PREDLOG SMERNIC ZA KLINIČNO
UPORABE SVEŽE ZMRZNJENE
PLAZME

Guidelines for clinical use of FFP proposal

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FFP - definition

Fresh frozen plasma (FFP) is a blood component for transfusion or for fractionation prepared either from whole blood or collected by apheresis, frozen within a period of time and to temperature that will adequately maintain the labile coagulation factors in functional state.

(Guide to the preparation, use and quality assurance of blood components, European committee(Partial agreement) on Blood transfusion (CD-P-TS) 14th ed. 2008)
FFP - properties

- Normal plasma levels of stable coagulation factors, albumin and immunoglobulins
- Total protein concentration > 50g/l
- Factor VIIIc > 70 IU/100 ml of FFP
- No clinically significant irregular antibodies
- AB0, RhD, ICT, Viral testing, QC testing
- Human plasma for fractionation properties - EU.Ph. 0853
- FFP prepared from whole blood and from plasmapheresis are therapeutically equivalent in terms of haemostasis and adverse effects.
FFP- methods of preparation

• Separation:
  – Hard spin centrifugation - from whole blood or platelet rich plasma (6 – 18 hours after collection)
  – Automated apheresis

• Freezing
  – Within one hour to temperature below -30°C

• Storage:
  – 36 months at below -25°C
  – 3 months at -18°C to -25°C
PRIPRENJE PLAZME

• Sveže zmrznjena plazma
  – SZP - navadna
  – SZP - odstranjen krioprecipitat
  – Krioprecipitat

• Dodatna postopki
  – Karantenska SZP
  – SZP z inaktiviranimi patogeni
Variations in coagulation factor levels

Good retention of relevant coagulation factor activity

Variations:
- Dilution by citrate anticoagulant
- Individual differences
- Age
- AB0 blood groups
- Collection
- Processing
- Freezing

FFP – thawing and infusion

• **Thawing**
  – in properly controlled environment
    – Water bath
    – Dry ovens (temperature controlled fan-assisted incubator).
    – Microwave ovens
  – integrity of the FFP pack should be verified

• **Infusion**
  – Immediately after thawing – max 2 – 24 hours
  – Normal blood administration set
  – Infusion line should be changed at least every 12 hours and after the completion of prescribed components
Principles of selection of FFP according to donor and recipient AB0 blood group (BSH, 2004)

<table>
<thead>
<tr>
<th>Recipient group</th>
<th>O</th>
<th>A</th>
<th>B</th>
<th>AB</th>
</tr>
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<tbody>
<tr>
<td><strong>(a) High titre (HT)positive or HT untested units</strong>*</td>
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</tr>
<tr>
<td>1\textsuperscript{st} choice</td>
<td>0</td>
<td>A</td>
<td>B</td>
<td>AB</td>
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<tr>
<td>2\textsuperscript{nd} choice</td>
<td>A</td>
<td>AB</td>
<td>AB</td>
<td>A\textsuperscript{†}</td>
</tr>
<tr>
<td>3\textsuperscript{rd} choice</td>
<td>B</td>
<td>B\textsuperscript{†}</td>
<td>A\textsuperscript{†}</td>
<td>B\textsuperscript{†}</td>
</tr>
<tr>
<td>4\textsuperscript{th} choice</td>
<td>AB</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td><strong>(b) HT negative units</strong>**</td>
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<tr>
<td>1\textsuperscript{st} choice</td>
<td>0</td>
<td>A</td>
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<tr>
<td>2\textsuperscript{nd} choice</td>
<td>A</td>
<td>B</td>
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<tr>
<td>3\textsuperscript{rd} choice</td>
<td>B</td>
<td>AB</td>
<td>AB</td>
<td>B</td>
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<tr>
<td>4\textsuperscript{th} choice</td>
<td>AB</td>
<td>-</td>
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Dosage

• 10 – 20 ml / kg BW
• Dependent on the clinical situation and its monitoring

Variation in usage according to coagulation profile
FFP issued SLO and ZTM
Clinical utilisation rates of FFP untis per 1,000 inhabitants in some EU countries 2008

FFP / 1000 inh. SLO
2003 16.34
2004 16.49
2005 16.71
2006 15.13
2007 15.48
2008 14.76
2009 15.65
Average 15.79
Guidelines for clinical use of FFP

- 11 guidelines on the good use of plasma identified
- British Committee for Standards in Haematology,
- Agence Française de Securité Sanitaire de Produits de Sante,
- Canadian Members of the Expert Working Group,
- American Society of Anesthesiologists Task Force on Blood Component Therapy
- National Health and Medical Research Council (NHMRC)/Australian Society of Blood Transfusion.
<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td><strong>Dose</strong></td>
<td>10–15 mL/kg</td>
<td>10–15 mL/kg</td>
<td>10–20 mL/kg</td>
<td>10–15 mL/kg</td>
<td>10–15 mL/kg</td>
</tr>
<tr>
<td><strong>Trigger</strong></td>
<td>Fibrinogen &lt;100mg/dL INR/aPTT &gt;1.5</td>
<td>Fibrinogen &lt;100mg/dL INR/aPTT &gt;1.5</td>
<td>Coagulation values &gt;1–1.5 n.r.</td>
<td>Fibrinogen &lt;100mg/dL INR/aPTT &gt;2</td>
<td></td>
</tr>
<tr>
<td><strong>Inherited deficiency of single clotting factors</strong></td>
<td>When specific, virus-safe or recombinant factors are not available. If the patient is bleeding.</td>
<td>When the specific factors are not available.</td>
<td>If the patient is bleeding or in preparation for surgery.</td>
<td>DDAVP and specific factors are ineffective /not available patient is bleeding or expectation of bleeding.</td>
<td>When the specific factors are not available.</td>
</tr>
<tr>
<td><strong>Disseminated Intravascular Coagulation (DIC)</strong></td>
<td>If the patient is bleeding</td>
<td>Indicated for DIC in obstetric patients</td>
<td>If the patient is bleeding and there are coagulation abnormalities</td>
<td>Patient is bleeding INR increase and APTT ≥ trigger unless the underlying cause can be treated effectively.</td>
<td>Not stated</td>
</tr>
<tr>
<td><strong>Haemolytic-uraemic Syndrome</strong></td>
<td>Not stated</td>
<td>Yes</td>
<td>Not stated</td>
<td>Yes (except in children)</td>
<td>Not stated</td>
</tr>
<tr>
<td><strong>Warfarin anticoagulation</strong></td>
<td>If the patient has severe bleeding (However, prothrombin complex in association with vitamin K is preferable)</td>
<td>If the patient is bleeding, in association with vitamin K and factor IX concentrate</td>
<td>If the patient is bleeding. (prothrombin complex + vitamin K, is preferable)</td>
<td>Yes (5–8 mL/Kg)</td>
<td></td>
</tr>
<tr>
<td><strong>Liver K deficiency</strong></td>
<td>No</td>
<td>Not stated</td>
<td>No</td>
<td>If the patient is bleeding</td>
<td>Not stated</td>
</tr>
<tr>
<td><strong>Liver diseases</strong></td>
<td>Routine use not appropriate</td>
<td>If the patient is bleeding and PT and aPTT ≥ trigger</td>
<td>If the patient is bleeding and PT and aPTT ≥ trigger</td>
<td>If the patient is bleeding and PT and aPTT ≥ trigger</td>
<td>Not stated</td>
</tr>
<tr>
<td><strong>Massive transfusion</strong></td>
<td>Use guided by updated coagulation test carried out at the patient’s bedside</td>
<td>In cases of traumatic haemorrhagic shock that cannot be managed immediately by surgery</td>
<td>If PT and aPTT ≥ trigger</td>
<td>microvascular bleeding and PT and aPTT ≥ trigger In preparation for invasive procedures/surgery</td>
<td>If the patient has microvascular bleeding and PT and aPTT ≥ trigger</td>
</tr>
<tr>
<td><strong>Heart surgery</strong></td>
<td>Prophylactic use not indicated</td>
<td>Prophylactic use not indicated</td>
<td>Not stated</td>
<td>Prophylactic and therapeutic use not indicated</td>
<td>Not stated</td>
</tr>
<tr>
<td><strong>Liver biopsy</strong></td>
<td>If PT ≥ 4 times higher than the normal value. Results unpredictable</td>
<td>Not stated</td>
<td>Not stated</td>
<td>If INR &gt;2</td>
<td>Not stated</td>
</tr>
<tr>
<td><strong>Not indicated</strong></td>
<td>Hypovolaemia Plasma exchange except for TTP Test of clotting correction in the absence of haemorrhage</td>
<td>Hypovolaemia Plasma exchange except for TTP Test of clotting correction in the absence of haemorrhage</td>
<td>Not stated</td>
<td>Hypovolaemia Plasma exchange except for TTP Test of clotting correction in the absence of haemorrhage</td>
<td>Hypovolaemia Albumin concentration</td>
</tr>
<tr>
<td><strong>Hypovolaemia</strong></td>
<td></td>
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<tr>
<td><strong>Hypoproteinaemia</strong></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td><strong>Hypogammaglobulinaemia</strong></td>
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## Indications for FFP

### Clinical condition

1. Correction of congenital or acquired deficiencies of clotting factors (for which there is not a specific concentrate), when the PT or aPTT ratio is >1.5:

   - Liver disease:
     - active bleeding
     - prevention of bleeding in the case of surgery or invasive procedure

   - During treatment with vitamin K antagonists (if prothrombin complex, which is the first choice treatment, is not available):
     - in the presence of major or intracranial haemorrhage
     - in preparation for surgery than cannot be delayed

   - Acute disseminated intravascular coagulation with active bleeding, in association with correction of the underlying cause

   - Microvascular bleeding during massive transfusions (>1 blood volume), even before the results of PT and aPTT

   - Deficiencies of single clotting factors, in the absence of specific concentrates (e.g. of FV), in the presence of active bleeding or to prevent bleeding during an invasive procedure

2. Apheretic treatment of thrombotic microangiopathies (thrombotic thrombocytopenic purpura, haemolytic-uraemic syndrome, HELLP syndrome), as a replacement fluid

3. Reconstitution of whole blood for exchange transfusions

4. Hereditary angioedema in the case that C1-esterase inhibitor is not available
Indications for FFP**

- TTP (A)*
- Massive transfusion & disseminated intravascular coagulation (B)
- Hemostatic defects of liver disease, with bleeding (C)
- Coumarin reversal, if bleeding (where prothrombin complex not available) (B)
- Single coagulation factor deficiencies where concentrate not available (B)
- Neonatal hemorrhagic disease (C)

*Level of evidence: A = randomized trial; B = nonrandomized trial; C = expert opinion

Therapeutic apheresis—TTP

- FFP may be used as a replacement fluid in patients undergoing therapeutic apheresis procedures.
- Plasma exchange with FFP has been recommended as the first-line treatment of choice for TTP, providing a source of ADAMTS13 (a disintegrin and metalloprotease with thrombospondin type 1 motif 13).
Liver disease

The coagulopathy is complex,

- abnormalities of platelets,
- fibrinolysis and inhibitors of coagulation
- coagulation factor deficiencies.

The lack of bleeding in cirrhotic patients despite diminished procoagulant synthesis (and abnormal PT/aPTT) may be explained by a parallel reduction in the production of anticoagulant proteins, such as proteins C and S, leading to equivalent thrombin generation potential on activation of both pro- and anti-coagulant pathways.
Reversal of warfarin effect

- In the absence of major bleeding associated with over anticoagulation due to vitamin K antagonists, primary treatment should be initiated with oral/intravenous vitamin K. In addition to vitamin K, guidelines recommend FFP or prothrombin complex concentrates (PCC) for reversal of overanticoagulation, but only in patients with major bleeding.
Massive transfusion and DIC

- From a pathophysiologic perspective, use of FP in this setting seems clinically appropriate.
- FFP indicated in association with correction of the underlying cause in patients with active bleeding.
Replacement of isolated factor deficiencies

• Inherited deficiency of single clotting factors II, V, VII, IX, X, and XI
• specific component therapy is neither available nor appropriate
• patient is bleeding
Neonatal hemorrhagic disease

- low vitamin K stores at birth,
- vitamin K passes the placenta poorly,
- the levels of vitamin K in breast milk are low and
- The gut flora has not yet been developed (vitamin K is normally produced by bacteria in the intestines)
Clinical effectiveness of FFP

- Many published trials on the use of FFP have enrolled small numbers of patients
- Inadequate information on the ability of the trial to detect meaningful differences in outcomes between the two patient groups is provided
- Dose of FFP used not considered
- No studies had taken adequate account of the extent to which adverse effects might negate the clinical benefits of treatment with FFP.
- Little evidence for the effectiveness of the prophylactic use of FFP.
- Need to consider how best to develop new trials to determine the effectiveness of FFP.
Cardiac surgery

• The multifactorial hemostatic changes related to cardiac bypass are,
  – contact with synthetic surfaces,
  – use of heparin,
  – hypothermia,
  – thrombocytopenia
  – defects in platelet function,
  – not solely related to coagulation factor deficiency.
### RCT evaluating clinical effectiveness of FFF

*(Stanworth, BJH, 2004)*

<table>
<thead>
<tr>
<th>Study design</th>
<th>No. of RCT</th>
<th>Mean size /arm</th>
</tr>
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<tbody>
<tr>
<td><strong>FFP vs. No FFP</strong></td>
<td></td>
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<tr>
<td>Liver</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>5</td>
<td>18</td>
</tr>
<tr>
<td>DIC</td>
<td>1</td>
<td>11</td>
</tr>
<tr>
<td>HUS</td>
<td>2</td>
<td>28</td>
</tr>
<tr>
<td>Neonatal</td>
<td>7</td>
<td>35</td>
</tr>
<tr>
<td>Other</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td><strong>FFP vs. Alternative colloid</strong></td>
<td>5</td>
<td>31</td>
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<tr>
<td>Cardiovascular</td>
<td>5</td>
<td>78</td>
</tr>
<tr>
<td>Neonatal</td>
<td>5</td>
<td>45</td>
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<tr>
<td><strong>FFP vs. Alternative/blood/plasma product</strong></td>
<td>4</td>
<td>19</td>
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<tr>
<td>Liver</td>
<td>3</td>
<td>28</td>
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<tr>
<td>Cardiovascular</td>
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<td>22</td>
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<tr>
<td>Warfarin treated</td>
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<td>20</td>
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<tr>
<td>DIC/Massive transfusion</td>
<td>2</td>
<td>23</td>
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<tr>
<td>TTP</td>
<td>5</td>
<td>69</td>
</tr>
<tr>
<td>Burns</td>
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<td>29</td>
</tr>
<tr>
<td>Other</td>
<td>5</td>
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</tbody>
</table>
Adverse effects

- Citrate toxicity
- Febrile non-hemolytic transfusion reactions
- Allergy - urticaria
- TRALI (transfusion related acute lung injury)
- Viral transmission
- Transmission of other pathogens
Begin to use the pathogen inactivated plasma in Slovenia