Transfusion reactions with respiratory symptoms: TRALI / TACO / TAD
TR with respiratory symptoms

- TRALI: Transfusion-Related Acute Lung Injury
- TACO: Transfusion Associated Circulatory Overload
- TAD: Transfusion Associated Dyspnea
- Allergic Reaction (not covered in this presentation)
Agenda

- Aim

- TRALI
  - Pathophysiology, incidence, diagnosis, treatment, risk factors

- TACO
  - Pathophysiology, incidence, diagnosis, treatment, risk factors

- DD TRALI/TACO

- TACO prevention

- TAD
  - Pathophysiology, incidence, diagnosis
Awareness of transfusion reactions with respiratory symptoms

- Blood transufision can be life saving, but can also be life-threatening!

- Some of the **risk factors** of respiratory transfusion reactions are well known.

- Knowing these is important, because it allows a personalized approach of transfusion (beyond blood groups, antibodies) and can reduce the risk of adverse events such as TRALI and TACO.
TRALI – Definition

● New acute lung injury (ALI) / acute respiratory distress syndrome (ARDS) occurring during or within six hours after blood product administration

● Consensus definition
  o Acute onset (during or within six hours)
  o Hypoxemia (defined as PaO2/FiO2 ≤ 300 or SpO2 ≤ 90%)
  o Bilateral infiltrates on frontal chest radiograph
  o No evidence of circulatory overload/left atrial hypertension
When a clear temporal relationship to an alternative risk factor for ALI/ARDS coexists, some authors suggest the diagnosis «possible TRALI»

In hemovigilance, we define any ALI/ARDS occurring during or within 6 hours after blood product administration as TRALI, and define the imputably separately. This means, even if the clinician is certain that the new ALI/ARDS is not imputable to the transfusion, a report has to be sent.
TRALI (Transfusion-Related Acute Lung Injury)

• Pathogenesis
  o «Two-hit model»:
    • first hit:
      – underlying patient factors
    • second hit:
      – **antibody-mediated** by HLA/HNA
      – **non-antibody-mediated** by proinflammatory mediators

Vlaar et al., Lancet, 2013
TRALI – Incidence

- Estimated between 0.08 and 15% (for all patients)
- Incidence in ICU patients is probably more important
TRALI – Diagnosis

- This is mainly a **clinical** diagnosis!
- Respiratory disorder (dyspnoea, tachypnoea, hypoxemia)
- Cx: Rigors, tachykardia, fever, hypotension.
- No response to diuretics
- Rx: bilateral interstitial abnormalities
- Lab: Leukopenia, Thrombopenia
TRALI - Treatment

- TRALI is a life-threatening condition!
- Transfusion must be discontinued immediately, alert blood bank
- No treatment exists
- Management is supportive (additional O2, fluid resuscitation, vasoactive support)
- Endotracheal intubation with invasive mechanical ventilation is often required. Consensus is that ventilator management should be fit treatment of other forms of ARDS
TRALI – Risk factors

- The first hit is bounded to underlying patient factors. Therefore, risk factors are important to know:

- Sepsis (OR 2.1-24.1)
- Emergency cardiac surgery (OR 17.6)
- Haematological malignancy (OR 13.1)
- Peak Airway pressure > 30cm (H2O) (OR 5.6)
- Shock (OR 4.3)
- Mechanical ventilation (OR 3.0)

(Vlaar et al., Lancet, 2013)
Hemovigilance role in TRALI

- As stated in the two-hit model, the products plays an important role
- Hemovigilance data showed a link between women plasma and TRALI cases was discovered
- In 2008, Switzerland introduced the **male-only donor policy for FFP**

![TRALI cases with FFP](image-url)
TACO – Definition & pathophysiology

- TACO is a form of circulatory volume overload that can occur in any individual and with transfusion of any blood component (UpToDate)

- (Part of the) Pathophysiology is not specific to transfusion...
  - Transfusion of blood / other fluids -> increases the intravascular volume and cardiac filling pressures -> pulmonary edema

- … however, some authors suggested that some inflammatory mechanisms or some product related components could co-exist and lead to TACO
TACO – Incidence

- Incidence of TACO varies greatly according to authors: numbers between 1 and 8% have been reported
- This variation is due to definition of TACO and to study population
- As for TRALI, incidence is higher in ICU patients (more or less 6% vs 1%)
- TACO cases are probably underreported and underdiagnosed
TACO / TRALI reports in Switzerland

Major cause of TR with severity 3 (life-threatening) or 4 (death) since 2015 in Switzerland
TACO Reports in Switzerland

- Significant increase in TACO reports with severity 3 and 4 in the last years
- This increase is not only at national level, but also at international level
- Factors for this increase are not known yet but two hypothesis:
  - More awareness for TACO → more reports
  - Aging population with more patients having risk factors for TACO
TACO – Diagnosis

- Reporting criteria proposal (ISBT, 2017)

- **Acute or worsening respiratory compromise** during or up to **12 hours** after transfusion + **2 or more** of the following:
  - Pulmonary oedema (clinical examination and/or radiographic)
  - Cardiovascular changes (tachycardia, hypertension, jugular venous distension, enlarged cardiac silhouette)
  - Fluid overload (positive fluid balance, response to diuretic, patient’s weight)
  - Elevation in BNP
TACO and fever

- 31.8% of TACO cases show new rise in body temperature (Parmar et al., 2016)

- Swissmedic, 2017: 45.7% of TACO cases show new rise in body temperature (> 1.0°C)

- TACO is often associated with fever.
  - While TRALI is almost always associated with fever, it is not a pertinent criterion to differentiate TACO and TRALI
  - If a patient presents fever and dyspnoea, do not classify it as FNHTR (exclusion diagnosis !)
TACO and pro-BNP

- Patients with TACO often have high pro-BNP before transfusion (cf. risk factors)
- Pro-BNP can be a help to discriminate between TACO / TRALI, but is not a definitive criterion

Li et al. Transfusion, 2009

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**TABLE 3. Comparison of BNP and NT-pro-BNP between TACO, TRALI, and possible TRALI**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>TACO (n = 50)</th>
<th>Possible TRALI (n = 31)</th>
<th>TRALI (n = 34)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BNP before transfusion, pg/mL (n = 23)*</td>
<td>521.5 (143-2180.3)</td>
<td>85 (49-291)</td>
<td>170.5 (41-407.3)</td>
<td>0.128</td>
</tr>
<tr>
<td>BNP after transfusion (n = 73), pg/mL*</td>
<td>559 (287.8-1347.8)</td>
<td>446 (128-743.3)</td>
<td>375 (122.5-780.5)†</td>
<td>0.038</td>
</tr>
<tr>
<td>NT-pro-BNP before transfusion (n = 61), pg/mL*</td>
<td>3410 (686-11951.5)</td>
<td>948 (232-2352)</td>
<td>664 (138.5-2402)†</td>
<td>0.024</td>
</tr>
<tr>
<td>NT-pro-BNP after transfusion, pg/mL (n = 84)*</td>
<td>5197 (1695-15714)</td>
<td>2349 (919-4610)</td>
<td>1558.5 (628.5-5114)‡</td>
<td>0.004</td>
</tr>
<tr>
<td>NT-pro-BNP ratio† (n = 61)*</td>
<td>1.3 (1.0-3.8)</td>
<td>3.0 (1.4-9.0)</td>
<td>2.0 (1.3-5.9)</td>
<td>0.257</td>
</tr>
</tbody>
</table>

* The data are presented as median (IQR).
† NT-pro-BNP after transfusion/NT-pro-BNP before transfusion.
‡ TRALI against TACO significantly different (p < 0.05).
TACO – Treatment

- Similar to treatment of cardiogenic pulmonary edema of other causes
  - **STOP** Transfusion
  - Oxygen for patients with $\text{SpO}_2 \leq 90\%$
  - Fluid mobilisation: diuretics
  - Ventilatory support: in severe TACO cases, first line noninvasive positive pressure ventilation, second line intubation
TACO prevention – What can you do?

- TACO is a preventable reaction!
- Known risk factors
TACO prevention – Risk factors

- Heart failure (OR 2.0-6.6)
- LV Dysfunction (OR 1.8-8.23)
- Positive fluid balance (OR 1.38-9.4)
- Acute / chronic renal impairment (OR 1.9-27.0)
- Elevated blood pressure (OR 1.9)
- Increased proBNP
- Patient on regular diuretic
- Recent (emergency) surgery (OR 2.2-3.9)

- Some other risk factors have been suggested: acute respiratory problem, hypoalbuminaemia, recent myocardinfarct)
TACO prevention – Reconsider / delay transfusion

- Do the patient really need to be transfused? (Think PBM)

- Do the patient really need to be transfused right now? (correct fluid balance, control blood pressure, …)

- If transfusion is needed and not deferable, take preventive measures

Risk of TACO

Severity of anemia, symptoms, relevant diagnosis, …
TACO prevention: preventive measures

- Meta-analysis: Sarai & Tejani, 2015
  - 4 studies, 100 participants with Furosemid
  - None of them assessed TACO, mortality, serious AE, acute heart failure, acute kidney injury as primary outcome.
  - Instead they assessed various markers of respiratory function
    - 1 study noted improvement in FiO2
    - 2 studies noted improvement of pulmonary capillary wedge pressure
  - Conclusion: «insufficient evidence to determine whether premediacting people undergoing blood transfusion with loop diuretics prevents clinically important transfusion-related morbidity».

→ Evaluate the use of diuretics for each patient individually
TACO prevention: monitor closely

- Andrzejewski et al., Transfusion, 2012

- In TACO patients, several parameters are already changed after 15 minutes (fever, systolic BP, MAP)

- At the end of the transfusion, most of the parameters are changed (fever, pulse, systolic BP, diastolic BP, MAP)

- Monitoring closely patients at risk is mandatory to stop the transfusion and to treat accordingly early enough
TACO prevention: single-unit, infusion rate

- Order only single-unit transfusion
- Re-assess anemia / symptoms (and the patient clinical status !) before ordering another unit
- According to most guidelines, in risk patient the infusion rate should be 1ml/kg/h. No RCT has been done for this rate, but a clear association exists between higher rates and TACO
TACO – Preventive measures - Summary

- Reconsider / delay transfusion!

- If transfusion is needed and not deferable:
  - Evaluate the use of pretransfusion diuretics
  - Slower rate of infusion (1ml/kg/min)
  - Monitory closely
  - Transfuse only one unit, then re-assess anemia
Swissmedic TACO Checklist (draft)

TACO Checklist

Consider the following risk factors for TACO

1. Patient’s history
   - LV Dysfunction
   - Heart failure
   - Patient is on regular diuretic
   - Chronic kidney disease
   - Known previous TACO

2. Current condition
   - Positive fluid balance
   - Acute kidney injury
   - Elevated blood pressure
   - Elevated pBP
   - Underwent emergency surgery

Does the patient suffer from any of those conditions?

- No
- Yes

Any other condition that could possibly lead to TACO?

- Yes
- No

Reconsider / delay transfusion

Transfusion is needed and not deferrable

Preventive measures
- Evaluate the use of pretransfusion diuretics
- Slower rate of infusion (1ml/kg/h)
- Monitor closely
- Transfuse only one unit, then re-assess anemoa

Transfusion

In case of adverse event

Treat accordingly, report to hospital ICU

Report to Swissmedic
Swissmedic TACO Checklist (draft)

Consider the following risk factors for TACO

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   - Elevated proBNP
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Swissmedic TACO Checklist (draft)
TACO prevention: what else could we do?

- Teaching, teaching, teaching
  - New staff (nurses, resident, …)
  - Continuous training
- IT integration
Definition: respiratory distress within 24 hours of transfusion that does not meet the criteria of TRALI, TACO or allergic reaction.

TAD is an exclusion diagnosis!
Incidence & pathophysiology

- Badami et al., Vox Sanguinis (2015): «We found that many TAD may have been TACO. TAD may represent mild, atypical or overlap entities, and there may be a residuum of cases with currently unexplained pathophysiology». 
HV - Reporting

- When reporting TR with respiratory symptoms:
  - Do not forget to report dyspnea (!) – ask nurses, they probably know this information / Add dyspnoe to your internal report form if you are using one
  - Report medical history (especially known risk factors)
  - Every clinical information is helpful (positive fluid balance, lung examination, SpO2 value, patient’s weight, …)
  - Report NT-pro-BNP value
TR with respiratory symptoms - Summary

Respiratory Symptoms

- Urticaria/Pruritus
  - Bronchospasm
  - Angioedema
  - Hypotension
- Fever +/- chills
  - Respiratory distress
  - Hypotension
  - No response to diuretics
- Fever +/- chills
  - Respiratory distress
  - Hypertension
  - Response to diuretics
  - Fluid overload
- Respiratory distress
  - No other symptom

- Allergic reaction suspected
- TRALI suspected
- TACO suspected
- TAD suspected
References

- Vlaar et al., Lancet 2013
- Li et al., Transfusion 2009
- Tobian et al., Transfusion 2008
- UpToDate (www.uptodate.com)
- Skeate et al., Curr Opin Hematol 2007
- Andrzejewski et al., Transfusion, 2012
- Sarai & Tejani, Cochrane Library, 2015
- Badami et al., Vox Sanguinis, 2015
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- ISBT Definitions, 2011 (www.isbtweb.org)