Pathogen Reduced Platelets

What is the real cost and benefit?

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Disclosures

- Advisory board and sponsored research – Werfen Corporation

Objectives

- Describe the mechanisms by which pathogen reduction technology enhances platelet safety and how in vitro testing is used to predict efficacy
- Evaluate the clinical evidence associated with pathogen-reduced platelets demonstrating 1) reduction of transfusion-transmitted infections and 2) hemostatic function
- Discuss the MiPLATE trial and the potential role pathogen reduced platelets have for patient care

Pathogen Reduction Technology

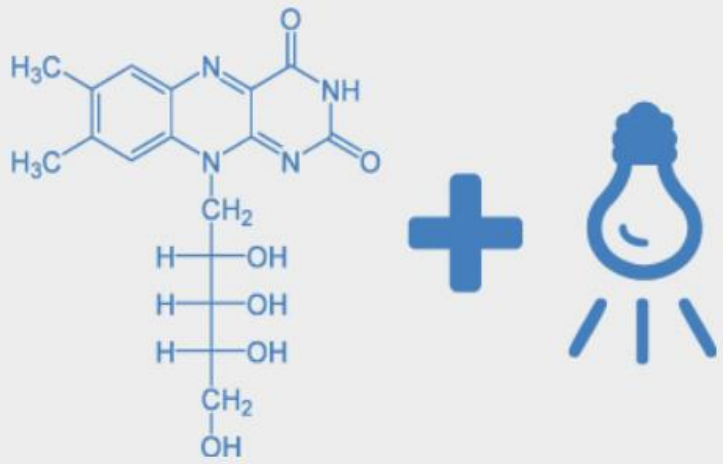
- From the AABB Glossary:
  - Exposure of blood components to a system designed to reduce the risk of transfusion-transmitted infections

- Three major systems exist for platelets
  - Intercept from Cerus (psoralen + UV)
  - Mirasol from Terumo (riboflavin + UV)
  - Theraflex from Macopharma (UVC alone)

Pathogen Reduction Technology

- Example: Mirasol

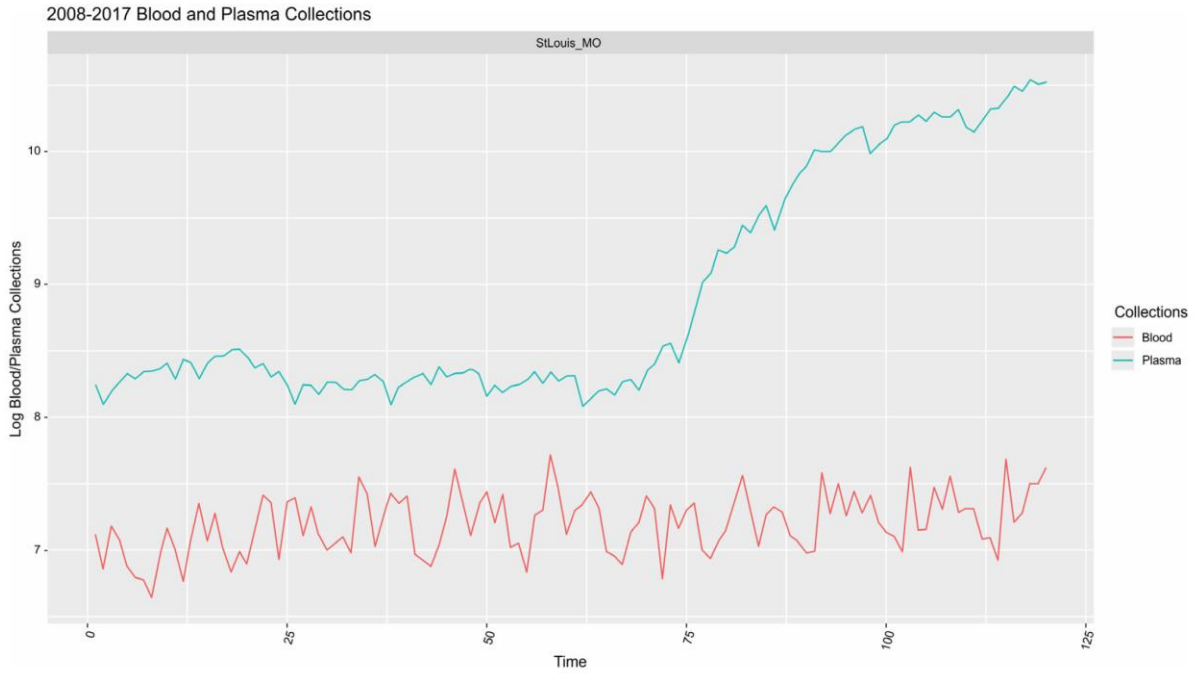
Riboflavin + UV light = irreversible inactivation of pathogens and white blood cells



PR Platelets and Infectious Disease Risk

- Ideal characteristics
  - Complete inactivation of known and unknown bacteria, viruses, fungi
  - Complete inactivation of cellular components (leukocytes)
  - No effect on functional aspects of platelets

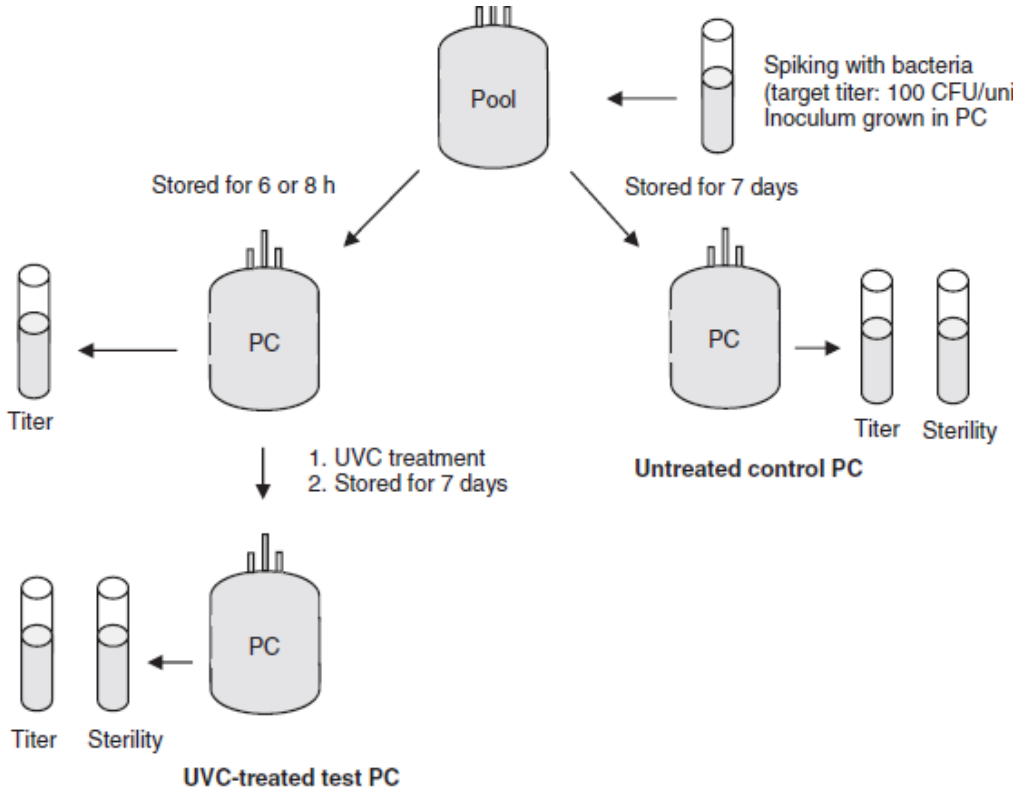
- In theory, “Pathogen Inactivation” could lead to paying donors for platelet donations without impacting volunteer blood donations



Stubbs, et al. Transfusion 2021;61:303-312

PR Platelets and Infectious Disease Risk: Bacteria

- Bacteria
  - How to assess pathogen reduction?
  - Typical experiment is to inoculate platelet products
    - Titers – plating platelet product, counting CFU/mL, calculate Log (pretreatment bacterial count / posttreatment bacterial count)
    - Sterility – By taking 10 mL and injecting into aerobic and anaerobic cultures for growth



Gravemann et al. Transfusion 2019;59:1324-1332

PR Platelets and Infectious Disease Risk: Log Reduction in Bacterial Growth

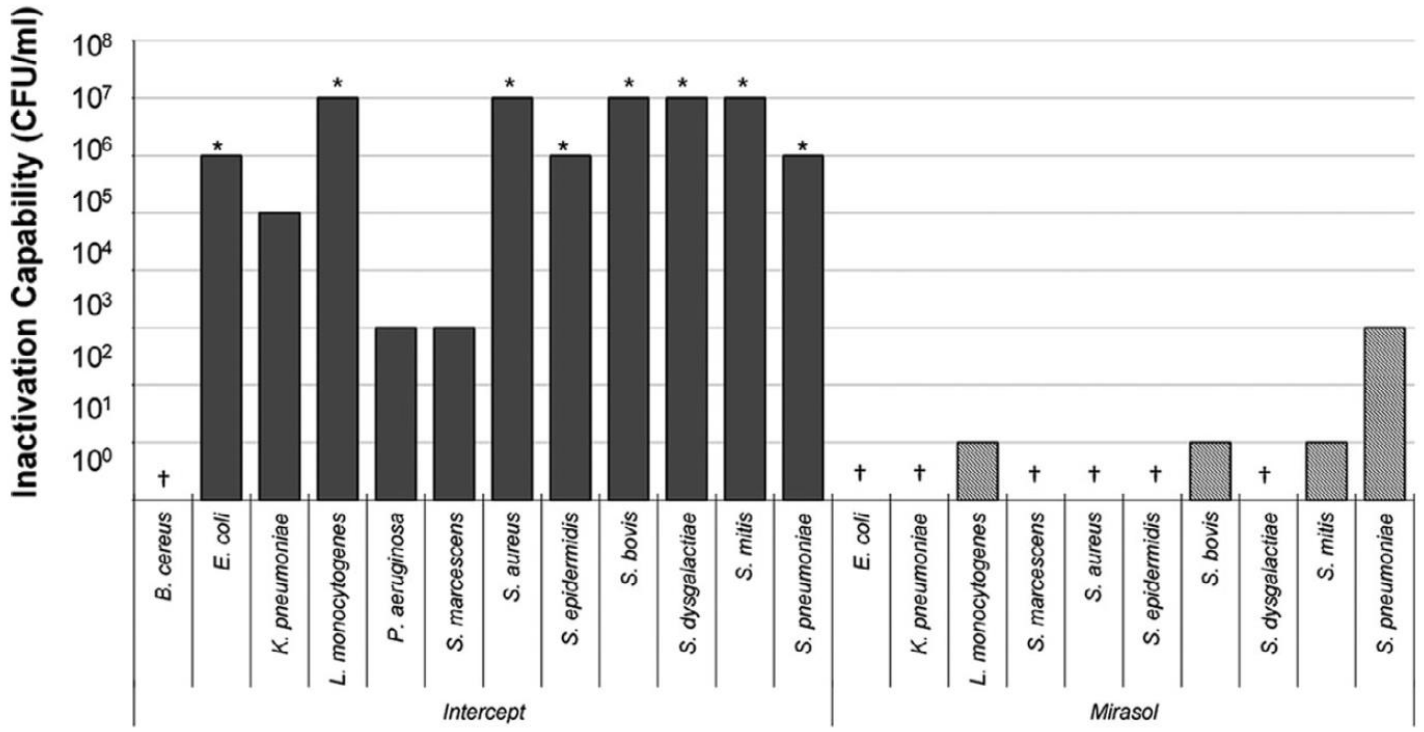
Bacteria	Mirasol	Intercept	Theraflex
E. cloacae		5.9	6.3 +/- 0.6
E. coli	>4.4	>6.4	7.3
S. aureus	3.6 to 4.8	6.6	4.4 to 6.6

This looks impressive!
How does Log reduction translate to safety for our patients?
Is there a better measure?

Gravemann et al. Transfusion 2019;59:1324-1332
Intercept package insert
Mirasol – Performance Report

PR Platelets and Infectious Disease Risk: Bacteria

- Bacteria
  - How to assess pathogen reduction?
  - “Inactivation Capability” – the highest concentration of bacteria that results in no viable bacterial growth



McDonald et al. Vox Sanguis 2021;116:416-424

PR Platelets and Infectious Disease Risk: Viruses

- Particularly may be of benefit for new or re-emerging threats (and not just for platelets)
  - M-pox virus infectivity likely reduced by Mirasol
  - SARS-CoV2 virus spiked into plasma were inactivated by Intercept technology
  - Ebola convalescent plasma

TABLE 1. EBOV IgG antibody titers pre- and post-PRT

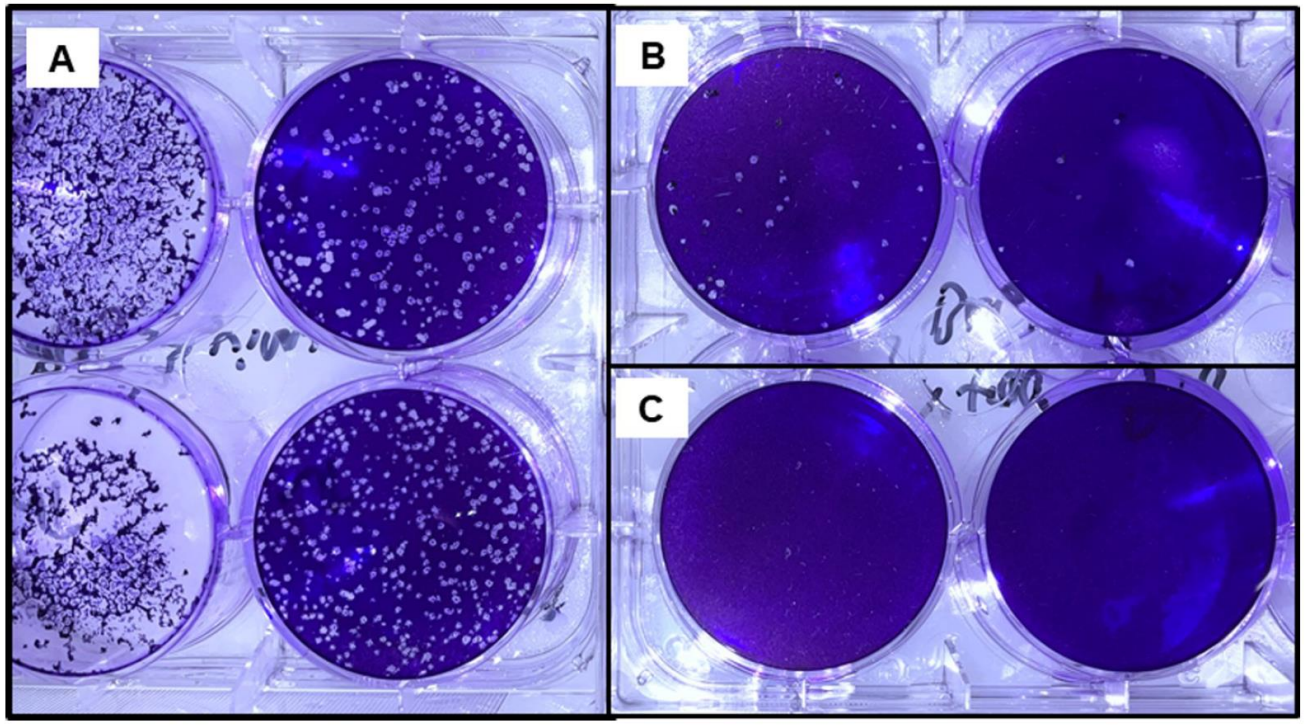
Subject (weeks post diagnosis)	Pre-PRT (N = 10)	Post-PRT (N = 10)	p value
PsVNA50 titer			
101 (19.8)	656	683.5	
101 (23.4)	264	755.5	
101 (27.4)	884	819	
102 (13.7)	416	502	
104 (17.7)	683	687	
105 (31.1)	852	1526	
105 (45.4)	497	729.5	
105 (57.7)	807	880	
106 (66.0)	1849	2932.5	
107 (61.5)	270	687	
GMT (SD)	612.4 (1.80)	882.9 (1.66)	**p = 0.016**
GP-ELISA titer			
101 (19.8)	5.235	2.859	
101 (23.4)	3.179	2.393	
101 (27.4)	2.564	3.046	
102 (13.7)	1.731	1.881	
104 (17.7)	0.846	0.904	
105 (31.1)	1.609	1.622	
105 (45.4)	1.349	1.348	
105 (57.7)	1.434	1.448	
106 (66.0)	1.974	1.603	
107 (61.5)	0.661	0.683	
GMT (SD)	1.739 (1.83)	1.617 (1.61)	**p = 0.345**
Irr-ELISA titer			
101 (19.8)	157.866	150.404	
101 (23.4)	205.146	152.686	
101 (27.4)	164.897	127.182	
102 (13.7)	67.123	60.239	
104 (17.7)	43.945	39.678	
105 (31.1)	67.099	62.146	
105 (45.4)	65.318	65.454	
105 (57.7)	91.497	77.269	
106 (66.0)	34.830	44.434	
107 (61.5)	14.290	13.294	
GMT (SD)	70.753 (2.24)	64.754 (2.08)	**p = 0.093**

Samples collected in ACD.
EBOV = Ebola virus; GP = glycoprotein; Irr = irradiated; PRT = pathogen reduction technology; PsVNA = pseudovirion neutralization assay.

Ragan et al. PLoS ONE 18(1):e0278862
Ashar et al. Vox Sanguinis 2021;116:673-681
Dean et al. Transfusion 2020;60:1024-1031

PR Platelets and Infectious Disease Risk: Viruses

- Virus Inactivation
  - Difficult to quantify in a clinically meaningful *in vitro* assay
    - Host susceptibility
    - Infectious dose
    - Some viruses cannot be cultured
    - Infectivity is assessed by viral plaque assays or plaque neutralization assays



M-pox plaque assay results. A = stock virus; B=virus with riboflavin; C=virus with riboflavin + UV

Ragan et al. PLOS One 18(1):e0278862

PR Platelets and Infectious Disease Risk: Viruses

- Virus Inactivation
  - Difficult to quantify in a clinically meaningful *in vitro* assay
    - Infectivity is assessed by viral cytopathic effect on cell culture exposed to spiked platelets ([a] = log Tissue Culture Infectious Dose 50%)

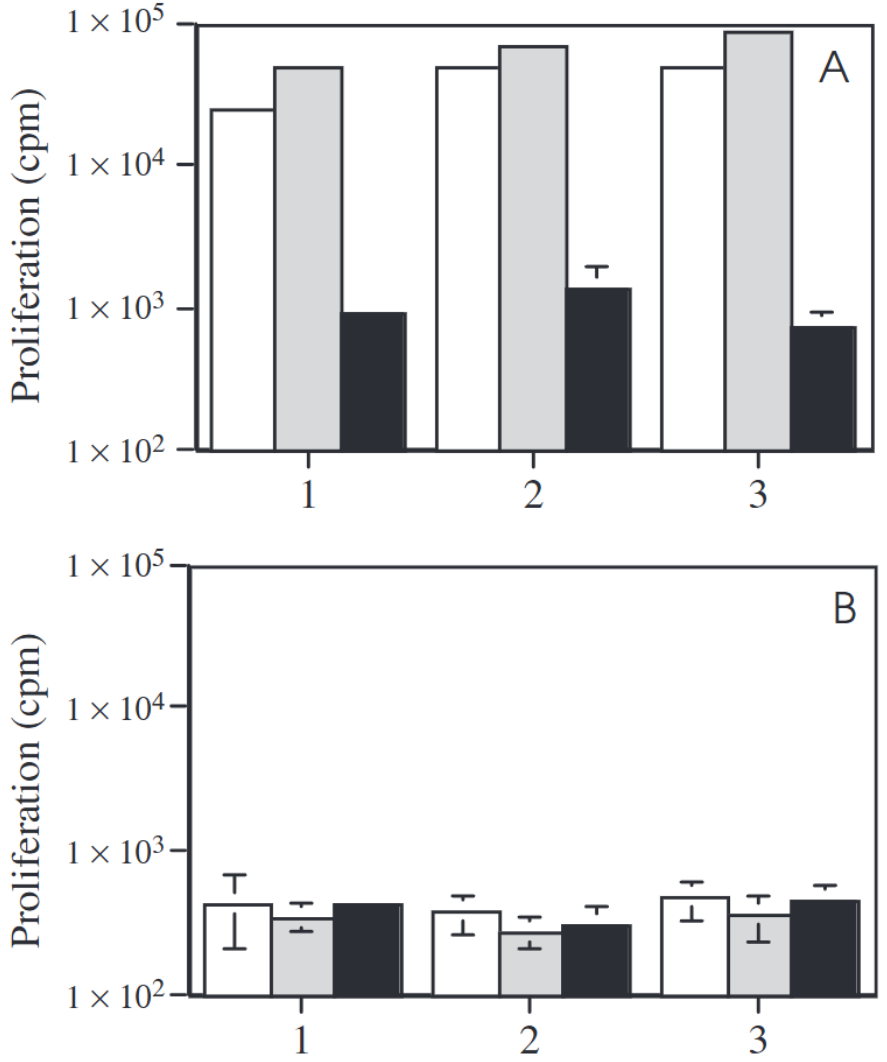
	Mirasol PRT System			Intercept Blood System		
Virus	Preinactivation total viral load[a]	Postinactivation total viral load[a]	Log reduction factor[b]	Preinactivation total viral load	Postinactivation total viral load	Log reduction factor
HIV-1	7·44 ± 0·04	≤3·25[c]	≥4·19 ± 0·04	7·47 ± 0·05	≤3·24[c]	≥4·23 ± 0·05
BVDV	8·97 ± 0·27	7·14 ± 0·26	1·83 ± 0·34	9·00 ± 0·27	≤2·97[c]	≥6·03 ± 0·26
PRV	8·22 ± 0·09	5·49 ± 0·15	2·73 ± 0·07	8·19 ± 0·19	≤2·99[c]	≥5·20 ± 0·18
HAV	8·47 ± 0·14	7·85 ± 0·15	0·62 ± 0·18	8·51 ± 0·14	7·75 ± 0·15	0·76 ± 0·21
PPV	7·87 ± 0·16	7·59 ± 0·07	0·28 ± 0·16	7·89 ± 0·16	7·52 ± 0·19	0·38 ± 0·18

Non-enveloped virus typically not inactivated well by PR: Hep A, ParvoB19, Hep-E

Kwon et al. Vox Sanguinis 2014;107:254-260

PR Platelets and Infectious Disease Risk: TA-GVHD

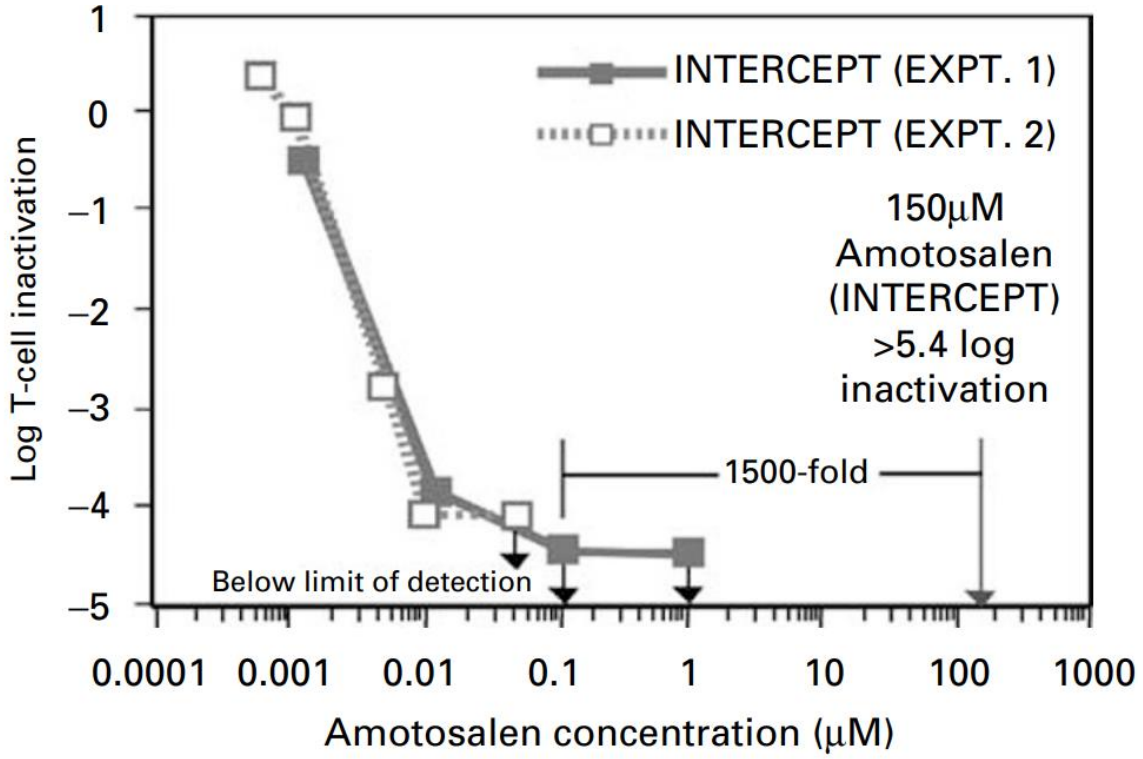
- Leukocyte Inactivation
  - Difficult to quantify in a clinically meaningful *in vitro* assay
    - Proliferation assays use stimulation of white blood cells such as mitogen and mitomycin C before and after treatment



Black bar = medium alone (Mirasol)
Fast et al. Transfusion 2006;46:642-648

PR Platelets and Infectious Disease Risk: TA-GVHD

- Leukocyte Inactivation
  - Difficult to quantify in a clinically meaningful *in vivo* assay
    - Murine model used Cerus technology to show TA-GVHD prevention in murine parent to F1 offspring



Corash, Lin. Bone Marrow Transplantation 2004;33:1-7

PR Platelets and Infectious Disease Risk: Not foolproof: Case Report

- Bacteria
  - Despite PR, transfusion-transmitted septic reactions can still occur
  - Male with ALL received a unit of Intercept platelets followed by sepsis
    - Peripheral blood and line cultures grew *Acinetobacter calcoaceticus/baumannii* complex
    - Saline rinse of implicated unit grew *Staphylococcus saprophyticus* and *Acinetobacter calcoaceticus/baumannii* complex
      - Both organisms were susceptible to the Intercept process
    - Likely contaminated bag as a source

Fridey et al. Transfusion 2020;60:1960-1969

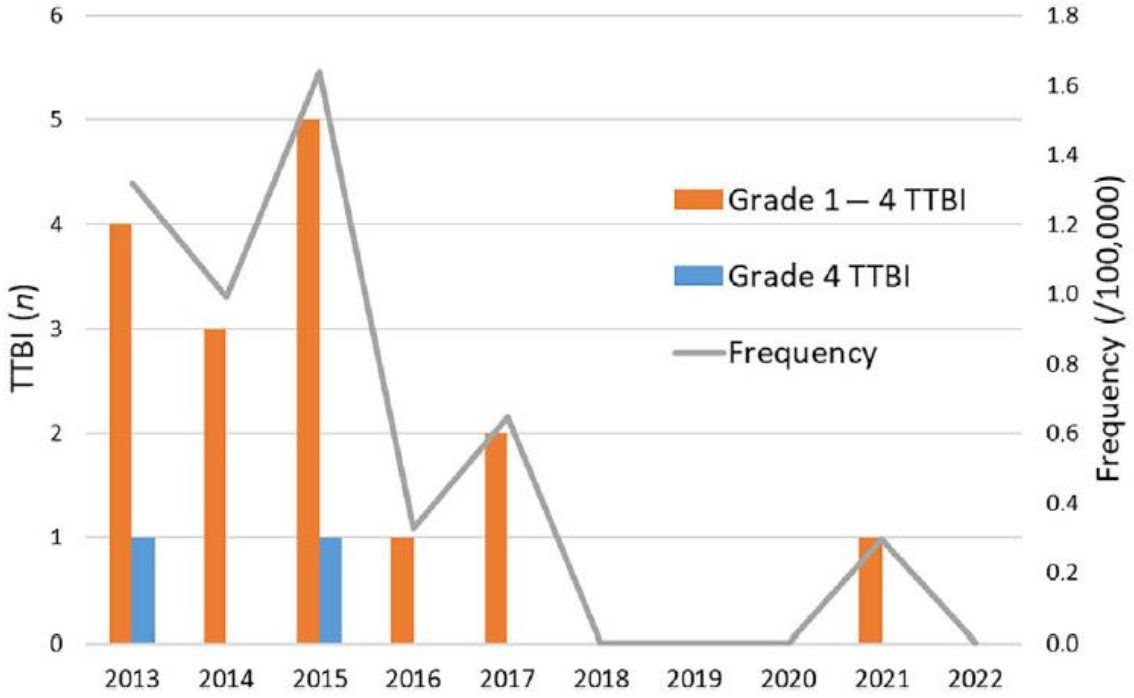
PR Platelets and Infectious Disease Risk: *in vitro* (and mouse) Summary

- Bacteria, viruses, parasites, and leukocytes all have nucleic acid damage by PR technology systems
  - Various levels of inactivation by technology
  - Some weaknesses include non-enveloped viruses

- What does real-world data tell us about the reduction of risk of transfusion-transmitted diseases with the use of pathogen reduced platelets?

PR Platelets and Infectious Disease Risk

- Best example is France
  - Completely switched to Intercept platelets in 2017
  - Average bacterial transfusion transmitted sepsis cases: 3/year before Intercept
    - 1/92,687 down to 1/1,645,295; $p < 0.001$
  - Three cases of TTBI after Intercept
    - *B. cereus* (spores?), *Citrobacter koseri,* and *Salmonella*



Richard et al. Vox Sanguinis 2024;119:212-218

PR Platelets and Infectious Disease Risk

- Transfusion-transmitted Hepatitis E occurred at a similar rate before and after implementation of Intercept (1 to 5 cases per year)

- Rate of Hepatitis C, B, or HTLV transfusion-transmission before or after implementation of Intercept was zero; one case of HIV positive blood in 2017 reported, without transfusion-transmission documentation

Richard et al. Vox Sanguinis 2024;119:212-218

PR Platelets and Economics

- Costs vary by institution for PR
  - $135.96 per unit for Intercept has been reported in the U.S.
  - $83 per unit for large-volume, delayed sampling of platelets has been reported in the U.S.

- Difference of $52.96 more for PR versus culture of platelets
  - Assumption: 329,059 x $50 = $16,452,950 per year for added safety from bacterial contamination (non-enveloped virus transmission about same)
    - About $1.5 million dollars per case saved

Richard et al. Vox Sanguinis 2024;119:212-218
Helander et al. Transfusion Medicine Rev 2021;35:60-61

PR Platelets – increased rate of use?

- Mean platelets transfusion per year
  - 301,233 before Intercept
  - 329,059 after Intercept
- Increased platelet usage in France after change to Intercept platelets – not addressed in paper
- Meta-reviews of published trials confirm that participant who receive PR platelets
  - Require more platelet transfusions
  - Lower CCI's
  - Shorter intervals between transfusions
- Does this translate into more bleeding risk?

Richard et al. Vox Sanguinis 2024;119:212-218
Estcourt et al. Cochrane 2017, Issue 7

PR Platelets: Clinical Bleeding Risk?

- In 2017, a review of 12 trials, none comparing PR platelets to each other
  - “No evidence of a difference between pathogen-reduced platelets and standard platelets in the incidence of clinically significant bleeding”
  - “Probably no difference in the risk of developing severe bleeding”

Estcourt et al. Cochrane 2017, Issue 7

PR Platelets: Clinical Bleeding Risk?

- How is bleeding assessed between recipients of PR platelets compared to standard of care platelets?
  - Corrected count increments
  - Bleeding assessments using WHO bleeding scale
    - Requires trained assessors and a bleeding assessment tool
    - Various studies evaluating bleeding assessment tools have shown mixed reproducibility

Rebulla et al. Transfusion 2020;60:1267-1277

PR Platelet Trial Summary

- Clinically significant bleeding is often discussed as WHO grade 3 and 4 (requires transfusion or results in fatality)
- Not enough WHO grade 3 and 4 bleeds in hospitalized patients to conduct a clinical trial with meaningful statistical comparisons
- Therefore, most clinical trials include Grade >= Grade 2 bleeds

WHO Bleeding Grade	Examples
Grade 1	Oropharyngeal bleeding ≤30 min in 24 h Epistaxis ≤30 min in previous 24 h Petechiae of oral mucosa or skin Purpura ≤1 inch in diameter Spontaneous hematoma in soft tissue or muscle Positive stool occult blood test Microscopic hematuria or hemoglobinuria Abnormal vaginal bleeding (spotting)
Grade 2	Epistaxis >30 min in 24 h Purpura >1 inch in diameter Joint bleeding Melanotic stool Hematemesis Gross/visible hematuria Abnormal vaginal bleeding (more than spotting) Hemoptysis Visible blood in body cavity fluid Retinal bleeding without visual impairment Bleeding at invasive sites
Grade 3	Bleeding requiring red blood cell transfusion over routine transfusion needs Bleeding associated with moderate hemodynamic instability
Grade 4	Bleeding associated with severe hemodynamic instability Fatal bleeding CNS bleeding on imaging study with or without dysfunction

PR Platelet Trial Summary: Primary Outcome

Trial (amotosalen)	euroSPRITE	SPRINT	IPTAS	EFFIPAP
Primary Endpoint	Platelet count increments and 1-hour CCI	% of patients with Grade 2 bleeding	% of patients with Grade 2 or higher bleeding	% of patients with Grade 2 or higher bleeding

Trial (riboflavin)	MIRACLE	PREPAReS	IPTAS
Primary Endpoint	1-hour CCI and <8 platelet tra1-hourons	% of patients with Grade 2 or higher bleeding	% of patients with Grade 2 or higher bleeding

IPTAS had a secondary outcome of number of days with Grade 2 or higher bleeding

Rebulla et al. Transfusion 2020;60:1267-1277
Rebulla et al. Transfusion 2017;57:1171-1183

PR Platelets: Riboflavin

- Clinical effectiveness of conventional versus Mirasol-treated apheresis platelets in patients with hypoproliferative thrombocytopenia (MiPLATE)
  - Prospective, multicenter, controlled, randomized, non-inferiority study
  - Enrolled subjects with a hematologic malignancy and hypoproliferative thrombocytopenia expected to have platelet counts ≤ 10,000/µl and ≥ 2 platelet transfusions
  - Non-blinded due to bright yellow appearance of MIRASOL platelets

Koepsell et al. Transfusion 2024;64:457-465

PR Platelets: Riboflavin

- Subjects were randomized to receive either leukoreduced apheresis single donor platelets stored in plasma or Mirasol-treated Trima Accel apheresis single-donor platelets, also in plasma
- Irradiation of platelets in both arms was done at the discretion of the treating physician

Are PR platelets as clinically-effective as conventional apheresis platelets?

Primary Endpoint for determination of “Clinically Effective”

- **Number of days with ≥ World Health Organization (WHO) Grade 2 bleeding in the 28 days after the first platelet transfusion or transfusion dependence (10 days without platelet transfusion)**
  - Non-inferiority margin of 1.6 evaluated using a negative binomial regression model with log link functions

Secondary endpoints

- **Proportion of subjects with ≥ WHO Grade 2 bleeding**
- 1-hour/24-hour corrected count increments
- Transfusion episodes per subject
- Days of platelet support
- Total RBC transfusions

Safety

- Assessed on the number, type, and relatedness of transfusion emergent adverse events

PR Platelets for Riboflavin

11 hospital sites with 422 subjects consented

- 92 subjects screen failed for 330 subject in Full Analysis Set (MIRASOL=164, CONTROL=166)
- 28 subjects received no transfusion
- 5 subjects received no transfusion per assigned group
- 297 subjects in the modified intent-to-treat (mITT, MIRASOL=145, CONTROL=152) were analyzed

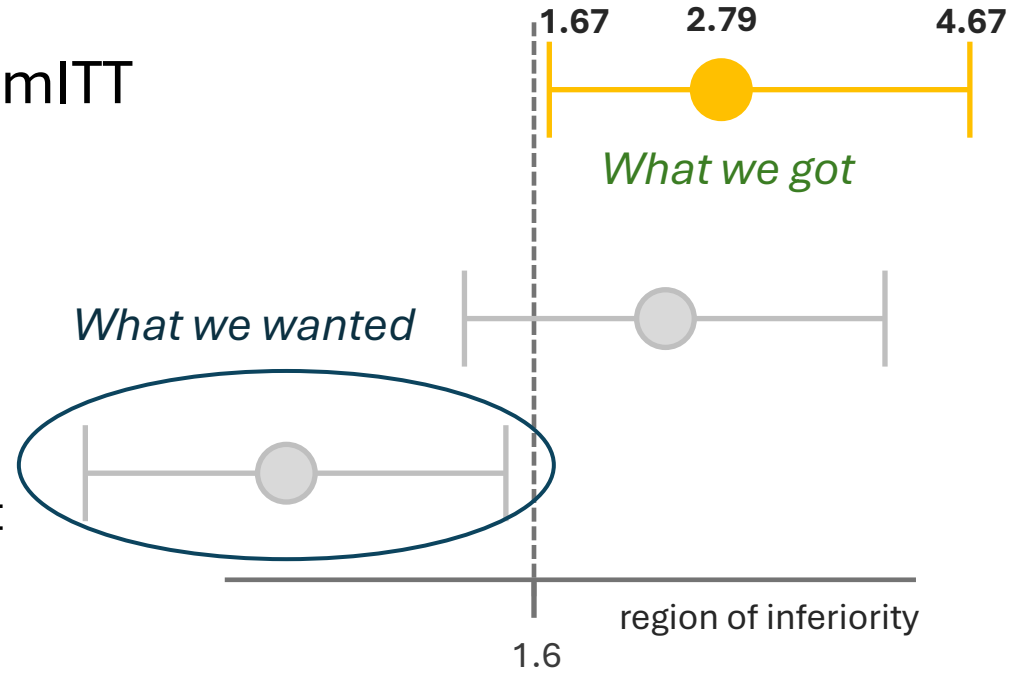
Subject Enrollment

Full Analysis Set	MIRASOL n = 164	CONTROL n = 166
Primary Diagnosis, n (%)		
Leukemia	50 (30.5)	54 (32.5)
Lymphoma	46 (28.0)	54 (32.5)
Plasma Cell Dyscrasias (including multiple myeloma)	43 (26.2)	42 (25.3)
Myelodysplastic/Myeloproliferative Neoplasms	24 (14.6)	13 (7.8)
Myeloproliferative Neoplasm	1 (0.6)	3 (1.8)
Treatment Type Strata, n (%)		
Chemotherapy (non-transplant)	20 (12.2)	19 (11.4)
Autologous Transplant	84 (51.2)	85 (51.2)
Allogeneic Transplant	60 (36.6)	62 (37.3)

mITT Set	MIRASOL n = 145	CONTROL n = 152
Age (years), mean (SD)	55.1 (16.26)	54.3 (17.65)
Age Group (years), n (%)		
<18	6 (4.1)	8 (5.3)
18-65	95 (65.5)	98 (64.5)
>65	44 (30.3)	46 (30.3)
Gender, n (%)		
Male	91 (62.8)	98 (64.5)
Female	54 (37.2)	54 (35.5)

WHO ≥ Grade 2 Bleeding Endpoint Result

- Relative Rate of Days ≥ Grade 2 bleeding rate (mITT population)
  - 2.79 (95% CI: 1.67-4.67)
  - Corresponds to:
    - MIRASOL mean (SD) = 1.7 days (4.05)
    - CONTROL mean (SD) = 0.6 day (1.51)
  - MIRASOL did not meet the non-inferiority end point



MIRASOL primary bleeding locations: Genitourinary & Pulmonary

Secondary Endpoints	MIRASOL n=145	CONTROL n=152	P-value
Subjects with ≥ Grade 2 Bleeding, n(%)	58 (40.0)	46 (30.3)	0.08
Subjects with ≥ Grade 3 Bleeding, n (%)	6 (4.1)	2 (1.3)	0.14

Bleeding Location, n (%)	MIRASOL n = 145	CONTROL n = 152
Oral or nasal	13 (9.0)	12 (7.9)
Skin, soft tissue, musculoskeletal	16 (11.0)	17 (11.2)
Gastrointestinal	27 (18.6)	19 (12.5)
Pulmonary	17 (11.7)	2 (1.3)
Body cavity	0	1 (0.7)
CNS	3 (2.1)	2 (1.3)
Invasive sites	0	2 (1.3)

Secondary and Safety Endpoint Results

	MIRASOL n = 145	CONTROL n = 152	Estimate	Significance
Subjects with CCIs < 5000 on 2 sequential transfusions at 1 hour, n (%)	41 (28.28)	20 (13.16)		P<0.01
CCIs at 1 hour, mean*	7070.0	10,148.5		P<0.01
Platelet transfusions per subject, mean	6.23	4.76	RR=1.22	95% CI 1.05-1.41*
Days between PLT transfusion episodes, mean	0.96	1.29		NS
Red blood cell transfusions per subject			RR=1.12	NS
Transfusion emergent adverse events, n (%)	687 in 119 subjects (84.4)	730 in 133 subjects (82.6)		NS

Abbreviations: CCI=Corrected Count Increments; RR=Relative Rate; 95% CI=95% confidence interval

*Mean estimates from a linear mixed-effect model which accounted for between-subject heterogeneity and accommodated a within subject-dependence in CCI values.

MiPLATE Conclusions

- Pathogen reduced (PR) platelets using the Mirasol system ***did not*** support the claim of non-inferiority using the novel primary endpoint of number of days with WHO ≥ Grade 2 bleeding for “clinical effectiveness”
- Subjects receiving Mirasol platelets had secondary endpoints comparable to previously published studies on pathogen reduced platelets
  - Similar proportions of subjects with WHO ≥ Grade 2 bleeding between PR or control groups
  - Lower CCIs and increased platelet transfusion requirements with PR platelets
  - No difference in RBC transfusions or days of platelet support in PR or control groups
- The safety profile was similar between subjects receiving Mirasol platelets or conventional platelets

MiPLATE

- Potential Issues with this study:
  - Unblinded: Bleeding studies were performed by trained staff while patients were hospitalized or in clinic, but by telephone when outpatient
  - Enrolled autologous BMT patients
  - Irradiation: >95% of the Mirasol platelets were irradiated
    - Irradiation alone decreases pH by 0.04 and increases P-selectin expression by 1.5%, with no difference in other *in vitro* platelet parameters
      - X-ray and gamma have not been directly compared
    - Irradiation plus PR (amotosalen) seemed to cause the same amount of damage to platelets (decreased pH, aggregation, ROS production) as PR alone compared to controls
    - Proteomic analysis of PR (riboflavin) compared to control platelets showed accelerated platelet storage lesions

Cain et al. Trans Med Rev 2024;38(4) 150840
Khoshi et al. Transfusion 2025:65(1): 10-16
Marrocco et al. Transfusion 2013:53(8):1808-20

PR Platelets

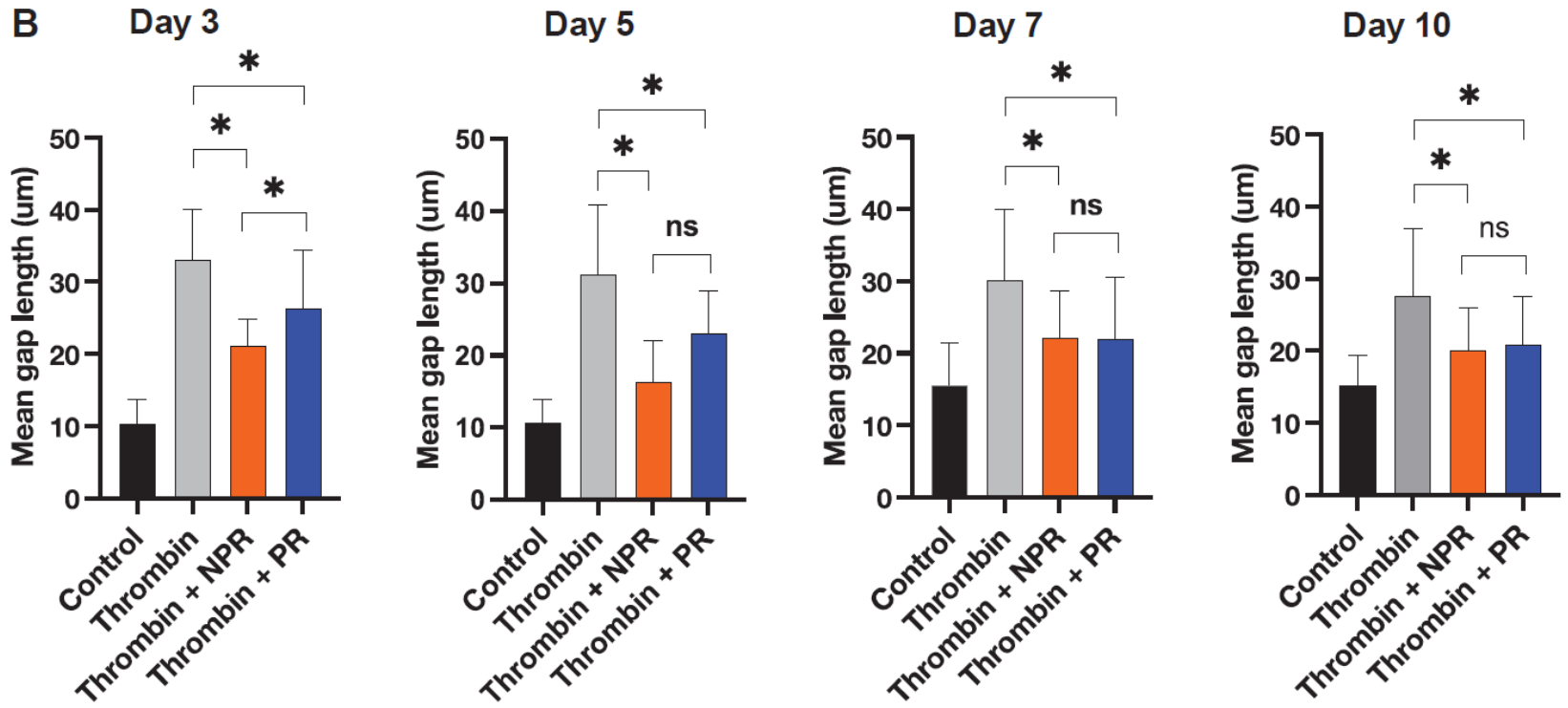
- Given the similar endpoint of proportion of subjects with >= Grade 2 bleeding in MiPlate to previous PR studies, can MiPlate conclusions be extended to other PR platelet studies?
  - MiPlate: 40.0% PR vs 30.3% control
  - SPRINT: 58.8% PR vs 57.5% control
  - PREPAReS: 54% vs 51% control

- What would happen if PR studies use number of days with bleeding as an endpoint for the other two PR technologies?

Rebulla et al. Transfusion 2020:60(1):1267-1277

PR Platelets – other biologic diffences?

- Endothelial permeability: Day 3 differences (PR more permeable)



Nair et al. Blood Vessels, Thrombosis, & Hemostasis 2025 *in press*

PR Platelets: Cost/Benefit

- Known costs:
  - Expensive (up to $50 more per unit than large-volume, delayed culture)
  - More transfusions (lower CCI)
- Known benefits:
  - Fewer transfusion-transmitted bacterial infections in real-world scenarios (France 3/year down to three over six years)
- Unknowns:
  - Hemostatic properties equivalent to non-PR platelets?
    - Trauma and surgical patients have not been studied (PR studies typically in patients with hematologic malignancies only)
    - *In vitro* parameters do not reliably predict clinical effectiveness
    - Studies of PR platelets have had a wide variety of clinical endpoints and little standardization in bleeding assessment

PR Platelets: Future Clinical and Pre-clinical Studies

- Consensus is needed to draw meaningful conclusions
  - Validated *in vitro* markers
  - Bleeding assessment standardization
  - Irradiation not needed
  - Clinical endpoints
    - Grade 2 bleeding not clinically concerning, but needed to achieve numbers for statistical significance
    - Days of bleeding versus proportion of patients with bleeding
  - Subjects
    - Trauma and surgical patients

Conclusion

- PR technology has the potential to make the blood supply safer from transfusion-transmitted infections, but it is not perfect
- The cost of implementing PR platelets is significant in terms of dollars paid as well as the use of more platelets
- The hemostatic function of PR platelets is likely close to conventional platelets, but attempts to compare to conventional platelets have many shortcomings
- Future studies need to include subjects that are not exclusively undergoing treatment for hematologic malignancies
- Future studies would benefit from standardization in the approach to assessing “Clinical Effectiveness”

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