Microbial Safety of Platelet Concentrates: updates and outlook

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Microbial Safety

- gene therapy products
- cell therapy products
- tissue engineered products
- vaccines
- sera, Ig's, mAb's
- blood/plasma deriv. products
- allergens

ATMP

- Marketing authorisation
- Licensing of clinical trials
- OMCL batch release
Platelet concentrates are the most frequent source of the transfusion related septic reactions

Measure to prevent bacterial contamination

- donor deferral criteria of risk patients
- effective skin disinfection procedures
- aseptic blood collection and processing
- utilization of sterile equipment
- predonation sampling
- leukocyte depletion
How frequent are septic episodes after transfusion of PCs?

**PEI hemovigilance report 2015**

<table>
<thead>
<tr>
<th>Transfusion-related bacterial infections (ppm)</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBCs</td>
<td>0.46</td>
<td>0.49</td>
<td>0.75</td>
<td>0.27</td>
</tr>
<tr>
<td>PCs</td>
<td>5.82</td>
<td>3.99</td>
<td>8.03</td>
<td>1.97</td>
</tr>
<tr>
<td>Plasma</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
</tbody>
</table>
Microbiological control strategies for TCs are not harmonized among EU member states

EC Directives
2002/98/EC and 2004/33/EC
differently implemented at national level

PEI questionery / EDQM survey
Risk mitigation strategies: overview

A) no screening, limited storage

B) QC / no routine screening

DE

/ RMM

MT IT ES CZ HR DE
AT FI BG LV LT LU

4 days 5 days 7 days
Platelet shelf-life
Risk mitigation strategies: overview

A) no screening, limited storage

B) QC / no routine screening

C) Routine screening: early sampling

D) Routine screening: late sampling

Platelet shelf-life
Early sampling screening strategy is suboptimal for detection of microbial contaminants

- Inefficient due to sampling error: only 10-50% of true contaminants are detected (Ramirez-Arcos 2017)
- False positive rates due to auto-sterilization
- Expenses ca. $50000 for prevention of a single septic episode
**State of the Art I: growth based Methods**

- Late sampling (>30-48 h after donation)
- Large Sample Volume > 8 ml / bottle
- Both aerobic and anaerobic bottle
- Quarantine before and during testing (6h)

- > 90% Reduction of septic reactions (McDonald 2017 NHSBT)
- false positive rate (anaerobic)
- „negative to date“ concept
- expenses
Risk mitigation strategies: overview

A) no screening, limited storage
- DE

B) QC / no routine screening
- MT IT ES CZ HR DE AT FI BG LV LT LU

C) Routine screening: early sampling
- NL IE UK DK PT

D) Routine screening: late sampling
- UK

E) Pathogen reduction
- BE CH FR

Platelet shelf-life
- 4 days
- 5 days
- 7 days
State of the art II: Pathogen reduction systems

Donation Day
Day 1
Day 2
Day 3
Day 4
Day 5
Day 6
Day 7

TC + Amotosalen + UV A
TC + Riboflavine + UV
TC + DNA crosslinking
⇒ Inactivation i.e.
(several logs) reduction of viability for bacteria, fungi and viruses
State of the art II: Pathogen reduction systems

- proactive strategy
- efficient

additional step in the manufacturing
quality of platelets?
expenses

Septic reaction before and after the implementation of PR in Swiss

<table>
<thead>
<tr>
<th>Year</th>
<th>Conventional platelet component transfusion-related sepsis (fatal)</th>
<th>INTERCEPT platelet component transfusion-related sepsis (fatal)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005</td>
<td>6 (2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>2006</td>
<td>2 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>2007</td>
<td>2 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>2008</td>
<td>2 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>2009</td>
<td>3 (1)</td>
<td>0 (0)</td>
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<tr>
<td>2010</td>
<td>1 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>2011</td>
<td>0 (0)</td>
<td>0 (0)</td>
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<tr>
<td>2012</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>2013</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>2014</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>2015</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>2016</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Total</td>
<td>16 (3)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

*Two-sided Fisher’s exact test p < 0.001.
*Total units 158,502.
*Total units 205,574.

Donation Day
Day 1 Day 2 Day 3 Day 4 Day 5 Day 6 Day 7
PI Freigabe
< 24h after donation

Jutzi et al 2018
Is it worth to implement microbial control strategy?

Reported incidence about 5 ppm = 0.0005%
What is the frequency of contaminated PC?

The frequency of contaminated TCs is 217-823 ppm (0.02-0.08%; 1:1200-1:5000) (6 studies)

(that means for EU = ca. 600-2300 infected TCs units / year)

=> These figures are usually significantly higher than hemovigilance reports
Possible reasons for underreporting of septic episodes after PC transfusion

- Passive vigilance report: only 10-20% from total incidence (Jacobs et al.)
- Only 10% of reports have verified a root cause of infection (PEI Data)
- Concomitant effective antibiotic treatment
- Only acute septic (pyrogenic) reactions (till 4h after transfusion)
Transfusion of contaminated PCs is frequently asymptomatic

long-term impact on patient health?

Hong et al 2016
Ca. 19000 Patients

Conclusions: After adjustment for confounders, including patient severity and other blood components, platelet transfusion was independently associated with ICU-acquired infection.
Summary

- Risk mitigation for bacterial contamination of platelet concentrates can be implemented through screening by growth-based methods or pathogen reduction technologies.

- Late (>36 h after donation) sampling strategy seems to be more effective than early sampling.

- Whenever possible, the microbiological control strategy should be implemented, since frequency of transfusion septic incidents might be much higher as hemovigilance data suggest.

- Necessity of harmonization of the microbiological strategies among EU member states.
Thank you for your attention!

Section Microbial Safety: Ingo Spreitzer, Marcel Prax, Holger Lößner, Oliver Karo, Birgit Blissenbach, Anja Schneider, Marie Anders-Mauer, Bjorn Becker, Philipp Windecker
Low titer spiking (ca. 30 CFU / Unit) of PCs from different donors
Colony count determination over time (22.5°C, agitation)

relevant differences between strains of the same bacterial species