REVIEW

Pathogen inactivation: emerging indications

Steven Kleinman

Purpose of review
To review data about transfusion-transmitted infections so as to assess potential safety benefits of applying pathogen inactivation technology to platelets.

Recent findings
Residual bacterial risk still exists. Multiple arbovirus epidemics continue to occur and challenge blood safety policy makers in nonendemic developed countries. There is new documentation of transfusion transmission of dengue and Ross River viruses, and new or increased concern about chikungunya and Zika viruses. Pathogen inactivation has been shown to inactivate almost all bacterial species and several epidemic arboviruses that pose a transfusion transmission risk. The two available platelet pathogen inactivation technologies show different levels of pathogen inactivation as measured by in-vitro infectivity assays; the clinical significance of this finding is not known.

Summary
Pathogen inactivation can mitigate infectious risk and should do so more completely than other interventions such as donor questioning, donor/component recall, or donor testing. However, pathogen inactivation increases the cost of the pathogen-reduced blood component, which is a significant obstacle in the current healthcare environment. This may inhibit the ability to move forward with an effective new paradigm for blood safety that fulfills the implicit public trust in the blood system.

Keywords
blood safety, emerging infectious agents, pathogen inactivation, pathogen reduction, transfusion-transmitted infection

INTRODUCTION

A recent publication notes that the terms pathogen inactivation and pathogen reduction have been used somewhat interchangeably in the literature and then proposes to standardize this terminology. The authors suggest that 'pathogen inactivation' should refer to the various treatment methods used to 'kill' pathogens whereas the term 'pathogen-reduced blood components' should be used to describe the actual treated blood component [1■■]. This review uses the new terminology, which hopefully will become widely accepted and thereby clarify further communications and discussions.

Pathogen inactivation techniques for single units of platelets and plasma have been licensed in many countries for over a decade. In addition, pathogen inactivation for red blood cell (RBC) units and for whole blood continues in development. The Intercept system (Cerus, Concord, California, USA) inactivates pathogens in platelets and plasma using UVA light to photoactivate amotosalen – a psoralen compound. The Mirasol system (Terumo BCT, Lakewood, Colorado, USA) uses riboflavin and a combination of different frequencies of ultraviolet light: UVA, UVB, and a small amount of UVC [2■■]. The most significant regulatory development in the past year has been US Food and Drug Administration (FDA) licensure in December 2014 of one of these pathogen inactivation systems (Intercept) for apheresis platelets and for plasma [2■■]. This review will primarily focus on risk reduction that can be achieved by using pathogen-reduced platelets.

BACTERIAL INFECTION

Despite automated bacterial culturing of apheresis platelet units at 24 h postcollection, residual bacterial risk remains. The risk of bacterial contaminated apheresis platelet units is estimated at 1 in 1500 to 1 in 3000, and the risk of a clinically identifiable septic reaction at 1 in 107 000; the latter

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KEY POINTS

- Breakthrough bacterial infections from platelets occur and can be prevented by pathogen inactivation.
- The continued occurrence of multiple explosive arbovirus outbreaks in many parts of the world pose a transfusion transmission threat, both in endemic and nonendemic countries.
- Data exist showing that one or more pathogen inactivation systems can inactivate many arboviruses to very high titers.
- An effective way to pay for pathogen-reduced platelets and other pathogen-reduced components is needed.

figure is probably an underestimate due to lack of recognition and/or reporting [3▪▪]. Moreover, since heme-onc and human stem cell transplant patients receive an average dose of 6 apheresis platelet units during their treatment course, the average per patient risk is six-fold higher [4].

In a recent US FDA Draft Guidance, multiple risk-reduction strategies have been proposed [5▪]. These include avoiding the use of platelets stored for 4 or 5 days (however, this is not logistically possible for most institutions), or performing secondary bacterial testing on these older platelet units using either a point-of-issue rapid bacterial immunoassay or a repeat culture. Another alternative suggested by others is to delay the initial culture to allow better bacterial outgrowth and detection; to be practical, this would require extension of platelet storage to day 7 [6▪]. Pathogen-reduced platelets prepared by the amotosalen/UVA technology have been shown by European Hemovigilance routine use data to provide an effective solution to this problem, with zero clinically recognized bacterial infections [4]; this corroborates prior in-vitro spiking studies demonstrating a high level of kill (4–6 logs) of multiple bacterial strains [3▪▪]. A head-to-head study and a summary of the existing literature indicate that the riboflavin/UV technology results in a lower level of kill for some strains [3▪▪,7▪▪]. On the basis of bacterial growth kinetics and one experimental study, it has been recommended that either of these pathogen inactivation methods would best be applied shortly after collection of an apheresis platelet unit rather than at the 24 h allowable time limit [3▪▪,8▪▪].

In summary, the available data indicate that the use of pathogen-reduced platelets prepared by the Intercept system provide robust protection against transfusion-transmitted bacterial infection; at present, the data for the Mirasol system are less definitive. Continued hemovigilance monitoring will be needed as one or both of these pathogen inactivation methods become more widely used in order to document whether breakthrough bacterial infections occur [9▪▪].

ARBOVIRAL INFECTION

Arboviruses (i.e. viruses transmitted by insect vectors) have emerged as a major transfusion safety concern over the past 15 years [10]. Most of these viruses are more prominent in the tropics where they can be both endemic and epidemic; epidemics can be explosive with a substantial portion of the population affected over weeks to months. Arboviruses are from different genera and include alphaviruses, bunyaviruses, and flaviviruses. The proportion of symptomatic to asymptomatic individuals varies across different viruses. Current viruses of most interest are the dengue virus group (a flavivirus), Zika virus (also a flavivirus), and chikungunya (an alpha virus). Symptoms which include fever, arthralgias, and rashes may be very similar in these three infections, making it difficult to distinguish between them in locations where all three viruses are circulating concurrently as has occurred recently in French Polynesia and Brazil [11▪]. More severe disease including neurological syndromes and mortality can occur.

Transfusion transmission can occur from blood donors who remain asymptomatic or who are presymptomatic, as there is an interval when donors feel well, but are viremic in the absence of antibody. In general, the duration of viremia (as documented by detection of viral nucleic acid) in the absence of protective antibody is about a week in the asymptomatic phase and shorter (several days) in presymptomatic persons [10,12▪,13,14▪,15▪▪,16▪▪].

The risk for and sources of transfusion transmission differ in endemic and nonendemic countries. In endemic countries, the donor population will show high rates of infection; however, if prior epidemics have occurred in the past several decades, many transfusion recipients may be immune due to protective antibody from a previous community-acquired infection with the same agent. In addition, in these settings, it will be difficult to detect a small number of transfusion-transmitted cases in a background of high-level insect-borne transmission. In contrast, in nontropical countries, TTD risk comes from two sources: blood donors who became infected when they travel to endemic regions and donate shortly after their return; and from autochthonous transmission if the virus has spread into the indigenous mosquito population in warmer regions within their borders. Examples of the latter are separate transmission events of both

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dengue and chikungunya virus (CHIKV) by mosquito vectors in Florida [17,18].

Transfusion-transmitted risk is determined from case reports, case series, or more rarely from carefully designed studies. Even in the absence of proof, it has been assumed that all arboviruses can be transfusion-transmitted; this is supported by the high rates of detectable donor viremia (RNAemia) often detectable during an epidemic. Risk is estimated using well developed modeling techniques which incorporate assumptions about viremia duration, infection incidence in the general and donor populations, ratio of symptomatic to asymptomatic cases, virus infectivity (usually assumed to be 100% for any nucleic acid reactive, antibody negative donation), and the susceptibility of the recipient population. These modeling techniques are now well standardized and have been applied to a wide range of arboviral epidemics in many locations [14▪,19–21].

The best documented transfusion-transmitted arbovirus is West Nile virus, which caused 23 recognized transfusion-transmitted cases in the United States in 2002 prior to implementation of donor nucleic acid testing (NAT) in minipools in 2003 [22]. A recent summary of over a decade of American Red Cross (ARC) data indicates that minipool-NAT donor screening reflexed to individual donation NAT based on a rigorous algorithm (e.g. the detection West Nile virus minipool-NAT-reactive donors in circumscribed geographical locations) was virtually 100% effective in preventing transfusion transmission from blood collected by the ARC [12▪].

Dengue viruses include four genetically related viruses (DEN-1 through 4); infection with one does not provide immunity against the others. Despite endemicity in over 100 countries along with numerous epidemics in many countries, only six cases of transfusion-transmitted dengue were reported prior to 2014, with most causing symptomatic disease in recipients [23–25]. The paucity of these case reports is in contrast to the high rate of dengue RNA detection in donated blood (0.06–0.8% over several months) in many studies [13,25,26,27▪▪], generating the hypothesis that transfusion-transmitted dengue is likely under-recognized and/or under-reported. Recently, two additional case reports and a detailed linked donor/recipient study yielding six transfusion-transmitted cases have more than doubled the number of cases [27▪▪,28,29]. In the linked study, over 7000 donors were retrospectively tested for dengue RNA, as were over 600 recipients transfused with these units during a 2012 epidemic of dengue 4 in Brazil. Transfusion transmission occurred in 6 of 16 susceptible recipients transfused with a dengue RNA-positive unit for a transfusion transmission rate of 37.5% (95% confidence interval 15.2–64.6%). Transfusion transmission occurred with RBCs, platelets, and plasma, and there was no association with donation viral load; transmitting units contained between 36 and 84 000 copies/ml. None of the six infected recipients had symptoms associated with severe dengue, nor was there clinical suspicion of transfusion-transmitted dengue.

Zika virus is a flavivirus that has caused multiple outbreaks since 2007 in Africa and Oceania; imported cases have occurred in multiple European countries. There is evidence for perinatal transmission and suggestive evidence for sexual transmission [16▪▪]. Moreover, RNAemia has been demonstrated in 2.8% of blood donors in French Polynesia during a recent epidemic, with a quarter of these donors reporting a fever-like syndrome 3–10 days postdonation [30▪▪]. These observations suggest that transfusion-transmitted Zika is likely to occur, though no transfusion-transmitted cases have yet been documented [30▪▪,31].

Ross River virus (an alphavirus) is the most common mosquito-borne human disease causing virus in Australia (over 5000 annual cases) and is endemic in several regions. The first case of transfusion-transmitted Ross River viral infection was reported from a donor, who, 2 months following donation, informed the blood collection center of fatigue and arthralgia 2 days following donation [32▪]. The recipient developed a clinically compatible illness, was positive post-transfusion for IgM antibody, and the archived donor unit tested positive for Ross River virus RNA. Despite the fact that transfusion transmission was postulated as early as 1995, it took close to 20 years to document an occurrence.

CHIKV is an alphavirus that results in symptomatic disease in approximately 85% of infections [15▪▪]. There are three genotypes, with the East/ Central/ South African (ECSA) strain having undergone a mutation which facilitates viral replication (and hence the capacity to transmit) in one of its mosquito vectors (*Aedes albopictus*) [15▪▪,33▪]. CHIKV has caused extremely large epidemics in Africa, India, Thailand, and, most recently (peaking in 2014), in the Caribbean and other parts of the Western Hemisphere. Peak incidence of viremic donations has been estimated to be extremely high, at 1500 per 10^5 donations in La Reunion and 38.2–52.3 per 10^5 in Thailand [14▪,20]. Due to this high estimated incidence, modeling studies predict a high risk of transfusion transmission, though no transfusion-transmitted cases have yet been documented. Actual data show donor NAT reactive rates from 0.1 to 0.4% during several weeks of testing in three separate epidemics [14▪,20,34▪▪].

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POTENTIAL INTERVENTIONS TO PREVENT TRANSFUSION-TRANSMITTED ARBOVIRUS INFECTION

A number of interventions have been adopted singly or in combination in multiple jurisdictions in the midst of arbovirus epidemics [15▪▪]. These include the following:

(1) Ceasing blood collections: This is highly effective, but is not always feasible given limitations of blood component availability. It is also highly costly.
(2) Enhancing postdonation symptom reporting by donors and linking it to component recall and/or temporary component quarantine: This can either be passive (emphasizing to donors to call the blood center with this information) or active (initiating a call to each blood donor and holding the component in quarantine until a negative symptom history is obtained). The latter is logistically complex. When adopted in a region in Thailand during a CHIKV epidemic, RBCs from donors categorized as high risk were quarantined for 7 days [14▪].
(3) RNA donor testing: This should have high efficacy, but is expensive and requires investment and a development effort by test manufacturers. A limitation is that the test will only be effective for the given virus for which it was developed (i.e. NAT for dengue will not detect Zika-infected donors) [25,30▪▪,34▪▪].
(4) Pathogen inactivation of platelets: This intervention was used in the 2007/2008 La Reunion CHIKV epidemic and the 2014 CHIKV epidemic in the Caribbean, specifically in the French West Indies and more recently in Puerto Rico [20,34▪▪,35]. This solution obviates the problem of platelet availability; however, it is expensive.
(5) Travel deferral: In nonendemic areas, the concern is transfusion transmission from travelers. Therefore, a proposed generic intervention is a temporary deferral for persons who travel to geographic regions where infection can be acquired. In December 2012, the Netherlands implemented a 28-day deferral for travel outside the European Union after a feasibility study indicated that such a deferral would have minimal impact on blood availability [36▪▪]. By casting this broad net (i.e. not specific to the geography of any specific epidemic), the deferral was operationally easy to implement. Prior to implementing similar policies in other countries (e.g. United States), seasonal travel patterns of that country's blood donors must be well characterized.

PATHOGEN INACTIVATION DATA FOR ARBOVIRUSES

Asymptomatic dengue and CHIKV infections are both characterized by a distribution of RNA concentrations that include very high titers (up to 10^8/ml) [25,37]; what is not known is how many RNA copies constitute an infectious dose [38]. Thus, for maximal efficacy, a pathogen inactivation technology should achieve a very high level of viral inactivation. Table 1 summarizes available data for the two pathogen inactivation technologies in plasma and in different types of platelets. As can be seen from the data, multiple studies indicate that Amotosalen/UVA inactivates arboviruses to the limit of the detection of the tissue culture infectivity assay system, whereas riboflavin/UV achieves only partial inactivation for most of these viruses. These in-vitro results indicate that providing pathogen-reduced platelets (at least by the amotosalen/UVA method) should be a robust intervention that could be put in place proactively, thereby obviating the need to react to unforeseen focal or epidemic spread of specific viruses. This same rationale supports the use of pathogen-reduced plasma for transfusion. More definitive proof of the clinical efficacy of each pathogen inactivation system requires studies which use sample repositories to retrospectively test pathogen-reduced and conventional platelet units for viral RNA and then evaluates recipients to ascertain whether transfusion-transmitted infection occurred.

OBSTACLES FOR IMPLEMENTATION OF PATHOGEN-REDUCED PLATELETS

The major impediment for use of pathogen-reduced platelets is increased cost [2▪▪,47▪]. In the United States, this is further complicated by the inability of the healthcare payment system to reimburse hospitals or blood centers for supplying this product. Depending upon circumstances in a particular geographic locale, costs can be partially controlled based on offsets; this was illustrated in a published cost analysis of pathogen-reduced platelets in a rural region in Spain [48]. Cost offsets include procedures that could be eliminated (e.g. bacterial culturing, irradiation for graft-versus-host disease prevention, and cytomegalovirus serology testing), new procedures that do not need to be implemented (point-of-issue bacterial testing, donor-screening assays for new arboviruses, new donor deferrals), and reduced outdating of apheresis platelets in jurisdictions that allow extended 7-day platelet storage [49▪▪].

The cost issue creates a tension between the goal of implementing a new paradigm of blood safety,

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Table 1. Pathogen inactivation of arboviruses

Virus[a]	Component	Method	Logs of inactivation[b]	Inactivated to limit of assay detection	Citation type/author affiliation	Citation
DEN-1	PAS	Amot	>5.0[c]	Yes	Manf	[39■]
DEN-1	Plasma	Amot	>5.61	Yes	Indp	[40■■]
DEN-2	AP in PAS	Amot	>5.0	Yes	Manf	[41]
DEN-2	AP	Amot	>3.01	Yes	Indp	[38]
DEN-2	AP	Ribo	0.76–1.58	No	Indp	[38]
DEN-3	PAS	Amot	>4.5	Yes	Manf	[39■]
DEN-4	PAS	Amot	>5.2	Yes	Manf	[39■]
DEN 1–4	BC[d] platelets	Ribo	1.28–1.81	?[e]	Indp/manf	[42]
CHIK	AP in PAS	Amot	>6.4	Yes	Indp/manf	[43]
CHIK	Plasma	Amot	>7.6	Yes	Indp/manf	[43]
CHIK	AP in PAS	Ribo	2.2	No	Indp/manf	[44]
CHIK	Plasma	Ribo	2.1	No	Indp/manf	[44]
CHIK	AP	Amot	>3.75	Yes	Indp	[38]
CHIK	AP	Ribo	>3.73	Yes	Indp	[38]
Zika	Plasma	Amot	>6.57	Yes	Indp	[45]
RRV[f]	BC platelets	Ribo	2.33	No	Indp/manf	[46■■]
BFV[f]	BC platelets	Ribo	1.97	No	Indp/manf	[46■■]
MVEV[f]	BC platelets	Ribo	1.83	No	Indp/manf	[46■■]

Amot, amotosalen/UVA; AP, apheresis platelet; BC, buffy coat; BFV, Barmah Forest virus; CHIK, chikungunya; DEN, dengue; Indp, investigators with nonmanufacturer affiliation; Manf, manufacturer study; MVEV, Murray Valley encephalitis virus; PAS, platelet additive solution (contains 35% plasma); Ribo, Riboflavin/UV; RRV, Ross River virus.
[a]This table does not include West Nile virus (WNV) as those data were generated approximately 10 years ago; both pathogen inactivation methods achieved high levels of WNV inactivation to the limit of detection.
[b]Inactivation is expressed as logarithm to the base 10. For example, 5 logs of inactivation indicates that the viral infectivity titer has been decreased by 10^5.
[c]The notation '>' indicates that the virus was inactivated to the limit of detection (LOD) of the assay system; this LOD is usually related to the maximum amount of virus that can be spiked into the blood component prior to performing the pathogen inactivation treatment.
[d]Buffy coat platelets are manufactured from units of whole blood and then multiple units are pooled prior to pathogen inactivation treatment.
[e]Inactivation of all four dengue viruses (DENV 1–4) was reported at these low levels, but it was unclear as to the LOD of the assay system.
[f]RRV, BFV, and MVEV are arboviruses indigenous to Australia; MVEV is closely related to WNV.

thereby reinforcing public trust in the blood system, and the competing goal of minimizing health-care expenditures [2■■,47■,50]. In the United States, there is no organization with the authority to reconcile these two goals; this may inhibit the ability to move forward with an effective new paradigm for blood safety that fulfills the implicit public trust in the blood system.

CONCLUSION

Blood safety would be improved if pathogen-reduced platelets were to be used; this includes immediate safety gains (e.g. bacteria and known viruses such as HIV), as well as insurance against potential future threats from arboviruses and other emerging infectious agents. The major impediments to implementation are cost and reimbursement.

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Conflicts of interest

Paid consultant for Cerus Corporation, manufacturer of the Intercept System.

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■ of special interest
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