood cells and site of infection compared between patients with and without fresh-frozen plasma (FFP) transfusion.

	FFP given	No FFP given	p-value <sup>a</sup>
Age, years, median (25-75%)	61 (41-67)	67 (56-74)	0.07
Male, %	68	58	0.60
SAPS II, median (25-75%)	59 (50-69)	50 (39-62)	0.07
SOFA admission, median (25-75%)	13 (9-15)	10 (7-11)	0.02
SOFA maximum, median (25-75%)	14 (11-17)	10 (9-13)	0.003
Platelet transfusion, n, median (25-75%)	2 (0-6.25)	0 (0-0)	0.0002
Red blood cell transfusion, n, median (25-75%)	3 (2-7)	1 (0-3)	0.004
Malignancy, %	21	19	0.85
Haematological malignancy, %	29	19	0.55
Known cardiac disease (NYHA >2), %	0	12	0.15
Chronic pulmonary disease, %	15	33	0.24

NYHA = New York Heart Association (Class I-IV); SAPS II = simplified acute physiology score II; SOFA = sequential organ failure assessment

a) Either by Mann Whitney test or  $\chi^2$ -test corrected for smaller trials.

TABLE 2

Fresh-frozen plasma (FFP) transfusion days compared with non-transfusion days.

	FFP given (n = 81)	No FFP given (n = 245)	p-value
INR, median (25-75%)	1.8 (1.4-2.3)	1.3 (1.2-1.6)	< 0.0001
PaO <sub>2</sub> /FiO <sub>2</sub> , median (25-75%)	21 (15-30)	23 (17-30)	0.19
SAGM RBC, n, median (25-75%)	1 (0-2)	0 (0-0)	< 0.0001
Platelets, n, median (25-75%)	1 (0-2)	0 (0-0)	< 0.0001
Procedures, %	42	16	< 0.0001
Bleeding, %	40	10	< 0.0001
CRRT/IHD, %	47	33	0.03

CRRT = continuous renal replacement therapy; IHD = intermittent haemodialysis.

INR = international normalized ratio; SAGM RBC = saline-adenine-glucose-mannitol stored red blood cell.

Consent was waived because all measurements and interventions were clinically indicated. The baseline characteristics of this cohort have been published as part of a larger cohort [5].

#### Data acquisition

The following general characteristics were recorded: Gender, age, source of infection, concurrent malignancy, chronic heart or lung disease and anti-coagulant treatment at admittance, daily sequential organ failure assessment scores (SOFA), simplified acute physiology score (SAPS) II based on observations during the first 24 hours of ICU admission and 30-day, 90-day and one-year mortality from the National Patient Registry (GS-Open). Four patients died within the first day of admission to the ICU. We were therefore unable to make SAPS IIs for these patients; three of these patients had FFP transfusions.

In the first seven days after inclusion, we made daily registration of FFP, red blood cell (RBC) and plate-

let transfusions. We registered episodes of bleeding, invasive procedures including surgery, ventilator treatment with associated PaO<sub>2</sub>/FiO<sub>2</sub> ratios, use of continuous renal replacement therapy (CRRT) or intermittent haemodialysis (IHD) and treatment with anti-coagulants (heparins, epoprostenol, etc.). Bleeding was registered as described in the patient files as either pulmonary, gastrointestinal or oozing from various sites. Data were obtained from observational charts (24 hours from 6 am to 6 am the next day), medical files and laboratory notes. Registrations were only done during ICU admittance and were stopped when the patients were discharged from either of the two ICUs. There were no specific local guidelines for FFP transfusions to patients in septic shock in the two ICUs.

#### Statistics

Data were expressed as medians with interquartile ranges for continuous variables and percentages of the total for categorical variables. We divided the cohort into two groups, one received FFP transfusions during the seven-day observation period, the other did not. Also, comparisons were made between days with and without transfusion. The Mann Whitney test was used for continuous variables and the  $\chi^2$ -test for categorical data. Paired data were analysed by Wilcoxon matched-pairs signed rank test.

A value of  $p < 0.05$  was used as the level of statistical significance. Data were analysed using GraphPad Prism v.5.

*Trial registration:* not relevant.

## RESULTS

### Total cohort

A total of 60 patients were included during the three-month study period,

36 patients (60%) at Rigshospitalet and 24 patients (40%) at Hillerød Hospital. Baseline characteristics and data on blood product use are shown in **Table 1**.

Patients in the FFP transfusion group had higher SOFA scores (admission and maximum), but there were no differences in SAPS II, 30-day, 90-day or one-year mortality compared with the untransfused patients. ICU length of stay for all patients was seven (3-14) days, seven (4-15) days for FFP transfused patients and five (3-13) days for untransfused patients ( $p = 0.42$ ).

### Fresh-frozen plasma transfusions

A total of 230 units of FFP were given during the seven-day observational period to 57% of the patients with a median of six (3-10) FFP units per patient. Two thirds (67%) of FFP transfusions were given to patients with clinical evidence of bleeding and/or as prophylaxis be-

fore invasive procedures, including insertion of central venous lines (n = 26), drainage tubes (n = 6) or tracheotomy (n = 1) or surgery (n = 10).

One third (30%) of FFP transfusions were given on the first day of septic shock, and 68% within the first three days of shock. In this period, there was no significant difference in the number of patients transfused with RBC, but the number of RBC transfusions was significantly higher in the FFP transfusion group than in the non-transfused group. On the first day, FFP transfused patients received significantly more platelets and also underwent surgery more often. In the first two days, the FFP-transfused patients had more episodes of bleeding and underwent invasive procedures more often. There were no differences in treatment with either CRRT or IHD on any of the days.

On days of transfusion international normalized ratio (INR) ( $p < 0.0001$ ), invasive procedures ( $p < 0.0001$ ), episodes of bleeding ( $p < 0.0001$ ), numbers of units of saline-adenine-glucose-mannitol stored red blood cell (SAG-M) ( $p < 0.0001$ ) and platelets ( $p < 0.0001$ ) were significantly higher than on days with no transfusion (Table 2). When given, the number of units of FFP was between one and eight; two units were given on 56% of the total transfusion days.

One patient had thrombotic thrombocytopenic purpura and received three units of FFP daily during seven days of observation, three of which were given on a day without bleeding or invasive procedures.

#### International normalized ratios

On FFP transfusion days without bleeding and/or invasive procedures, we assessed if INR could be a possible FFP transfusion trigger. On these days, INR was 2.0 (1.6-2.5) which was significantly ( $p > 0.001$ ) higher than on days without FFP transfusion 1.3 (1.2-1.6). Pre-transfusion INR was 1.5 or below on 30% of transfusion days, in the intervals 1.6-2.5 on 53% of the transfusion days and 2.6-3.5 on 12% of the transfusion days, and above 3.5 on 5% of transfusion days. Post-transfusion INR was only significantly lower if pre-transfusion INR was between 1.6 and 2.5 ( $p = 0.01$ ) (Figure 1).

#### Anticoagulation therapy

Eight patients in the FFP group were receiving anticoagulation therapy at admission compared with four in the non-FFP group ( $p = 0.65$ ). There was no difference in administration of epoprostinol (eight versus 12%,  $p = 0.76$ ) or heparin (34 versus 48%,  $p = 0.25$ ) as anticoagulation therapy for CRRT/IHD or thrombosis prophylaxis with low-molecular-weight heparin (47 versus 58%  $p = 0.1$ ) on days with or without FFP transfusion. Four patients received anti-thrombin III, coagulation factor VIIa (recombinant) was administered to one patient, vitamin

K<sub>1</sub> (phytomenadion) to three patients and tranexamic acid to two patients. No patients received activated protein C.

#### Mortality

ICU mortality (32 versus 38%,  $p = 0.80$ ), 30-day mortality (35 versus 46%,  $p = 0.56$ ), 90-day mortality (50 versus 54%,  $p = 0.97$ ) and 365-day mortality (59 versus 62%,  $p = 0.79$ ) were comparable between FFP transfused and non-transfused patients.

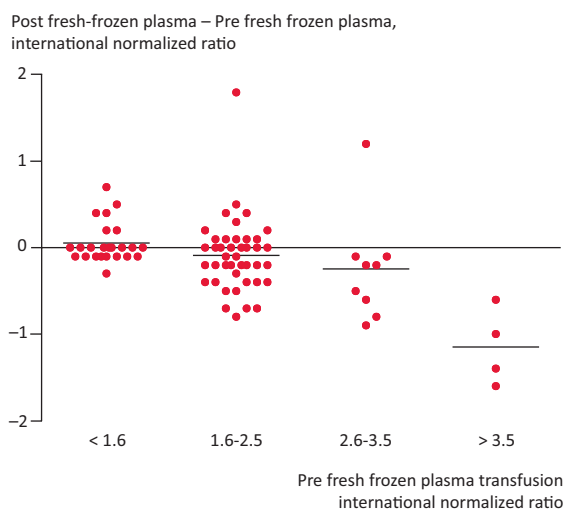
#### DISCUSSION

We found that 57% of patients in septic shock were transfused with FFP. These patients had a higher degree of organ failure (SOFA scores) and had more transfusions of RBC and platelets than those not transfused with FFP. In contrast hereto, there were no differences between the groups with regard to SAPS II, mortality or length of ICU stay. The majority of FFP transfusions were given in relation to bleeding episodes or the performance of invasive procedures, but one third of the transfusions were given unrelated to these indications.

The use of FFP represents a clinical dilemma because FFP transfusion may be harmful. Complications and adverse reactions could be allergic, anaphylactic, due to ABO mismatch, infection, transfusion-related acute lung injury, transfusion-associated circulatory overload and transfusion-related immune modulation. When FFP is given for severe bleeding, the indication is to substitute coagulation factors, which may be beneficial in severe bleeding.

FIGURE 1

Change in international normalized ratios by the infusion of fresh-frozen plasma dependent on pre-transfusion international normalized ratio. Dots represent the change in patient international normalized ratios and bars medians and interquartile ranges.



Wide variation in practice is seen with FFP transfusion. We have tried to describe the current use of FFP transfusion to Danish ICU patients in septic shock. We found that the majority of FFP transfusions were given for recommended indications, including bleeding and pre-procedural prophylaxis [2]. However, one third of transfusions may have been given without obvious clinical indication as it was also observed in a recent British cohort of general ICU patients [6].

From our data, we are not able to answer whether an elevated INR may have been a possible FFP transfusion trigger. But we did find that INR was significantly higher on transfusion days without bleeding or invasive procedures than on non-transfusion days. There is no good evidence for establishing a certain INR threshold for plasma transfusions, and the multitude of evidence points to the clinical inefficacy of plasma transfusion in patients with mild to moderate increases in INR even in the face of invasive procedures. Routine, minimally invasive critical care procedures can be safely performed by experienced clinicians in the setting of mildly abnormal coagulation test results, and there is no evidence that FFP transfusion alters the risk of bleeding [7].

We found that post-transfusion INR was only significantly lower if pre-transfusion INR was between 1.6 and 2.5. A study by Holland and Brooks demonstrated that the potential benefits of FFP transfusion in terms of normalization of coagulation test results are minimal in patients with an INR below 1.7 [8]. The small sample size may be one reason why, contrary to expectations, we demonstrated no significant change in post-transfusion INR if pre-transfusion INR was above 2.5.

The clinical use of FFP is not supported by evidence from randomised clinical trials (RCTs) [9]. If the use of FFP transfusions in patients with septic shock remains high, RCTs will be needed to assess the efficacy and safety of FFP transfusion in these patients. As with any other blood component, the decision to transfuse FFP should be based on predictable benefit and clinically necessity.

The strengths of this study are the prospective, consecutive inclusion in two ICUs. The study was an observational study and thereby represents current practice. Data were registered by a single investigator in each unit who knew that unit very well.

The weaknesses of this study include a limited sample size of only 60 patients and an observation period restricted to three months for practical and financial reasons. Patients were included from only two ICUs, and data may not be representative for the majority of Danish ICUs. Data are from 2007-2008 and transfusion practice may have changed in the past five years. Identification and inclusion of patients and collection of baseline characteristics were done prospectively, but

the collection of data on coagulation, procedures and bleeding episodes were done retrospectively. We were therefore unable to obtain relevant laboratory findings for all observation days, either because they were not analysed or because we were unable to access them.

We did not survey the clinicians regarding indications for FFP transfusion, so we had to rely on the documentation of bleeding episodes or performance of invasive procedures in the patient notes and observation charts. If undocumented, we assumed the patient had no bleeding episodes and that invasive procedures were not undertaken.

In case of bleeding, we have no data to suggest the amount of bleeding and for patients operated during the observation period, we have not collected data regarding blood loss or transfusion of blood products during surgery. As the study was purely observational, we can make no inferences about the effects of transfusion on INR values, bleeding or outcome.

Our study of FFP transfusion practice in intensive care patients with septic shock sets the base for a greater Danish cohort study with inclusion of more patients from more ICUs.

## CONCLUSION

The majority of ICU patients with septic shock received FFP transfusion. One third of the FFP transfusions were given unrelated to invasive procedures or bleeding. Lack of trials describing the safety and efficacy of FFP in septic patients may explain this apparent inappropriate use.

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## LITERATURE

1. Balk RA. Pathogenesis and management of multiple organ dysfunction or failure in severe sepsis and septic shock. *Crit Care Clin* 2000;16:337-52.
2. Dellinger RP, Levy MM, Carlet JM et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2008. *Crit Care Med* 2008;36:296-327.
3. Gajic O, Rana R, Winters JL et al. Transfusion-related acute lung injury in the critically ill. *Am J Respir Crit Care Med* 2007;176:886-91.
4. American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Crit Care Med* 1992;20:864-74.
5. Perner A, Carlsen S, Marcussen K et al. Septic shock in intensive care. *Ugeskr Læger* 2010;172:1206-10.
6. Stanworth S, Walsh TS, Prescott RJ et al. A national study of plasma use in critical care: clinical indications, dose and effect on prothrombin time. *Crit Care* 2011;15:R1-R8.
7. Gajic O, Dzik WH, Toy P. Fresh frozen plasma and platelet transfusion for nonbleeding patients in the intensive care unit: benefit or harm? *Crit Care Med* 2006;34:S170-S173.
8. Holland LL, Brooks JP. Toward rational fresh frozen plasma transfusion. *Am J Clin Pathol* 2006;133-9.
9. Stanworth SJ, Brunskill SJ, Hyde CJ et al. Is fresh frozen plasma clinically effective? A systematic review of randomized controlled trials. *Br J Haematol* 2004;126:139-52.