

Bacterial contamination of platelet concentrates



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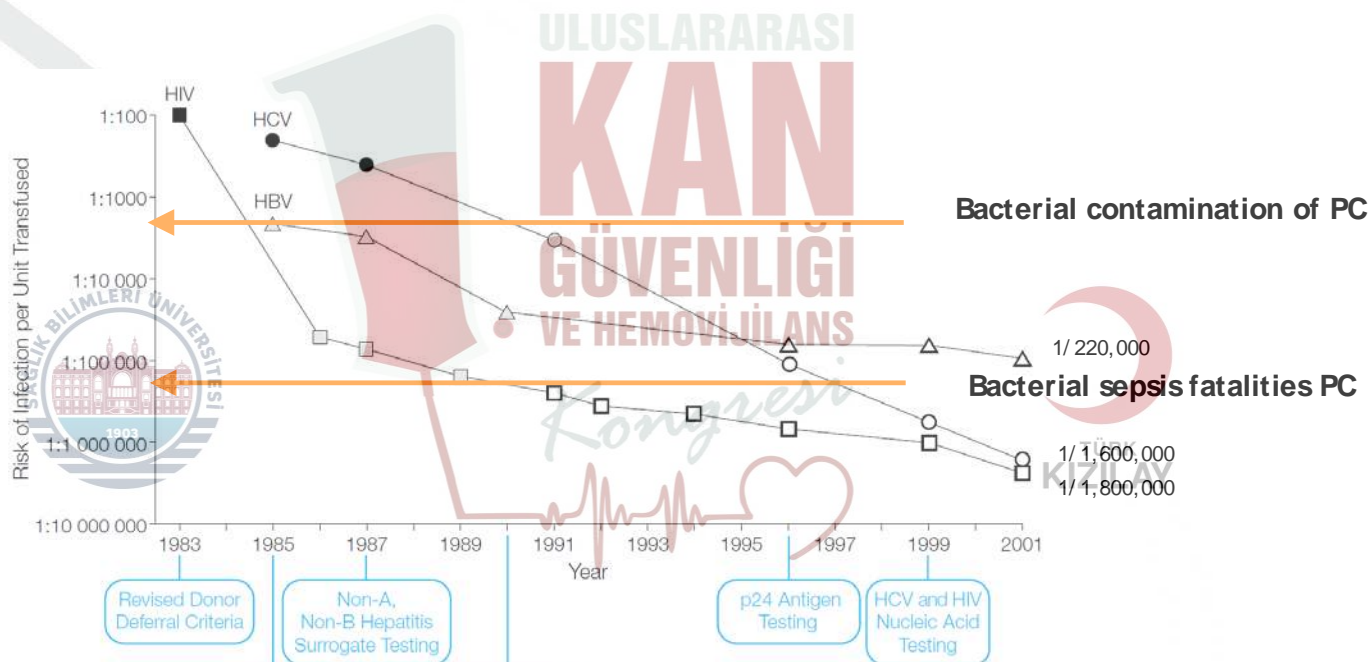


Disclosures

- Speaker honoraria from Cerus, Terumo BCT, Fresenius Kabi and Grífols
- Research support from Terumo BCT, Sanofi-Genzyme and Maco Pharma
- Member of advisory board for Grífols and Aenitis Technologies



HBV, HCV and HIV Infectious Risk per Transfused Unit



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Bacterial Contamination of Platelet Concentrates

- Incidence
- Origin
- Bacteria species
- Clinical consequences
- How to avoid it:
 - Prevent
 - Detect
 - Inactivate



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Incidence: depends on

- Method:
 - Bacterial culture
 - Oxygen consumption
- Time of culture:
 - After preparation
 - At the end of storage
- Volume cultured
- Culture medium
 - Aerobic
 - Aerobic–Anaerobic
- Positive vs positive confirmed

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Table 18-1. Rates of Confirmed Positive Cultures Using the BacT/ALERT 3D System with Sampling on Day 0 to 1, Showing the Variation in Use of Culture Conditions, Volume Tested, Delay in Sampling, and Type of Platelets Tested

Reference	Culture Conditions	Volume (mL) per Bottle	Component Type	Delay before Sampling (hours)	Units Tested	Confirmed Positive	Rate Confirmed Positive per Million
Eder et al ⁶	Aerobic	8-10	Apheresis	24-36	781,936	130	166 (1:6024)
Souza et al ¹⁰	Aerobic	8	Apheresis	24-36	180,263	25	138 (1:7194)
Dumont et al ⁷	Aerobic, anaerobic	4-5	Apheresis	24-36	388,903	90	231 (1:4329)
Murphy et al ¹¹	Aerobic, anaerobic	7.5-10	Apheresis	>12	12,823	4	311 (1:3205)
Schrenzenmeier et al ¹²	Aerobic, anaerobic	7.5-10	Apheresis	18	15,198	13	855 (1:1169)
Pearce et al ⁸	Aerobic, anaerobic	8-10	Apheresis, buffy coat	>16	54,828	35	638 (1:1567)
Murphy et al ¹¹	Aerobic, anaerobic	7.5-10	Buffy coat	>36	30,407	10	328 (1:3039)
Schrenzenmeier et al ¹²	Aerobic, anaerobic	7.5-10	Buffy coat	18	37,045	24	647 (1:1543)
Benjamin et al ¹³	Aerobic	8-10	Platelet-rich plasma	24-36	20,725	20	965 (1:1036)

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Table 18-4. Delayed and Outdate Culture Retesting of Platelet Components Using Both Aerobic and Anaerobic Cultures*

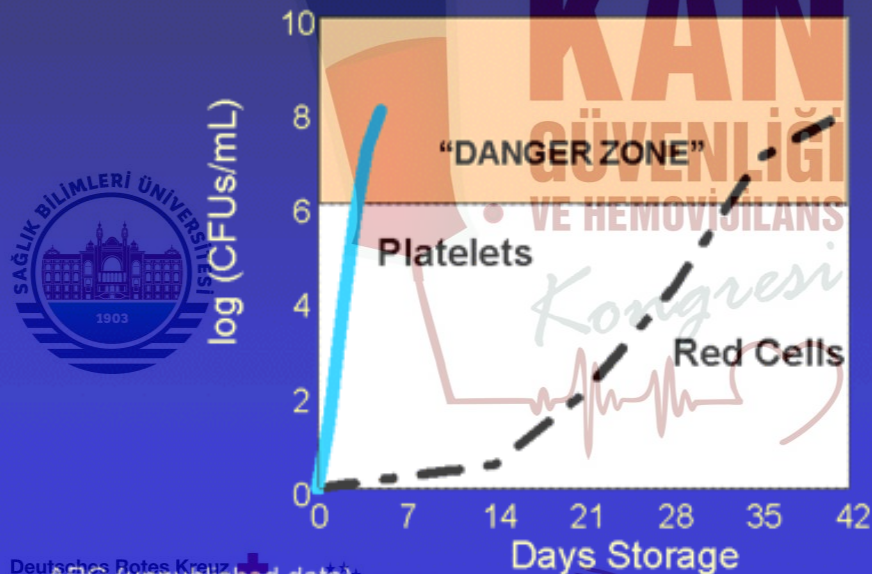
Reference	Day of Reculture	Component Type	Units Tested	Confirmed Positive	Rate per Million	Lower 95% CI	Upper 95% CI
Dumont et al ⁷	Day 8	Apheresis	6,039	4	662 (1:1,509)	210 (1:4,762)	1,596 (1:627)
Murphy et al ¹¹	Day 7	Apheresis, Pooled BC	8,282	18	2,173 (1:460)	1,329 (1:752)	3,365 (1:297)
Murphy et al ¹¹	Day 4	Apheresis, Pooled BC	3,310	4	1,208 (1:828)	382 (1:2,618)	2,912 (1:343)
Pearce et al ⁸	Day ≥6	Apheresis, Pooled BC	6,438	6	932 (1:1,074)	375 (1:2,667)	1,934 (1:517)
Walther-Wenke et al ³¹	Day ≥6	Apheresis	11,452	13	1,135 (1:881)	634 (1:1,577)	1,893 (1:528)
Walther-Wenke et al ³¹	Day ≥7	Pooled BC	8,850	14	1,581 (1:633)	899 (1:1,112)	2,591 (1:386)
Total			44,371	59	1,329 (1:752)		

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Characteristic Growth of Bacteria in Platelets and Red Cells



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Origin of the Contamination

- Skin of the donor
- Bacteremia in the donor
- Contamination during the collection or the process:
 - Environment
 - Equipment



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Clinical Consequences

718

MMWR / June 29, 2018 / Vol. 67 / No. 25

US Department of Health and Human Services/Centers for Disease Control and Prevention

Morbidity and Mortality Weekly Report

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Fatal Sepsis Associated with Bacterial Contamination of Platelets — Utah and California, August 2017

Roberta Z. Horth, PhD^{1,2,3}; Jefferson M. Jones, MD⁴; Janice J. Kim, MD⁵; Bert K. Lopansri, MD⁶; Sarah J. Ilstrup, MD⁶; Joy Fridey, MD⁷; Walter E. Kelley, DO⁸; Susan L. Stramer, PhD⁹; Ashok Nambiar, MD¹⁰; Lynn Ramirez-Avila, MD¹⁰; Amy Nichols, MBA¹⁰; Wendy Garcia¹¹; Kelly E. Oakeson, PhD¹²; Nicholas Vlachos, MS⁴; Gillian McAllister⁴; Robert Hunter, MS⁵; Allyn K. Nakashima, MD³; Sridhar V. Basavaraju, MD⁴

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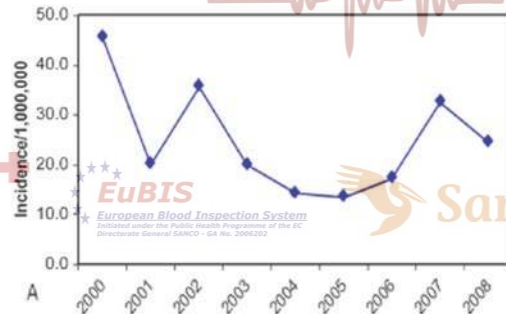
Residual risk and retrospective analysis of transfusion-transmitted bacterial infection reported by the French National Hemovigilance Network from 2000 to 2008

Bruno Lafeuillade, François Eb, Nadra Ounnoughene, Rachel Petermann, Gérald Daurat, Gérard Huyghe, Mai-Phuong Vo Mai, Cyril Caldani, Danielle Rebibo, and Pierre Weinbreck

Annual variation of the incidence of transfusion transmitted bacterial infection related to platelet concentrates



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Heinrich's Law



1 Accident with major injury



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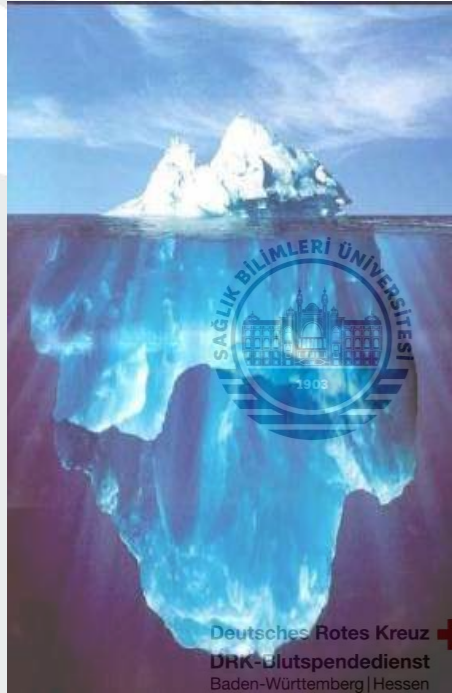


https://en.wikipedia.org/wiki/Herbert_William_Heinrich





Heinrich's Law



1 Accident with major injury

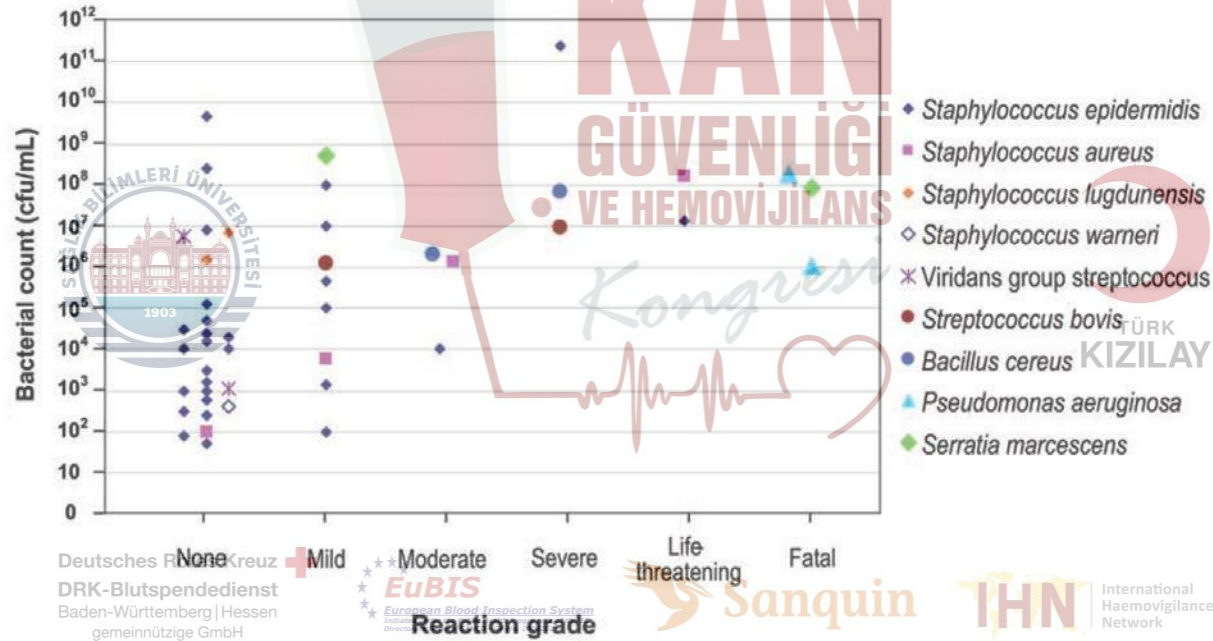
29 Accidents that cause minor injuries

300 Accidents that cause no injuries

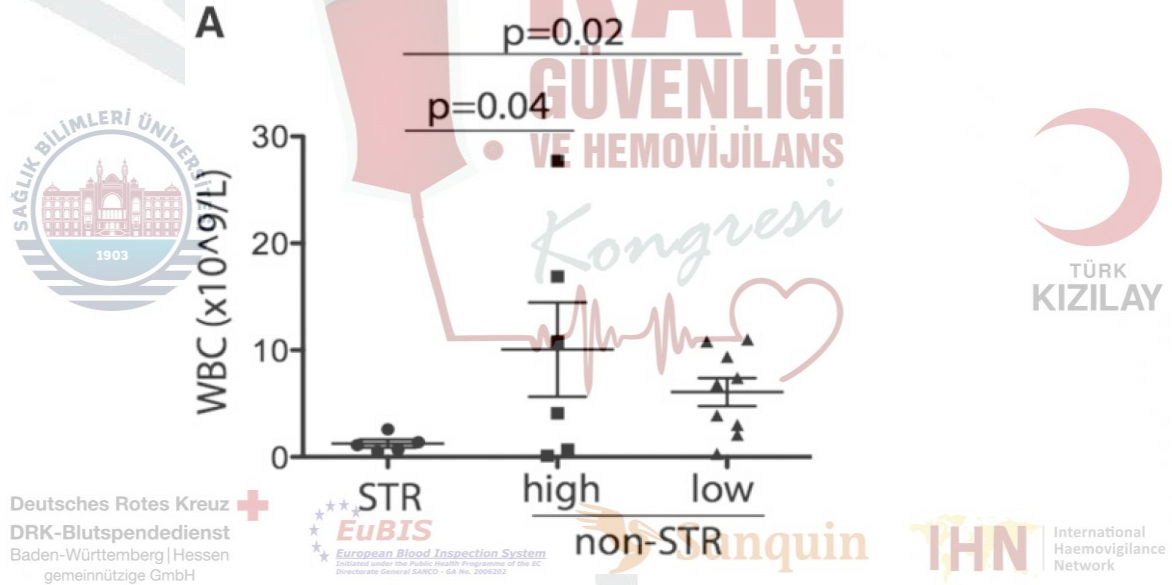
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Relationship of bacterial species and bacterial load to occurrence and severity of transfusion reactions in 45 cases, at the hospitals of the University of Cleveland, Ohio, USA, between 1991 and 2006



Correlation of white blood count in patients who received bacterially contaminated platelets with presence or absence of septic transfusion reaction, at the hospitals of the University of Cleveland, Ohio, USA, between 2007 y 2013



Detection of septic transfusion reactions to platelet transfusions by active and passive surveillance

Hong Hong,* Wenbin Xiao,* Hillard M. Lazarus, Caryn E. Good, Robert W. Maitta, and Michael R. Jacobs

Departments of Pathology and Medicine, University Hospitals Case Medical Center and Case Western Reserve University School of Medicine, Cleveland, OH

Key Points

- Bacterial sepsis from contaminated platelet transfusions continues to occur despite recent interventions; additional measures are needed.
- STR to platelet transfusion is frequently not recognized or reported; use of recent AABB criteria showed highest diagnostic sensitivity.

Septic transfusion reactions (STRs) resulting from transfusion of bacterially contaminated platelets are a major hazard of platelet transfusion despite recent interventions. **Active and passive surveillance for bacterially contaminated platelets was performed over 7 years (2007-2013) by culture of platelet aliquots at time of transfusion and review of reported transfusion reactions.** All platelet units had been cultured 24 hours after collection and released as negative. Five sets of STR criteria were evaluated, including recent AABB criteria; sensitivity and specificity of these criteria, as well as detection by active and passive surveillance, were determined. **Twenty of 51 440 platelet units transfused (0.004%; 389 per million) were bacterially contaminated by active surveillance and resulted in 5 STRs occurring 9 to 24 hours posttransfusion; none of these STRs had been reported by passive surveillance. STR occurred only in neutropenic patients transfused with high bacterial loads.** A total of 284 transfusion reactions (0.55%) were reported by passive surveillance. None of these patients had received contaminated platelets. However, 6 to 93 (2.1%-32.7%) of these 284 reactions met 1 or more STR criteria, and sensitivity of STR criteria varied from 5.1% to 45.5%. These results document the continued occurrence of bacterial contamination of

1/2,570

platelets resulting in STR in neutropenic patients, failure of passive surveillance to detect STR, and lack of specificity of STR criteria. These findings highlight the limitations of reported national STR data based on passive surveillance and the need to implement further measures to address this problem such as secondary testing or use of pathogen reduction technologies. (*Blood*. 2016;127(4):496-502)

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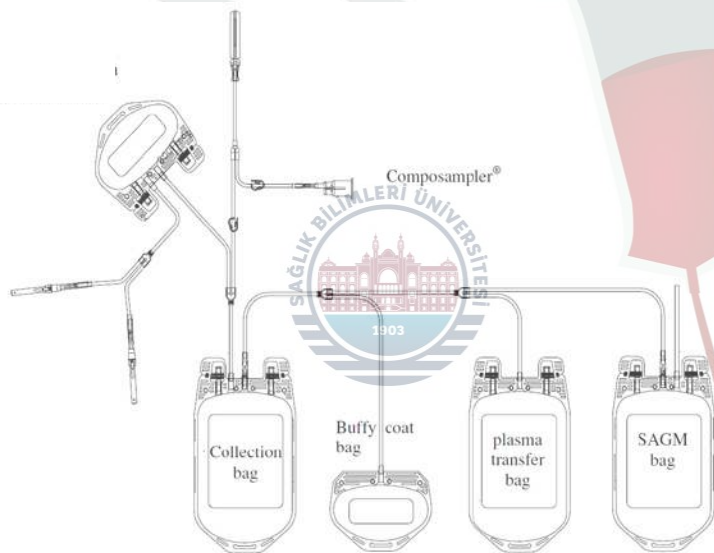


Prevention of Bacterial Contamination

- Donor selection
- Donor arm disinfection technique
- Diversion of the first milliliters of blood of the donation



Diversion of the first 10 mL of the blood during donation



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Donations tested
 Positive cultures
 Contamination rate^a
 95% CI of rate^b

Diversion of
 the first 10 ml

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 n = 7087
 n = 15
 0.21%
 0.12-0.35%



Standard, whole-
 blood collections [2]

n = 18 257
 n = 63
 0.35%
 0.27-0.44%

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Detection of the contaminated units

- Culture:
 - Bact-Alert[®], Biomerieux
- Rapid testing (Platelet PGD[®] test) at the time of issuing the unit:
 - Gram positives: lipoteichoic acid
 - Gram negatives: lipopolysaccharide
- Oxygen consumption:
 - eBDS[®], Pall
- Detection of bacteria using
 - Flow cytometry with fluorescent probes (Scansystem[®])
 - 16S ribosomal RNA gene PCR

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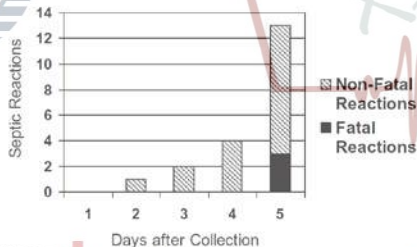
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BLOOD COMPONENTS

Bacterial screening of apheresis platelets and the residual risk of septic transfusion reactions: the American Red Cross experience (2004-2006)

Anne F. Eder, Jean M. Kennedy, Beth A. Dy, Edward P. Notari, John W. Weiss, Chyang T. Fang, Stephen Wagner, Roger Y. Dodd, Richard J. Benjamin, and the American Red Cross Regional Blood Centers



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Fig. 2. Septic transfusion reactions analyzed by the interval between collection and transfusion. (■) Fatal reactions; (▨) nonfatal reactions.

1,004,206 units cultured
1:5,399 confirmed positives
20 septic transfusion reactions
3 Fatalities 1:498,711

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Bacterial Risk Control Strategies for Blood Collection Establishments and Transfusion Services to Enhance the Safety and Availability of Platelets for Transfusion

Guidance for Industry



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
September 2019

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<https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics/biologics-guidances>



APPENDIX A: BACTERIAL RISK CONTROL STRATEGIES ASSOCIATED WITH SPECIFIC PLATELET STORAGE DURATION AND TYPE OF PLATELET UNIT

Storage duration

	Apheresis	Pre-storage pools of WBD platelets
5 days	LVDS ≥ 36 hours	LVDS ≥ 36 hours
	Pathogen reduction	Primary culture ≥ 24 hours + secondary culture ≥ day 3
	Primary culture ≥ 24 hours + secondary culture ≥ day 3	Primary culture ≥ 24 hours + secondary rapid testing
	Primary culture ≥ 24 hours + secondary rapid testing	N/A
7 days	LVDS ≥ 48 hours	N/A
	LVDS ≥ 36 hours + secondary rapid testing	N/A
	LVDS ≥ 36 hours + secondary culture ≥ day 4	N/A
	Primary culture ≥ 24 hours + secondary culture ≥ day 4	N/A

LVDS: large volume (≥ 16 mL), delayed sampling, inoculated evenly into aerobic and anaerobic culture media



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Pathogen inactivation technologies for platelet concentrates approved in the European Union

- Amotosalen + ultraviolet A light, Intercept® Blood System, Cerus Co. Approved in 2002
- Riboflavin + ultraviolet light, Mirasol® PRT, Terumo BCT. Approved in 2009



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Pathogen inactivation: efficacy against bacteria

Amotosalen

Bacterial species	Extent of inactivation* (log ₁₀ reduction)
Gram-negative bacteria	
<i>Escherichia coli</i>	>6.4
<i>Serratia marcescens</i>	>6.7
<i>Klebsiella pneumoniae</i>	>5.6
<i>Pseudomonas aeruginosa</i>	4.5
<i>Salmonella choleraesuis</i>	>6.2
<i>Yersinia enterocolitica</i>	>5.9
<i>Enterobacter cloacae</i>	5.9
Gram-positive bacteria	
<i>Staphylococcus epidermidis</i>	>6.6
<i>Staphylococcus aureus</i>	6.6
<i>Streptococcus pyogenes</i>	>6.8
<i>Listeria monocytogenes</i>	>6.3
<i>Corynebacterium minutissimum</i>	>6.3
<i>Bacillus cereus</i> (includes spores)	3.6
<i>Bacillus cereus</i> (vegetative)	>6.0
<i>Bifidobacterium adolescentis</i>	>6.5
<i>Propionibacterium acnes</i>	>6.7
<i>Lactobacillus species</i>	>6.9
<i>Clostridium perfringens</i> (vegetative form)	>6.0
Spirochete bacteria	
<i>Treponema pallidum</i> (syphilis)	>6.8
<i>Borrelia burgdorferi</i> (Lyme disease)	>6.8



*> refers to inactivation below the limit of detection of the assay.

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Bacteria	Type	Occurrence	Mirasol % effectiveness
<i>Staphylococcus epidermidis</i>	Gram-positive	20	100
<i>Escherichia coli</i>	Gram-negative	8	100
<i>Bacillus cereus</i>	Gram-positive	7	100
<i>Staphylococcus aureus</i>	Gram-positive	6	90
<i>Streptococcus agalactiae</i>	Gram-positive	5	100
<i>Streptococcus mitis</i>	Gram-positive	5	100
<i>Streptococcus pyogenes</i>	Gram-positive	5	100
<i>Enterobacter cloacae</i>	Gram-negative	4	100
<i>Propionibacterium acnes</i>	Gram-positive	3	100
<i>Serratia marcescens</i>	Gram-negative	3	100
<i>Klebsiella pneumoniae</i>	Gram-negative	2	100
<i>Acinetobacter baumannii</i>	Gram-negative	1	66
<i>Yersinia enterocolitica</i>	Gram-negative	1	100
Overall % effectiveness			98

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Irsch J, et al. Transfus Med Hemother 2011;38:19-31
Marschner S, et al. Transfus Med Hemother 2011;38:8-18

Table 5-8. The Frequency of Transfusion-Transmitted Bacterial Infection Associated with Conventional and Intercept-Treated Platelet Concentrates*

Year	Conventional PCs			Pathogen-Inactivated PCs		
	PCs (n)	TTBIs (deaths) [†]	TTBIs/10,000 PCs	PCs (n)	TTBIs (deaths)	TTBIs/10,000 PCs
2006	231,853	4 (0)	0.17	6,420	0 (0)	0
2007	232,708	9 (2)	0.39	15,393	0 (0)	0
2008	239,349	6 (1)	0.25	15,544	0 (0)	0
2009	241,634	9 (0)	0.37	21,767	0 (0)	0
2010	253,149	2 (1)	0.08	22,632	0 (0)	0
2011	267,785	3 (1)	0.11	22,392	0 (0)	0
2012 (6 months)	≥135,000	4 (2)	0.30	11,500	0 (0)	0
Total[‡]	1,601,478	37 (7)	0.23	115,648	0 (0)	0

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Septic transfusion reactions (fatalities) per year before and after amotosalen implementation in Switzerland

Year	Conventional platelet component transfusion-related sepsis (fatal) ^b	INTERCEPT platelet component transfusion related sepsis (fatal) ^c
2005	6 (2)	
2006	2 (0)	
2007	2 (0)	
2008	2 (0)	
2009	3 (1)	
2010	1 (0)	
2011	0 (0)	0 (0)
2012		0 (0)
2013		0 (0)
2014		0 (0)
2015		0 (0)
2016		0 (0)
Total	16 (3)	0 (0)

^aTwo-sided Fisher's exact test $p < 0.001$.

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Total units 158,502

Total units 205,574

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Conclusions

- The safest blood components ever, however, still a significant risk of transfusion transmitted bacterial infection by platelet transfusion
- In recent years several strategies have been developed to reduce the risk of transmitting bacterial infections through platelet transfusion
- Pathogen inactivation has been the only one that has shown its efficacy in eliminating completely the risk

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Thank you very much for your attention!!



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In conjunction with the Spanish Society of Blood
Transfusion and Cellular Therapy (SETS)

Barcelona, Spain, June 6 - 10, 2020



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