Haemovigilance Workshop, 19. Mai 2014

Pathogeninaktivierung für Plättchen: Einführung und klinische Auswirkungen

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2009 Verfahrenszulassung

Intercept Platelets 58789 Cerus Europe B.V. 11.08.2009

Haemovigilance Jahresbericht

CH Haemovigilance Daten 2005 – 2009

- 15 gemeldete Transfusionsreaktionen aufgrund bakteriell lontaminierter TK (high imputability)
- davon 3 Todesfälle(2 Klebsiella, 1 E. Coli)
- 1 TR pro 8’000 TK
- 1 schwerwiegendeTR pro 14’000 TK
- 1 Todesfall pro 40’000 TK
  = 1 Todesfall alle 1.6 Jahre

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Einschreiben
BSD SRK
z.H. von Dr. Rudolf Schwabe
Laupenstrasse 37
Postfach 5510
3001 Bern

Bern, 13. Oktober 2009

„…ist es klar angezeigt, geeignete Massnahmen zur zuverlässigen Vermeidung klinisch relevanter bakterieller Kontaminationen von TK anzugehen, und diese in der Schweiz so bald wie möglich flächendeckend und für alle Patientengruppen einzuführen.“

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AABB 2009 – Abstract book

P5-020A

Clinical Effectiveness and Safety of Pooled, Random Donor Platelet Concentrates, Leucoreduced and Stored up to Seven Days in Either Plasma or Additive Solution with and Without Pathogen Reduction in Hemato-oncological Patients

J H Kerkhoffs[1] (j.kerkhoffs@sanquin.nl), V M Novotny[2], P A Te Boekhorst[3], M R Schipperus[4], J J Zwaginga[5], L van Pampus[2], W L van Putten[6], P C Huijgens[7], A Brand[1], D J van Rhenen[1]. [1]*Research*

(P < 0.0001). 24 patients in the PR PAS-III arm experienced bleeding episodes as compared to 14 in the plasma PC arm (P = 0.045). After reviewing these data, the independent Data Safety Monitoring Board advised us to halt inclusion in the PR-PAS III-PC. **Conclusion:** Although the final analysis of the study still has to be completed, data of the second interim analysis strongly suggest inferiority of platelets stored in PAS III treated with pathogen reduction. As the study has just finished enrolling patients we expect

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edqm
European Directorate for the
Quality of Medicines & HealthCare

COUNCIL OF EUROPE CONSEIL DE L'EUROPE

Department of Biological Standardisation, OMCL Network & HealthCare (DBO)

TS056-SYMPOSIUM ON
"IMPLEMENTATION OF PATHOGEN REDUCTION/INACTIVATION TECHNOLOGIESFOR BLOOD COMPONENTS"

2nd and 3rd September 2010

Venue: 7 Allée Kastner, Strasbourg, France
(Room 100)

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Preventive measure

- Pathogen inactivation (Intercept®)
- for all platelet concentrates
- Implementation in 3 pilot centres between October and December 2010 (accounting for up to 50% of all platelet concentrates produced in Switzerland)
- Nationwide introduction planned to be completed by mid / end 2011
- Clinical trials with Mirasol® possible

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Studien

Kerkhoffs JL, van Putten WL, Novotny VM, Te Boekhorst PA, Schipperus MR, Zwaginga JJ, et al. Clinical effectiveness of leukoreduced, pooled donor platelet concentrates, stored in plasma or additive solution with and without pathogen reduction. Br J Haematol. 2010;150:209–217.

> "Despite the potential advantages of pathogen (and leucocyte) inactivation of amotosalen-HCl/UVA-treated platelet products, their **clinical efficacy is inferior** to platelets stored in plasma, warranting a **critical** reappraisal of employing this technique **for clinical use**."

Lozano M, Knutson F, Tardivel R, Cid J, Maymó RM, Löf H et al. A multi-centre study of therapeutic efficacy and safety of platelet components treated with amotosalen and ultraviolet A pathogen inactivation stored for 6 or 7 d prior to transfusion. Br J Haematol. 2011;153:393–401

"Primary endpoint

- A-PC, when stored for 6 or 7 d, provided sufficient 1-h post-transfusion CCI compared to C-PC stored for 6 or 7 d.

Seondary endpoints

- patients treated with A-PC platelets had significantly **lower 24-h CI (P = 0.01) and 24-h CCI** (P = 0.003) compared to patients receiving C-PC
- The median **time to the next platelet transfusion after the study transfusion** was 2.2 d for the A-PC group and 2.3 d for the reference group (P = 0.717, log-rank test, Fig 1)
- There was **no significant difference** in the distribution of the **number of RBC units transfused** between the treatment groups (P = 0.821).
- There were **no statistically significant differences** between treatment groups **in the frequency of any AE** deemed by the investigator as related to the study transfusion

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Meta-Analysen

Vamvakas, E. C. (2011). "Meta-analysis of the randomized controlled trials of the hemostatic efficacy and capacity of pathogen-reduced platelets." Transfusion **51(5): 1058-1071.**

- Pathogen-reduced PLTs were associated with a significant
  ($p < 0.05$) reduction in 1- and 24-hour posttransfusion corrected count increments
- …significant increase in all and in clinically significant bleeding complications (odds ratio 1.58 and 1.54)
- frequency of severe bleeding complications did not differ.

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Expectations & possible concerns

- No more septic transfusion reactions due to PC and …
- Decreased number & severity of transfusion reactions
- Increase in PC collection / use (~ 15%)
- Acceptance problems with clinicians possible
- Possibly lower CCI → clinical significance??

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Meta-Analysen

Cid J, Escolar G. Lozano M. Therapeutic efficacy of platelet components treated with amotosalen and ultraviolet A pathogen inactivation method: results of a meta-analysis of randomized controlled trials. Vox Sanguinis. 2012;103;322–30.

- Randomized controlled trials were statistically homogeneous when we analysed CCI-24 h, and the transfusion of **C-P was associated with a higher CCI-24 h** when compared with the transfusion of I-P
- Regarding the **CCI-1 h, transfusion interval and OR of bleeding**, there was a **high variation among** the findings of the **RCTs**
- Moreover, **we extracted data as reported in the RCTs, and we did not perform any recategorization** of this outcome, such as severe haemorrhage or clinically significant bleeding, **as Dr Vamvakas did**.
- However, **we did not find statistically significant differences in the OR of bleeding** between I-P and C-P, when doubleblinded and high methodologic quality trials were combined

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Transfused PC units (CH 2011)

~ 80% PCs pathogen inactivated, ~ 20 % conventional PCs

2011 increase of transfused PC of ~10%, possibly due to:

- General increase in the number of patients needing PC transfusions
- Precautionary raise of the transfusion trigger (from 5 to 10 G/l) for prophylactic platelet transfusions in some clinics
- PC transfused more readily in others (PI-PC considered to be safer)
- PI procedure as contributing factor to increase not excluded

But: Observed increase in line with experience of last 10 y!

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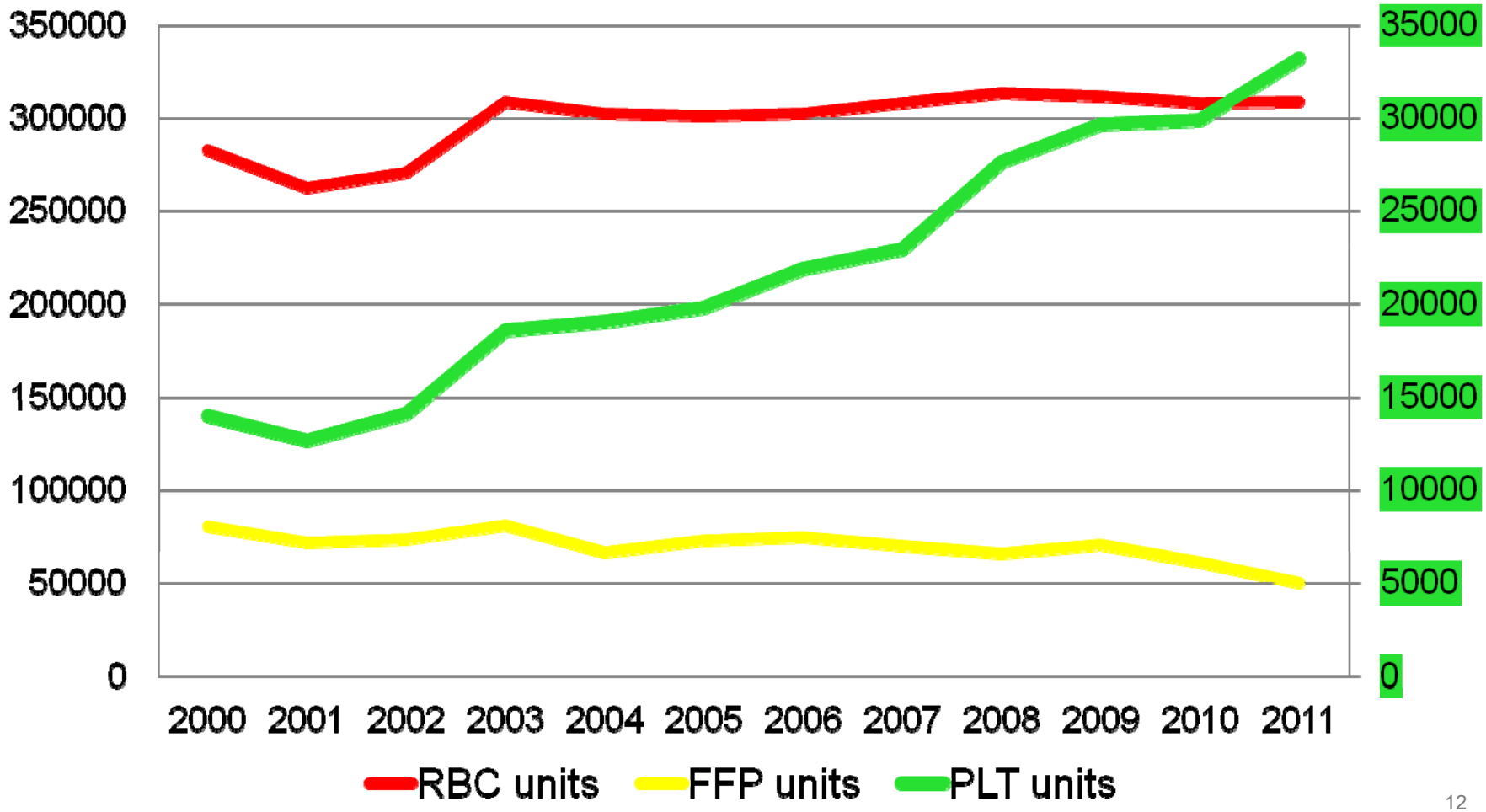
Observations: Transfused blood



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Transfused PC units in CH 2011

With the introduction of pathogen inactivation, the proportion of whole blood derived buffy-coat PCs increased from 14 to 23%

- Reflecting the reduced significance of possible bacterial contamination
- To meet the rising need
- As contribution to cover the costs of pathogen inactivation

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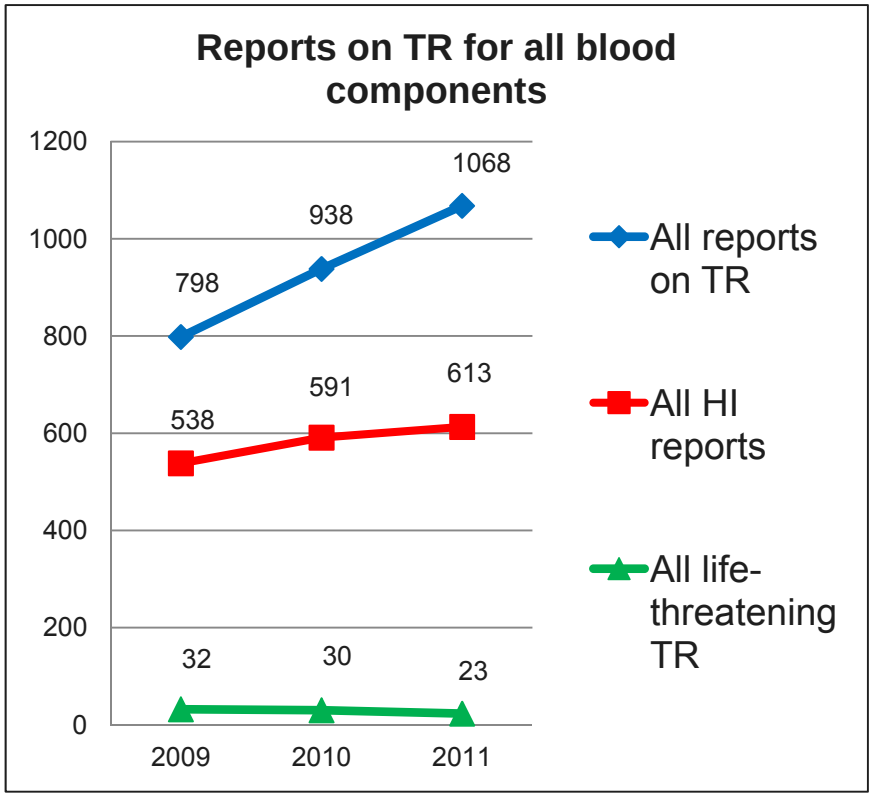
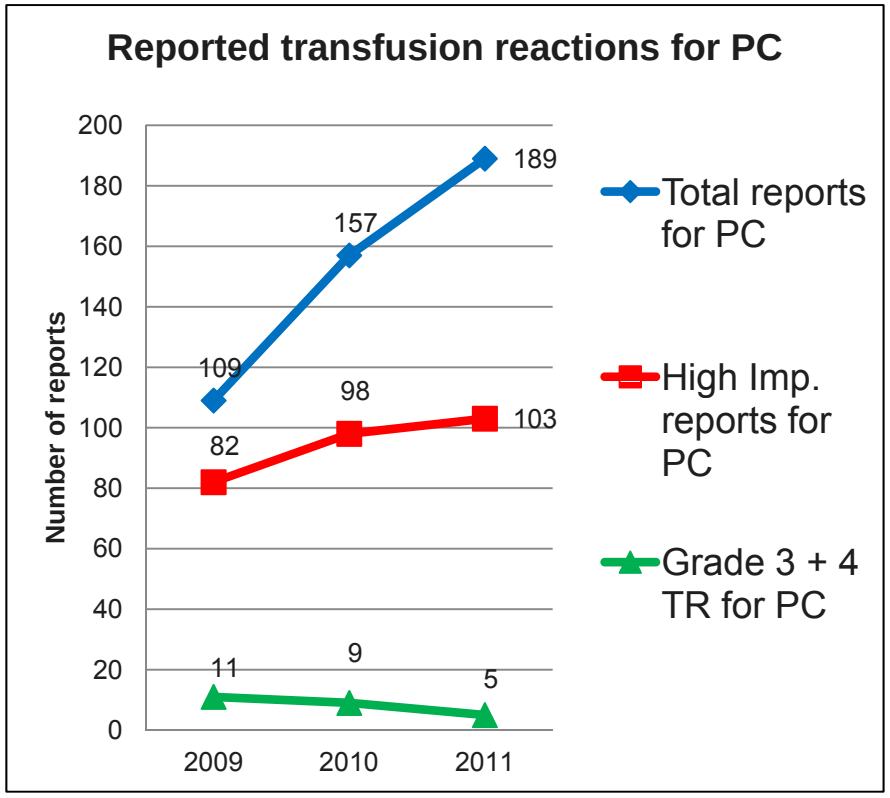
Observations 2011– Haemovigilance





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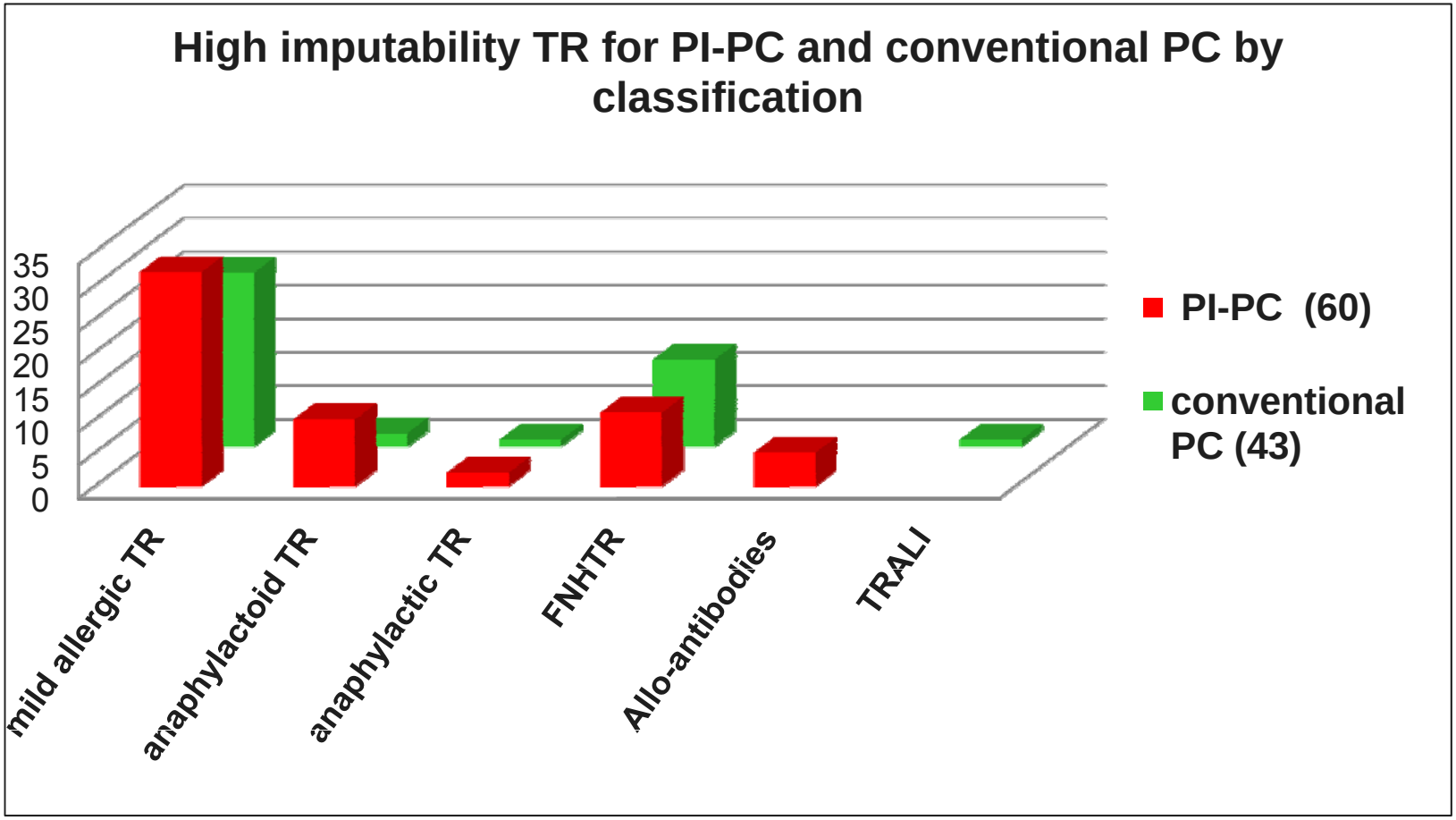
Observations 2011– Haemovigilance



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Risk of transfusion for PCs 2011

Transfusion reactions	2011 PI-PC‘s		2011 conventional PC‘s		2010 (only conventional PCs)	
Units transfused	26‘454		6‘614		29‘900	
Risk = 1 reaction per x PC transfusions	Reports	Risk	Reports	Risk	Reports	Risk
All high imputability reports	60	~1: 440	43	~1:150	98	~1:330
High imputability grade 3 reactions	3	~1:8800	2	~1: 3300	9	~1:3300

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Summary (2011)

- As expected, no transfusion transmitted bacterial infections after PC transfusions in 2011
- < 2/3 of TR after PI-PC (80% of PCs)
  ~ 20% cPC's → >30% of all PC-related reports.
- Lower risk for adverse events, especially life threatening reactions; risk reduction from 1:3'300 to 1: 8'800
- Demand for PC increased by 10.5 %

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Conclusion (2011)

- PI for platelet concentrates substantially reduces the risk for bacterial TTIs and also for platelet related transfusion reactions in general
- Our findings underline the superior safety profile of pathogen inactivated PCs
- It remains to be seen how this trend towards declining platelet related TRs develops over the next few years when more Haemovigilance data become available

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Studien

Sigle JP, Infanti L, Studt JD, Martinez M, Stern M, Gratwohl A, et al. Comparison of transfusion efficacy of amotosalen-
based pathogen-reduced platelet components and gamma-irradiated platelet components
Transfusion 2012 Nov TRANSFUSION 2013;53:1788-1797

44 patients assigned to PR-PLTs received 220 PR-PLTs and 136 conventional PCs;
72 controls received 517 conventional PCs.

No significant differences between the two treatement groups in:

- 1-hour CCI (Mean and median)
- 24-hour CCI
- 1- and 24-hour CI.
- mean time to next PLT transfusion
- number of patients who received two or more PCs on the same day
- Number of RBC units per patient
- Number of days to RBC transfusion after initial study PLT transfusion
- Number of FFP units per patient

- With 1.4% of PR-PLT transfusions associated with an ATR, our results are in line with our previous experience and with that of larger studies showing a generally low incidence of transfusion reactions for PR-PLTs

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Meta-Analysen

Vamvakas EC. Meta-analysis of the studies of bleeding complications of platelets pathogen-reduced with the Intercept
system. Vox Sanguinis. 2012;102:302–16.

- "The RCT of Kerkhoffs et al was criticized for its lack of blinding and for other design attributes"

- The method for recording bleeding complications was **blinded in all studies, except in Kerkhoff's** study were it was unblinded
- "For **all bleeding complications** (…) there is **no difference** in the risk of bleeding between recipients of pathogen-reduced vs. non-pathogen-reduced platelets (…).
- "For clinically significant bleeding complications (…) there is a statistically significant increase (P<0.05) in the risk of bleeding in assosciation with the receipt of non-pathogen-reduced (compared with pathogen-reduced) platelets (…)."
- "For **severe bleeding** complications (…) there is **no difference**…"

- Even if individual clinicians are sufficiently convinced about the benefit-to-risk ratio of Intercept to prescribe treated platelets fot their own patients, policymakers must demand more definitive evidence about the lack of toxicity of a new treatment before they can approve such an expensive technology for routine clinical use"

CH Haemovigilance Daten bis Ende 2013

Tabelle 10 Gemeldete Transfusionsreaktionen mit konventionellen und pathogeninaktivierten TK

Transfusionsreaktionen	2009 – 2011 kTK		2011 – 2013 PI-TK	
Transfundierte Einheiten	66‘000		95‘515	
Risiko = 1 Reaktion pro x TK	Meldungen	Risiko	Meldungen	Risiko
Alle HI Meldungen	223	~ 1:300	251	~ 1:400
HI Meldungen Grad 3 & 4	23*	~ 1:3‘000	13*	~ 7‘000

*p=0.04 (Fisher exact test)

Nutzen: Vermeidung bakterieller Infekte

(Häufigkeit bakteriell kontaminierter TK)

The residual risk of receiving a bacterially contaminated platelet component with clinical consequences is estimated at approximately 1 in 75’000, if culture negative and 1 in 33’000 if not tested by culture.
Arch Pathol Lab Med. 2007;131:702–707

Schweizer Daten 2005 - 2010:

Todesfälle	**1:50‘000 TK**
Lebensbedrohliche Transfusionsreaktionen (TR)	**1:12‘000 TK**

ca 152‘000 Tk Transfundiert, dabei 3 Todesfälle und 13 Lebensbedrohliche Reaktionen

Seit 2011 keine TR durch bakteriell kontaminierte TK

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Potentielle Risiken 2013

- (toxische) Langzeit-Effekte
  - Bisher keine Hinweise, zur Zeit keine Aktivitäten
- Verminderte Wirksamkeit / Lagerdauer
  - Klinische Daten von > 5000 PI-TK Transfusionen inkl. CCI, EK- und TK-Bedarf sowie Transfusionsintervall
- Respiratorische Komplikationen
  - TRALI Auswertung CH HV Daten 2002-2013 (Ausblick HV Jahresbericht 2013)

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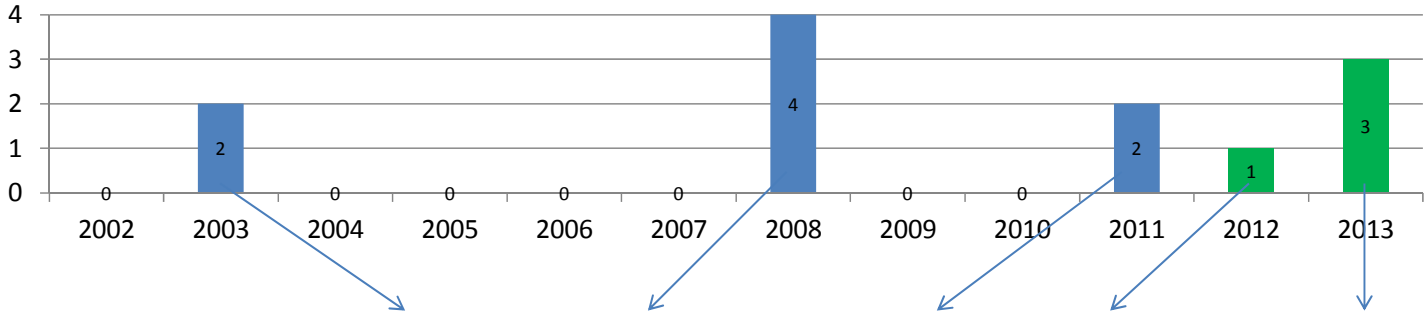
TRALI Fälle mit TK in der Schweiz



Jahr	2003 (2 Fälle)	2008 (4 Fälle)	2011 (2 Fälle)	2012 (1 Fall)	2013 (3 Fälle)
Imputability	Sicher Wahrscheinlich	Möglich/unwahrscheinlich Möglich Wahrscheinlich Möglich	Möglich Wahrscheinlich	Wahrscheinlich	Wahrscheinlich Wahrscheinlich Wahrscheinlich
Immunes versus Nicht-Immunes TRALI	Immun Nicht-Immun	Unbekannt Unbekannt Immun Immun	Immun Immun	Immun	Nicht-immun Immun Immun
Produkt(e) erhalten	TK FGP + TK	TK (Apherese) + EK TK (Apherese)+FGP+EK TK (Apherese) TK (Apherese)	TK + EK TK (Apherese)	TK (Apherese)	TK (buffy coat) TK (buffy coat) TK (Apherese)
Schweregrad	3 3	3 3 4 3	3 3	3	3 3 2