Experience with Introduction of Pathogen Reduction for COVID-19 Convalescent Plasma

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Conflict of Interest

- **No conflict of interest.**
- **Nothing to declare.**

Outline

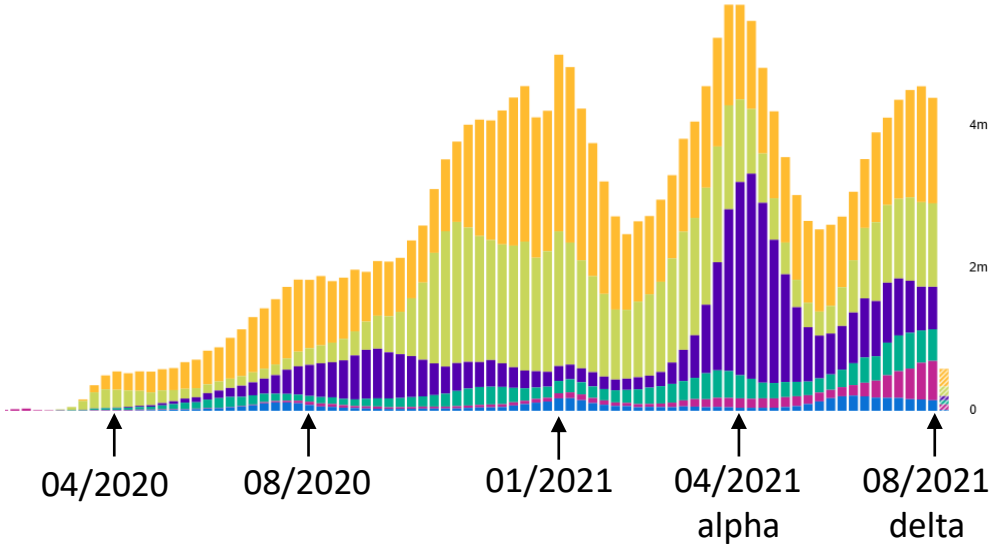
1. Introduction
2. Practical Tasks/Challenges
3. The role of Pathogen Reduction Methods
4. Conclusion

Introduction

Global & Local situation of COVID-19 Pandemic

- Internationally

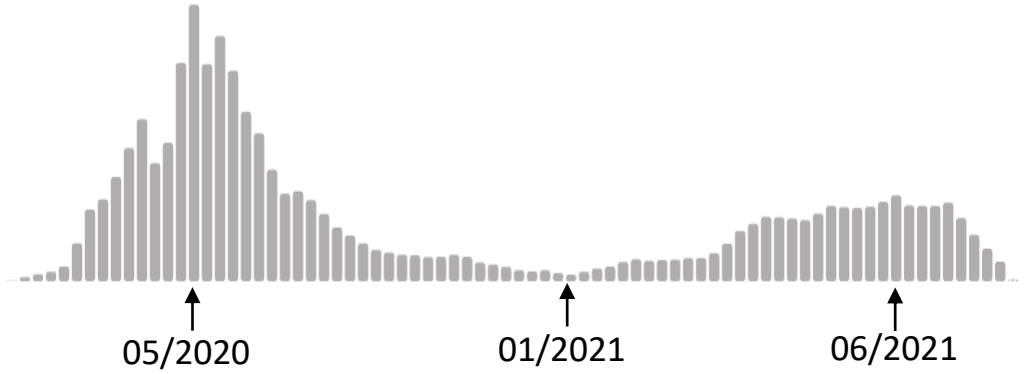
World Health Organization



Americas	83,479,049 confirmed	
Europe	64,991,125 confirmed	521,035 new cases
South-East Asia	41,178,198 confirmed	
Eastern Mediterranean	14,555,962 confirmed	216,867,420 confirmed cases
Western Pacific	6,477,611 confirmed	
Africa	5,620,667 confirmed	4,507,837 deaths

Aug 30, 2021

- Saudi Arabia



208
new cases

544,004
confirmed cases

8,532
deaths

COVID-19 Convalescent Plasma (CCP)

- Plasma collected from recovered COVID-19 patients with certain eligibility criteria containing a pre-defined minimum titer of neutralizing antibodies.

- Transfusion of convalescent plasma to newly infected individuals could potentially provide clinical benefit by passive transfer of these antibodies (in early stage of disease according to current state of knowledge, but not later stage of disease, before seroconversion), preventing progression of disease severity

- Transfusion of convalescent plasma to healthy individuals (which for example cannot be vaccinated) could protect against infection (passive immunization).

Al Riyami AZ et al., 2021. Clinical use of Convalescent Plasma in the COVID-19 pandemic: a transfusion-focussed gap analysis with recommendations for future research priorities. *Vox Sang* 116: 88-98
Cohn CS et al., 2021. COVID-19 convalescent plasma: interim recommendations from the AABB. *Transfusion* 61: 1313-1320
Libster R et al., 2021. Early High-Titer Plasma Therapy to Prevent Severe Covid-19 in Older Adults. *New Engl J Med* 384: 610-618
Simonovich VA et al., 2021. A Randomized Trial of Convalescent Plasma in Covid-19 Severe Pneumonia. *New Engl J Med* 384: 619-629

Eligibility Criteria for CCP Donors at our Center

- Confirmation of **previous infection with SARS-CoV-2** through validated test
- An interval of at least **14 days after full recovery**
- **Standard donor selection criteria** and recommended blood testing
- Exclusion of female donors with **history of pregnancy or abortion**
- **High titer neutralizing antibody** quantity

High-Titer Convalescent Plasma

The US FDA have limited the use of **high titer COVID-19 convalescent plasma** for: FDA Clinical Memorandum EUA 26382

- the treatment of hospitalized patients with COVID-19 early in the disease course.
- hospitalized patients who have impaired humoral immunity and cannot produce an adequate antibody response.

Assay to identify high titer CCP at our center: Local Ab titration test
Minimum titer eligible for treatment in our center: 1:80
The range of Ab titer in CCP units at our center: 1:20 – 1:360
Percentage of CCP units with eligible titer at our center: <25%

Reports of correlation of CCP high anti-SARS-CoV-2 nAB titers with:

- increased **donor age**
- increased donor COVID-19
- donor **ABO blood group** (increased nAB **disease severity**titers with blood group B)
- male **sex**

Bloch EM et al., 2021. ABO blood group and SARS-CoV-2 antibody response in a convalescent donor population. *Vox Sang*: DOI: 10.1111/vox.13070
Klein SL et al., 2020. Sex, age, and hospitalization drive antibody responses in a COVID-19 convalescent plasma donor population. *J Clin Invest* 130: 6141-6150

Practical/Organizational Tasks and Challenges

Practical Tasks – CCP-Production

- Regulatory approvals: production of pharmaceutical
- Labeling of CCP product (in our center: ISBT labeling system)
- Implementation of plasmapheresis system and operator training (supplier support)
- On-site validation of plasmapheresis system (at our center: Trima, collection of 600 mL)
- Adjustment of pathogen reduction process (at our center: INTERCEPT Blood System for Plasma, Cerus Corp.)
- On site validation of total process

Challenges – CCP-Production

- **scarce resources;** (supplies, budgets, human resources)
  Processing sets for plasmapheresis and pathogen reduction **availability**

(interrupted distribution due to flight cancellations and supply shortages)

- **CCP neutralizing titer/activity**: In early phase no testing, later ELISA, then in-house neutralization assay. Treatment in first wave often with unknown antibody titer.

- **Education and training of staff**: no live application support and staff training by suppliers/manufacturers due to pandemic closure of borders, restricted travels and restricted visitor entry to our center. Virtual trainings and consulting instead.

Challenges – CCP-Production

- **lockdown and social distancing** – reduced personnel capacity and donor availability
- **Communication & coordination** between hospitals and blood centers is often not well established
- **Limited number of trained staff and lack of experience** in collecting CCP leading to production delays and/or breaks
- **Donor related issues**: Recruitment, Awareness, first time donors

Challenge: often heterogenous ntAB titers between different donations of the same donor

Annen K et al., 2021. Presence and short-term persistence of SARS-CoV-2 neutralizing antibodies in COVID-19 convalescent plasma donors. *Transfusion* 61: 1148-1159

During an emerging pandemic, it is too late to think about the implementation of PR technology. The implementation is a process of weeks to months. Borders close rapidly, transport of equipment and travel of engineers and application specialists could be impaired

Preparedness is Key

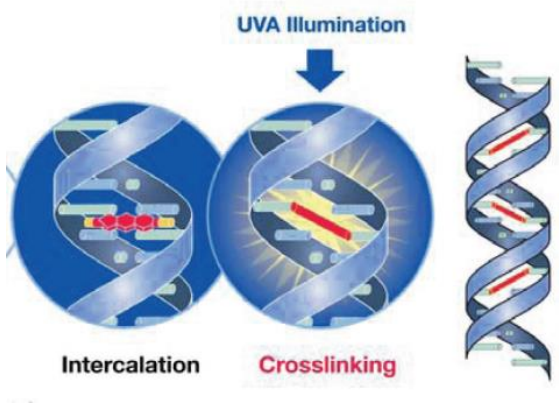
Pathogen Reduction of CCP

Commercially Available PR Technologies for Plasma - Overview

INTERCEPT Blood System™ (Cerus Corporation)

AS

Photochemical
Amotosalen + UVA
DNA crosslinking

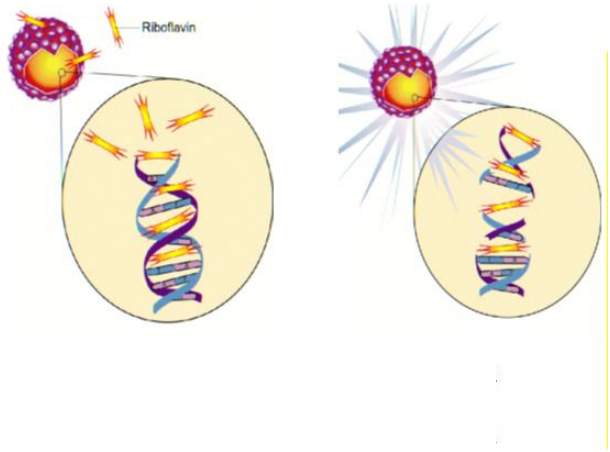


Irsch J and Lin L, 2011. Pathogen Inactivation of Platelet and Plasma Blood Components for Transfusion Using the INTERCEPT Blood System™. *Transfus Med Hemother* 38: 19-31

Mirasol™ PRT System (Terumo BCT)

RB

Photodynamic
Riboflavin + UVB/C
ROS + Irradiation

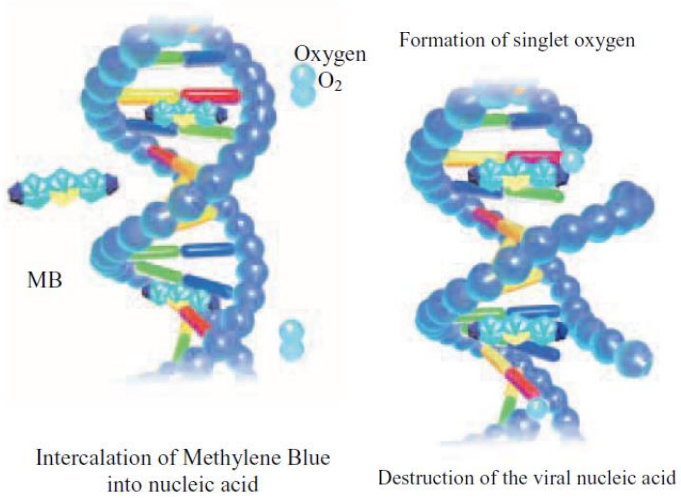


Terumo BCT product brochure

Theraflex™ MB (Plasma) (Macopharma)

MB

Photodynamic
Methylene Blue + light
ROS



Seghatchian J. et al., 2011. Main Properties of the THERAFLEX MB-Plasma System for Pathogen Reduction. T*ransfus Med Hemother* 38: 55-64

CCP – The Role of Pathogen Reduction (PR) Technology

CCP donors are not regular donors with awareness of risk behavior and no time for quarantine

Risk of window-period TTI and untested (HIV/HBV/HCV)

Potential SARS-CoV-2 viremia after convalescence (blood transmissibility not shown and unlikely with currently circulating variants)

Risk of SARS-CoV-2 transmission post convalescence

Impact of PR-treatment on the anti-SARS-CoV-2 antibody quantity and neutralizing activity?

BUT PR system must preserve antibody quantity and quality

Risk of window-period TTI and untested (HIV/HBV/HCV/)

Inactivation Efficacy against Routinely Tested Pathogens with Window Period Risk in Human Plasma Units

	RB	AS	MB
HIV-1 (cell-free)	5,97 log*	>6.8 log	>5.5 log
HBV	ND	>4.5 log	ND
HCV	ND§	>4.5 log	>3.8 log
total	1/3	3/3	2/3

*data from platelet experiments was extrapolated to plasma
§experiments were not conducted with the original PR system
ND = Not Determined

Keil SD et al., 2015. Inactivation of viruses in platelet and plasma products using a riboflavin-and-UV–based photochemical treatment. *Transfusion* 55: 1736-1744
Ruane PH et al., 2004. Photochemical inactivation of selected viruses and bacteria in platelet concentrates using riboflavin and light. *Transfusion* 44: 877-884
Seghatchian J. et al., 2011. Main Properties of the THERAFLEX MB-Plasma System for Pathogen Reduction. Tr*ansfus Med Hemother* 38: 55-64
Singh Y et al., 2006. Photochemical treatment of plasma with amotosalen and longwavelength ultraviolet light inactivates pathogens while retaining coagulation function. *Transfusion* 46: 1168-1177
Steinman E et al., 2013. Two pathogen reduction technologies—methylene blue plus light and shortwave ultraviolet light—effectively inactivate hepatitis C virus in blood products. *Transfusion* 53: 1010-1018

Risk of SARS-CoV-2 transmission post convalescence

Inactivation Efficacy against Human Coronaviruses in Human Plasma Units

	RB	AS	MB
SARS-CoV-1	ND	>5.5 log	>3.1 log
SARS-CoV-2	>4.7 log	>3.3 log	ND
MERS-CoV	>4.4 log	>4.6 log	>3.3 log
total	2/3	3/3	2/3

ND = Not Determined

Azhar EI et al., 2021. Efficient Inactivation of SARS-CoV-2 in Human Plasma with amotosalen and ultraviolet A light treatment. *Vox Sang* 116: 673-681

Eikmann M et al., 2018. Inactivation of Ebola virus and Middle East respiratory syndrome coronavirus in platelet concentrates and plasma by ultraviolet C light and methylene blue plus visible light, respectively. *Transfusion* 58: 2202-2207

Eickmann M et al., 2020. Inactivation of three emerging viruses – severe acute respiratory syndrome coronavirus, Crimean–Congo haemorrhagic fever virus and Nipah virus – in platelet concentrates by ultraviolet C light and in plasma by methylene blue plus visible light. *Vox Sang* 115: 146-151

Hindawi SI et al., 2018. Inactivation of Middle East respiratory syndrome-coronavirus in human plasma using amotosalen and ultraviolet A light. *Transfusion* 58: 52-59

Keil SD et al., 2016. Inactivation of Middle East respiratory syndrome coronavirus (MERS-CoV) in plasma products using a riboflavin-based and ultraviolet light-based photochemical treatment. *Transfusion* 56: 2948-2952

Ragan I et al., 2020. Pathogen reduction of SARS-CoV-2 virus in plasma and whole blood using riboflavin and UV light. PLoS ONE 15: e0233947

Singh Y et al., 2006. Photochemical treatment of plasma with amotosalen and longwavelength ultraviolet light inactivates pathogens while retaining coagulation function. *Transfusion* 46: 1168-1177

Studies in relation to CCP at the King Abdulaziz University

- Study on the **inactivation efficacy of AS Pathogen Reduction** for SARS-CoV-2 in plasma & platelets in 100% plasma.
- Study on the **impact of PR on the neutralizing activity** of CCP
- Our **local group** at KAUH started a clinical study on:
  - Donor recruitment for CCP & using CCP for treatment of Patients
  - Only few patients received this treatment option
  - Still early in the study / no results yet

ORIGINAL RESEARCH

Inactivation of Middle East respiratory syndrome-coronavirus in human plasma using amotosalen and ultraviolet A light

Salwa I. Hindawi,[1,2] Anwar M. Hashem,[3,4] Ghazi A. Damanhouri,[2] Sherif A. El-Kafrawy,[3,5] Ahmed M. Tolah,[3] Ahmed M. Hassan,[3] and Esam I. Azhar[3,6]

TABLE 1. Reduction in MERS-CoV titers after inactivation by amotosalen and UVA in pooled plasma*

	Viral load (log pfu/mL)				
Experiment	Positive control	Negative control	Pretreatment sample	Inactivated sample	Log reduction
A‡	7.85	ND	4.52	ND†	>4.52
B	8.18	ND	4.51	ND‡	>4.51
C	7.60	ND	5.04	ND§	>5.04
D	7.60	ND	4.60	ND§	>4.60
Mean ± SD	7.80 ± 0.27	ND	4.67 ± 0.25	ND	>4.67 ± 0.25

* Data are shown as log pfu/mL.
† No infectious virus was detected in 1.5-mL assayed volume.
‡ No infectious virus was detected in 15-mL assayed volume.
§ No infectious virus was detected in 30-mL assayed volume.
ND = not detected.

VoxSanguinis
The International Journal of Transfusion Medicine
ISBT International Society of Blood Transfusion
Vox Sanguinis (2020)

ORIGINAL PAPER

DOI: 10.1111/vox.13043

Amotosalen and ultraviolet A light treatment efficiently inactivates severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in human plasma

Esam I. Azhar,[1,2] Salwa I. Hindawi,[1,3] Sherif A. El-Kafrawy,[1,2] Ahmed M. Hassan,[1] Ahmed M. Tolah,[1,2] Thamir A. Alandijany,[1,2] Leena H. Bajrai[1,4] & Ghazi A. Damanhouri[1,3]

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ble 1 Reduction of infectious SARS-CoV-2 titres in human plasma units after amotosalen/UVA treatment

	Viral infectivity titre, log_{10} PFU/ml				
periment	Positive control	Negative control	Pretreatment sample*	Inactivated sample	Log reduction
	5·5	ND	3·4	ND	>3·4
	5·7	ND	3·2	ND	>3·2
	5·6	ND	3·6	ND	>3·6
	5·9	ND	3·3	ND	>3·3
	5·3	ND	3·1	ND	>3·1
an ± SD	5·6 ± 0·20	ND	3·32 ± 0·19	ND	>3·32 ± 0·19[$]

) indicates not detected.
*After addition of amotosalen.
[$]This indicates complete inactivation of the virus.

Efficient Inactivation of SARS-CoV-2 in human plasma with amotosalen and ultraviolet A light treatment

Esam I Azhar[1,2], Salwa I Hindawi[1,3], Sherif A El-Kafrawi[1,2], Ahmed M Hassan[1], Ahmed M Tolah[1,2], Thamir A Alandijany[1,2], Qossay Abunada[4], Marcus Picard-Maureau[4], Ghazi A Damanhouri[1,3]

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Objective: During the ongoing pandemic of COVID-19, SARS-CoV-2 RNA was detected in plasma and platelet products from asymptomatic blood donors, raising concerns about potential risk of transfusion transmission, also in the context of the current therapeutic approach utilizing plasma from convalescent donors. The objective of this study was to assess the efficacy of amotosalen/UVA light pathogen reduction treatment to inactivate SARS-CoV-2 in human plasma to reduce the risk of potential transmission through blood transfusion.

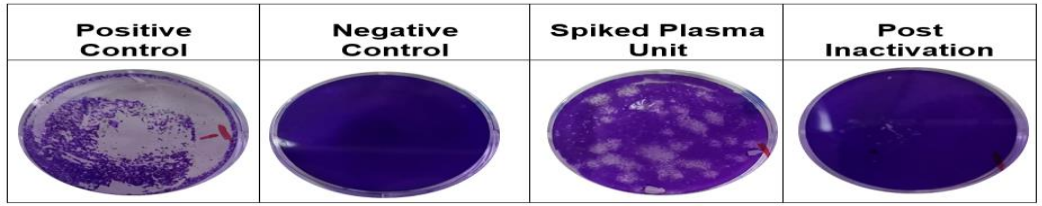

Figure 1. Inactivation of SARS-CoV-2 in plasma by amotosalen/UVA light treatment assessed by a plaque assay. SARS-CoV-2 viral stock (Positive Control), human plasma (Negative Control), plasma from a SARS-CoV-2 spiked pretreatment sample (Spiked Plasma Unit) and amotosalen/UVA-treated, SARS-CoV-2 spiked plasma (Post Inactivation). Photographs (4X) are shown from one of five representative experiments.

Experiment	SARS-CoV-2 Viral load (log_{10} PFU/mL)				Log reduction
	Positive Control	Negative Control	Pre-treatment	Post-inactivation	
A	5.5	ND	3.4	ND	3.4
B	5.7	ND	3.2	ND	3.2
C	5.6	ND	3.6	ND	3.6
D	5.9	ND	3.3	ND	3.3
E	5.3	ND	3.1	ND	3.1
Mean ± SD	5.6±0.20	ND	3.32±0.19	ND	>3.32±0.19

Table 1. Reduction of infectious SARS-CoV-2 titers post inactivation by amotosalen/UVA light in plasma. Data from plaque assay titration on Vero E6 cells (log_{10} PFU/mL). ND indicates not detected. (SD) standard deviation.

Methods: Pools of three whole-blood derived human plasma units (630-650 mL) were inoculated with a clinical SARS-CoV-2 isolate (SARS-CoV-2/human/SAU/85791C/2020, gene bank accession number: MT630432). Spiked units were treated with amotosalen/UVA light (INTERCEPT™ Blood System, Cerus Corporation, U.S.A) to inactivate SARS-CoV-2. Infectious titers and genomic viral load were assessed by plaque assay and real-time quantitative PCR (RT-qPCR, RealStar SARS-CoV-2 RT-PCR Kit 1.0, Altona Diagnostics, Germany). Genomic titers are expressed as PFU equivalents (PEq/mL). Inactivated samples were subject to three successive passages of three days respectively on permissive tissue culture (Vero E6 cells) to exclude the presence of replication-competent viral particles in inactivated plasma.

Results: Inactivation of the infectious viral titer in spiked plasma units below the limit of detection was achieved by treatment with amotosalen/UVA light with a mean log reduction of >3.32 ± 0.2 assessed by plaque assay (Fig. 1, Tab. 1). Passaging of inactivated samples on Vero E6 cells showed no viral replication even after nine days of incubation and three passages (Fig. 2, Tab. 2), confirming complete inactivation. The treatment also inhibited NAT detection by nucleic acid modification with a mean log reduction of 2.92 ± 0.87 PFU genomic equivalents (Tab. 3).

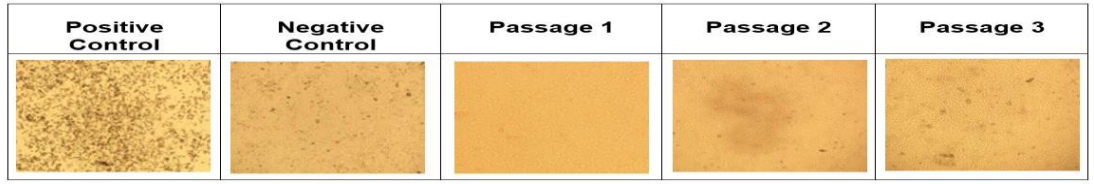

Figure 2: Assessment of complete inactivation of replicative SARS-CoV-2 post amotosalen/UVA light treatment by passaging experiments on Vero E6 cells. SARS-CoV-2 spiked pretreatment sample (Positive Control), human plasma (Negative Control) and amotosalen/UVA treated, SARS-CoV-2 spiked plasma (Passage 1-3). Photographs (4X) are shown from one of five representative experiments on day 3 post-inoculation in each passage.

Experiment		Passage 1	Passage 2	Passage 3
		SARS-CoV-2 genomic load (log_{10} PEq/mL)		
A	pre-treatment	5.05	4.54	4.14
	post-inactivation	ND	ND	ND
B	pre-treatment	5.12	4.61	4.31
	post-inactivation	ND	ND	ND
C	pre-treatment	5.24	4.05	4.01
	post-inactivation	ND	ND	ND
D	pre-treatment	4.96	4.01	3.95
	post-inactivation	ND	ND	ND
E	pre-treatment	5.16	4.21	3.97
	post-inactivation	ND	ND	ND

Table 2. Replication of SARS-CoV-2 in Vero E6 cells before and after inactivation of spiked plasma (genomic titer): Data is shown as log_{10} PEq/mL. Genomic viral load was determined on day 3 post-inoculation for each passage. ND indicates not detected.

Experiment	SARS-CoV-2 genomic load (log_{10} PEq/mL)			
	Positive control	Negative control	Pre-treatment	Post-Treatment
A	5.99	ND	3.60	ND
B	5.88	ND	2.82	ND
C	5.53	ND	3.96	ND
D	5.36	ND	2.44	ND
E	5.18	ND	1.79	0.24
Mean ± SD	5.59±0.34	ND	2.92±0.87	0.04±0.11

Table 3. SARS-CoV-2 genomic titers before and after inactivation by amotosalen/UVA in plasma . Data is shown as log_{10} PEq/mL (determined by real-time RT PCR). Titers were determined from the same samples used in Table 1. ND indicates not detected. (SD) standard deviation.

Conclusion: Amotosalen/UVA light treatment of plasma spiked with SARS-CoV-2 inactivated SARS-CoV-2 to the limit of detection and resulted in a >3.3 log reduction in infectious titers. This study indicated that treatment of plasma with amotosalen/UVA could reduce the risk of SARS-CoV-2 transfusion transmission.

BUT PR system must preserve antibody quantity and quality

First Published Assessment of the Impact of PR (AS) on CCP Quality

Correspondence

Stability and neutralising capacity of SARS-CoV-2-specific antibodies in convalescent plasma

Convalescent plasma is a promising

from patients who have recovered from COVID-19. Our data show that pathogen inactivation of convalescent plasma does not impair the stability and neutralising capacity of SARS-CoV-2-specific antibodies compared with non-pathogen-inactivated controls. Although SARS-CoV-2 IgG titre and neutralising capacity seem

We declare no competing interests.

Torsten Tonn, Victor M Corman, Matthias Johnsen, Anja Richter, Roman N Rodionov, Christian Drosten, Stefan R Bornstein
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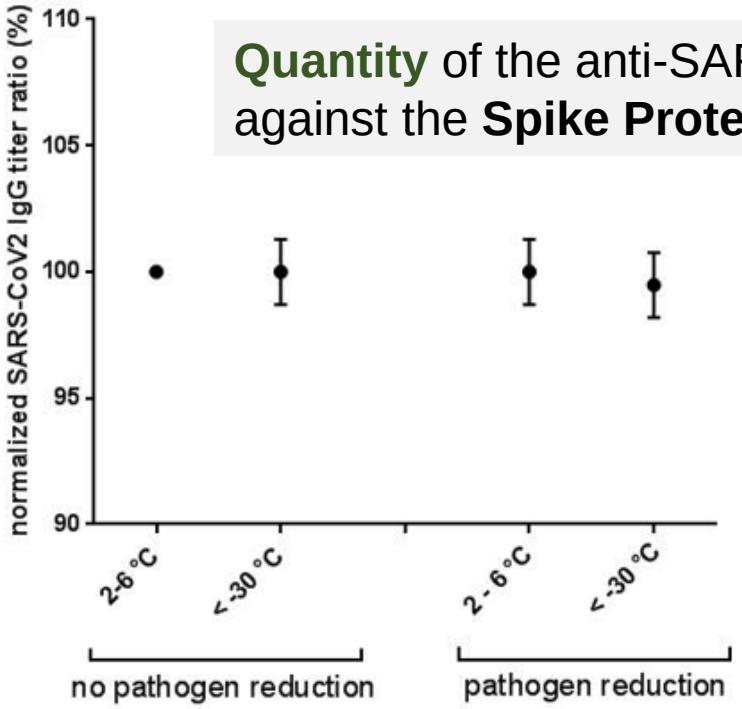
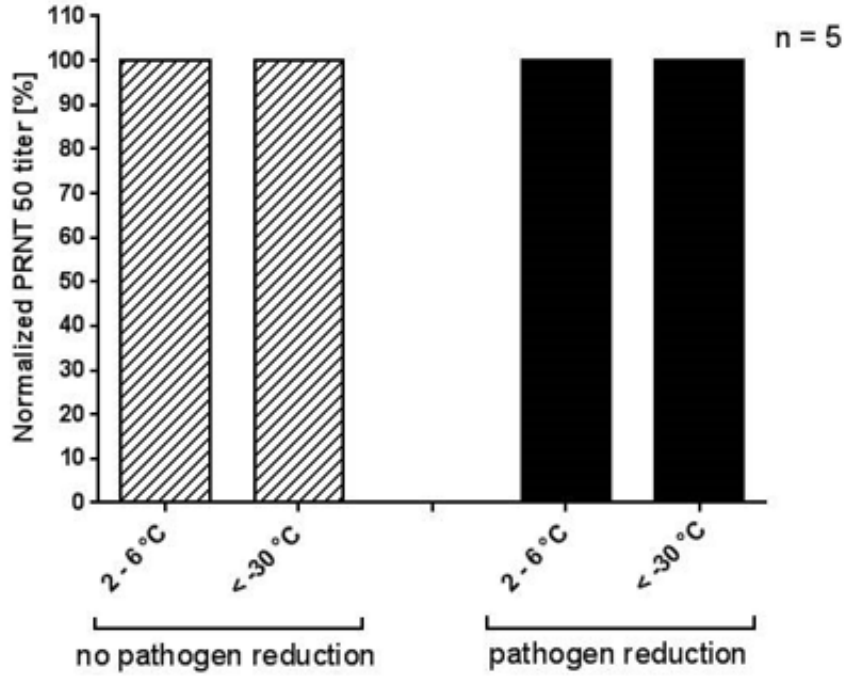


Quantity of the anti-SARS-CoV-2 IgG against the **Spike Protein** (S1-domain)



Quality (Neutralizing Activity of the CCP) with a plaque number reduction test

Tonn T et al., 2020. Stability and neutralising capacity of SARS-CoV-2-specific antibodies in convalescent plasma. *Lancet Microbes* 1: e63

Side-by-side comparison of the impact of PR on CCP Quality

ELISA: Anti-SARS-CoV-2 IgG semi-quantitative ELISA test system developed in Gamaleya NRCEM and registered for clinical use in the Russian Federation

Neutralization Assay: NtAb titre was determined by a microneutralization test developed in Gamaleya NRCEM

Table 1 Individual methods of pathogen reduction, comparison of the initial values vs. post-treatment values using two sample paired *t*-test

Method (sample size)	NtAbs*	Anti-RBD IgG (AU)	Anti-S + N IgG (U/ml)	Anti-S + N IgM (COI)
Methylene blue (n = 104)	**0·10** (0·01)	**0·03** (0·03)	1·1 (0·23)	0·007 (0·59)
Amotosalen (n = 88)	**0·23** (0·0003)	0·0 (0·99)	**1·7** (0·008)	0·01 (0·53)
Riboflavin (n = 83)	**0·40** (<0·0001)	**0·07** (0·001)	**8·9** (<0·0001)	**0·19** (<0·0001)

The numbers show the average decline of values of NtAbs, anti-RBD IgG, anti-S + N IgG and anti-S + N IgM after treatments by each of the three methods (M/A/R, respectively). The *P*-values in the parentheses below indicate how statistically different from zero these values are; those with $P < 0{\cdot}05$ are in bold font.

*The shown values are $\log_2$-transformed and divided by 10.

Studies assessing the Impact of PI on CP (CCP indicated in yellow)

Table 1
Impact of different PRT on overall immunoglobulin levels and/or anti-SARS-CoV-2 neutralizing antibodies.

PRT brand	PRT effect on IgG or nAb levels	# of treated plasma units	Ref
Intercept®	No significative difference in EBOV nAb titer	10	[37]
	−2% to −4% EBOV IgG	1	[38]
	No significative difference in SARS-CoV-2 nAb titer	5	[25]
	−3.8% anti-SARS-CoV-2 N protein IgG	48	[39]
	No difference in SARS-CoV-2 nAb titer and N-protein antibodies	110	[26]
	No significative difference in SARS-CoV-2 nAb titer	30	[27]
	Among units with the initial SARS-CoV-2 nAb titre ≥ 80:	140	[28]
	60% (47%–73%, CI) were unchanged		
	40% decreased by one dilution		
Mirasol®	−13% to −22% total IgG after 69 week storage at −30 °C	6	[40]
	−17.1% total IgG and −23.6% IgG_1 (significant)	6	[29]
	−16.6% total IgG and −32.3% IgG_1 (significant), but no significant difference in Tetanus, Diphteria and Pneumococcal protective antibody titers	6	[30]
	−12.7% anti-SARS-CoV-2 N-protein IgG	20	[39]
	Among units with the initial SARS-CoV-2 nAb titre ≥ 80:	140	[28]
	43% (26%–61%, CI) were unchanged		
	50% had a one-dilution decrease		
	7% had a two-dilution decrease		
Theraflex MB®	−4.8% anti-SARS-CoV-2 N-protein IgG	22	[39]
	Among units with the initial SARS-CoV-2 nAb titre ≥ 80:	1401	[28]
	81% (71%–91%, CI) of units remained unchanged		
	19% decreased by one dilution		

Conclusion

Conclusion I (CCP Collection)

- Measures to restore and gain public and donor confidence in blood donation are extremely important during any Pandemic
- Early implementation of measures which can enable us to secure blood / CCP safety and supply
- We have to learn from this Pandemic to be ready with a clear, effective plan to secure blood / CCP safety and availability during this pandemic & any future Pandemic

Conclusion II (Pathogen Reduction)

PR has the potential to increase the safety of CCP. There may be differences in PR-technology broadness of effectiveness and impact on CCP antibody quantity as well as quality, which need to be considered when adopting PR.

Conclusion III (Therapeutic Efficacy)

Clinical benefit most likely in patients treated early in course of disease (pre-seroconversion) with high-titer COVID-19 Convalescent Plasma to prevent progression of disease severity. Also for immunocompromised patients which cannot be vaccinated for passive immunization.

Thank you