Review

Not peer-reviewed version

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Posted Date: 29 May 2023

doi: 10.20944/preprints202305.1972.v1

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Review

Emerging Pathogen Threats in Transfusion Medicine and the Role of Pathogen Reduction Technologies

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Abstract: Emerging infectious disease threats are becoming more frequent due to various social; political and geographical pressures including increased human-animal contact; global trade; transportation and changing climate conditions. As a result; the threat that emerging agents can be spread by blood contact or transfusion of blood products also becomes increasingly problematic. Blood transfusion is essential in treating patients with anemia; blood loss; and other medical conditions. However; these lifesaving components can become a vector for spreading diseases; particularly to vulnerable populations. New methods have been implemented on a global basis for prevention of transfusion transmission via plasma; platelet; and whole blood products. Implementing proactive pathogen reduction methods can significantly reduce the likelihood of disease transmission via blood transfusion; even for newly emerging agents whose transmissibility and susceptibility are still being evaluated as they emerge. In this review; we consider the Mirasol PRT system for blood safety which is based on a photochemical method involving Riboflavin and UV light. We provide examples of how emerging threats such as Ebola; SARS-CoV-2; Hepatitis E; monkeypox and other agents have been evaluated in real time regarding effectiveness of this method for reducing the likelihood of disease transmission via transfusion.

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1. Introduction

Historically diseases were spread under conditions of war, trade, and travel. Today, in the age of globalization, mobility of goods and persons are extremely high [1]. Moreover, human population growth has led to increased urbanization of wild habitats, and over-exploitation of water and fossil fuels which is culminating in a remarkable increase in land and ocean temperature since 1981 [2–4]. The effects of these changes are seen in the increased number of floods, intense storms, thawing of permafrost and melting of the sea ice which will continue to push people and animals into more restricted geographical areas [5]. We now see an increased proximity of humans to wild animals including primates as well as the presence in temperate regions of insect vectors previously only found in the tropics [3]. All of this propagates the impact of the disease triangle comprised of environment, pathogen and society [6].

Over the past 40 years, we have seen the increasing emergence and re-emergence of infectious diseases. HIV was identified as the agent of a pivotal species cross-over infection leading to the global AIDS epidemic. Its spread was facilitated by modern human practices and social behaviors, e.g. sexual activity, blood transfusion and intravenous drug abuse [7,8]. Outbreaks from Severe Acute Respiratory Syndrome coronavirus (SARS-CoV) in South-East Asia, Ebola virus disease in Africa, Middle East respiratory syndrome coronavirus (MERS-CoV) in the Middle East and Zika virus

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disease, chikungunya, yellow fever and dengue in the Americas followed in the ensuing two decades [9,10]. Finally, in 2020 the WHO declared the pandemic of COVID-19 caused by SARS-CoV-2 which has caused over 6.8 million human deaths globally [11].

Emerging and re-emerging pathogens pose an important risk to transfusion medicine. Along with the classical blood-borne pathogens, HIV, HBV, HCV, arbovirus transmission through blood transfusion has been increasingly reported in the past 20 years [12,13]. West Nile and Dengue viruses are the two most frequent agents suspected of transmission by transfusion. Other arboviruses tentatively implicated in disease transmissions are Zika virus, yellow fever virus, tick-borne encephalitis virus, Japanese encephalitis virus, Powassan virus, St. Louis encephalitis virus, Ross River virus and Colorado tick fever virus [14].

In the past 40 years blood transfusion safety measures have been developed and implemented as a reaction to the identification of new infectious threats. Initially, detection of infection was based on immunological assays. Currently, tests rely on the detection of the agent's nucleic acid presence in the donated blood which carries a significantly shorter development time [15]. Nevertheless, the climate/social developments of the past several years make the emergence of novel pathogens unpredictable and highlights the inadequacy of reactive prevention strategies to quickly address emergent needs in a timely way.

Pathogen reduction (PR) is a proactive strategy to mitigate the risk of transfusion-transmitted infections (TTI). Available PR methods involve physicochemical disruption of pathogen structural elements or photochemical modification of nucleic acids to prevent replication [16]. The plasma fractionation industry has the longest and most successful experience with PR, starting 30 years ago with the systematic application of methods of pathogen inactivation/removal in the manufacturing process to bring the safety of plasma-derived medicine products to the highest levels observed today [17].

As for labile blood components, methods of PR have been gradually implemented in Europe in the last 10 years and lately in the USA, mostly for the treatment of platelet concentrates and plasma for transfusion [18]. A treatment for whole blood for transfusion has also shown effectiveness and feasibility in a malaria high-endemic country [19,20]. Componentization of whole blood treated with Riboflavin and UV light and the transfusion of the processed red cell concentrate has proven to be safe and therapeutically effective [21]. Treatments to inactivate pathogens in red cell concentrates is still under development [22,23].

Doubtless, worldwide adoption of such proactive technology will depend on the availability of a technology for treatment of all blood derived components universally and at acceptable cost. Yet, component treatment has proven that the concept of a universal pathogen inactivated transfusion is possible, as demonstrated by the recent report of patients receiving all blood components treated with the Riboflavin plus UV technology [24].

In this article we will review strategies to respond to and protect the human population from infectious threats, with special focus in transfusion medicine. We will describe the most recent outbreaks of viral pathogens (monkeypox, SARS-CoV-2, Ebola virus, and Hepatitis E virus) with potential to challenge the established reactive protective measures in place for several decades. Moreover, we will describe how pathogen reduction technology based on Riboflavin (vitamin B2) and UV light may contribute to improve the preparedness of the transfusion community for future emergent virus threats to blood supply safety and integrity.

2. Pandemic preparedness for emerging pathogen threats

The rapid emergence and spread of SARS-CoV-2 has emphasized the importance of pandemic preparedness for emerging pathogen threats. Global pandemic preparedness involves a range of strategies and tools to detect, respond to, and control the spread of infectious diseases. Current strategies and tools are designed to detect outbreaks early, prevent and control their spread, and reduce their impact on human health, society and economy. Some of the most common strategies and tools used for global pandemic preparedness include:

 doi:10.20944/preprints202305.1972.v1

1. Disease surveillance and laboratory capacity. Monitoring infectious disease incidence and spread, as well as, testing of samples to confirm presence is critical in early detection of outbreaks.
2. Strategic medical stockpiles: Stockpiling essential medical supplies such as therapeutics, vaccines, and personal protective equipment ensures that healthcare workers have the necessary resources to respond rapidly to an outbreak.
3. Emergency preparedness planning: This involves developing plans to address disease outbreaks, including activation of emergency response teams, isolation and quarantine measures, and communication strategies to the public.
4. Infection control measures: These involve implementing measures to reduce the spread of infectious diseases. They include hand hygiene, proper disposal of infectious waste, proper use of personal protective equipment, social distancing, and isolation/quarantine of infected individuals.
5. Vaccination: Vaccination can play a key role in preventing and controlling the spread of infectious diseases. As seen with the COVID-19 pandemic, vaccines can mitigate disease impacts and reduce pathogen transmission.
6. Communication: Effective communication is critical in any pandemic response, as it helps to provide accurate information to the public and to prevent panic and the spread of misinformation.
7. Research and development of new tools: Continuous support of research is needed for developing new countermeasures, such as vaccines and therapeutics, to prevent and control outbreaks of new and re-emerging pathogens.

While these strategies and tools are essential for global pandemic preparedness, there remains limitations and gaps in the current system. Some of those challenges include the need for better surveillance and data analysis systems, more rapid and effective response mechanisms, and for increased funding and resources to support preparedness activities.

3. Threats from emerging viruses

Emerging and re-emerging viruses have become a major concern to public health in more recent years. They can cause significant impacts on daily life including social, economic, geopolitical and health impacts [25]. The COVID-19 pandemic demonstrated how emerging threats can quickly disrupt the healthcare system [26], leading to widespread illness, death, and social and economic upheaval. In addition to SARS-CoV-2, monkeypox virus, Ebola virus, and Hepatitis E virus have emerged in recent years and have posed significant threats to public health**.** Of interest is the impact these viruses had on blood transfusion medicine. These pathogens are zoonotic and have the potential to cause severe illness and even death. Therefore, understanding the transmission risk of emerging viral pathogens and implementing proactive mitigation strategies is critical to reduce transmission risk through blood transfusion.

3.1. Monkeypox

Monkeypox, also known as mpox, is a zoonotic viral pathogen that has recently re-emerged and quickly spread globally. As of April 2023, there have been over 87,000 reported cases [27]. The virus is a double-stranded DNA virus in the genus *Orthopoxvirus*. Clinical symptoms may include rash, fever, chills, lymphadenopathy, headaches, and muscle aches [28]. The incubation period ranges from 5-21 days depending on route of exposure [29]. The current mpox outbreak has been primary transmitted human-to-human by sexual contact, although fomite, direct contact with infected lesions, and respiratory modes have also been documented [30]. Rapid systemic spread and viremia in infected patients has been reported, raising concerns of potential blood-borne transmission and questioning blood transfusion safety [31–33].

Numerous studies have reported the detection of mpox DNA in blood samples taken from infected patients using PCR [34–46]. Although the infectious dose required for blood-borne transmission is unknown at this time, several case reports have documented hematogenous spread of the virus through accidental needle sticks with contaminated needles [47–49]. To determine the

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infectious potential of blood samples, researchers have correlated infectious viral titer with viral DNA levels in skin lesions and oropharyngeal swabs. Paran et al. determined that 172 DNA copies correlates to 1 plaque forming unit (pfu) and suggested that samples with PCR values of less than 4,300 copies/mL should be regarded as having no to minimal infectivity [50]. Given that the PCR values observed in blood samples from infected individuals exceeds this amount, the likelihood of blood-borne transmission cannot be ruled out.

3.2. SARS-CoV-2

The emergence of a novel coronavirus, SARS-CoV-2, has led to global spread of COVID-19 disease and continues to impact human health. SARS-CoV-2 is one of three major coronaviruses that have emerged in the last 20 years. The rapid emergence and spread of this new virus raised concern of its potential impacts on blood transfusion medicine. We now know the primary route of transmission is via respiratory routes. However, the COVID-19 pandemic did demonstrate how the safety of blood transfusion products can be questioned in the face of a pandemic threat.

To date, there have been no known cases of transfusion transmission of the three recently emerged human coronaviruses, SARS-CoV, MERS-CoV and SARS-CoV-2. Studies have been conducted to evaluate the potential risk of blood transmission and RNA has been detected in patients infected with SARS-CoV and MERS-CoV [51–55]. RNA was also detected in asymptomatic and symptomatic SARS-CoV-2 patients [56–60]. This includes the detection of RNA at time of blood donation [61]. However, a case report from Asia describes an asymptomatic SARS-CoV-2 infected donor did not transmit the virus to recipients of the donated units[62]. Furthermore, infectious virus has not yet been isolated from RNA-positive blood *in vitro* [63–67] and *in vivo* models [68]. Experimental studies in a mouse model found that 10^4-10^5 plaque forming units given intravenously are needed to develop an infection. However, such dose equivalents have not been detected in donated human blood samples and the authors conclude that the risk of blood transmission to be minimal [68]. Lastly, the prevalence of RNA in blood from donors is low [69]. Therefore, the current risk level for SARS-CoV-2 transmission via blood transmission is minimal.

Due to the uncertainty to transmission risk early in the COVID-19 pandemic, blood donation centers implemented protocols to prevent infected people from donating. This led to devasting impacts on the blood supply, causing a significant blood shortage. The World Health Organization estimated a 20%–30% reduction in global blood supply [70]. Additionally, the American Red Cross reported a 10% decline in the number of donations since the start of the pandemic [71]. In a recent meta-analysis, the decrease in blood donations during the COVID-19 pandemic was estimated at 38% in average, reaching 76% in some regions [72]. Even after lockdown restrictions had been lifted, blood services continued to observe lower whole blood donor availability [70,73]. Donation centers must now focus efforts to regain willingness/intentions to donate among individuals who were deferred [74]. The COVID-19 pandemic highlights the short and long-term impacts emerging viruses can have on blood transfusion medicine.

3.3. Ebola

Ebola viruses continue to re-emerge and cause significant outbreaks and epidemics in Africa. Belonging to the *Filoviridae* family, this highly infectious zoonotic virus can result in acute hemorrhagic fever and death. While a wide range of mammals and primates can act as hosts, fruit bats are thought to be the natural reservoirs [75]. The highest risk for human-human transmission is by direct contact of infected bodily fluids and tissues. However, the virus can also spread by fomites, droplets, and aerosols [76]. The incubation period can be up to 21 days [77] which can make containment of spread more challenging during an outbreak. Mortality rates can range from 25-90% during outbreaks [78]. Due to the high mortality rates, as well as the various routes of transmission, the CDC lists ebolaviruses as a Category A bioterrorism agent and require biosafety level 4 facilities to safely handle infected samples.

The virulence in human patients varies depending on the viral strain, with Ebola Zaire being the most fatal. Patients are considered infectious at time of clinical illness presentation, which includes

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flu-like symptoms, rash, hemorrhaging, gastrointestinal signs, myalgia, and fatigue [79]. In severe cases, viremia can be very high in the blood [80,81]. Therefore, there is risk of blood-borne transmission. There have been reported cases of blood borne transmission including direct contact of bodily fluids, needle-stick [82] and shared needle injections [83]. Blood transfusions continue to be a valuable treatment for infected patients [84] and therefore there is a high demand for transfusion products at the time of outbreaks. It is unlikely that during an outbreak viremic patients infected with Ebola virus (EBOV) would be allowed to donate blood since viremia is associated with symptomatic disease. However, infectious virus and RNA has been detected in various bodily fluids several months after resolution of clinical disease [85]. Furthermore, the infectious dose is believed to be about 10 viral particles [86], which is very low. Therefore, precaution must be taken to avoid potential transfusion transmission.

3.4. Hepatitis E

Hepatitis E virus (HEV) is a hepatotropic virus that causes acute hepatitis, which typically is self-limiting in most adults but can progress to chronic infection in immunocompromised individuals. This virus was first identified in 1983 during an outbreak of unexplained hepatitis in Soviet soldiers returning from Afghanistan [87]. HEV is classified into four genotypes: genotypes 1, 2, 3 and 4. Genotypes 1 and 2 are primarily found in developing countries in Africa and Asia and have been associated with waterborne epidemics. Genotypes 3 and 4 can infect both humans and pigs. Genotype 3 has a global distribution while genotype 4 has been primarily detected in Asia [88].

The incubation period of HEV ranges from 2-8 weeks and clinical symptoms include fever, nausea, abdominal pain, jaundice, and malaise [89]. HEV is typically spread by fecal-oral transmission in developing countries. However, other modes of transmission have been reported such as vertical transmission [90–94], and zoonosis from contacting infected pigs, consuming undercooked pig meat or environmental contamination from pig slurry [95].

Of concern are the increasing reports of blood transfusion transmission. Donors are typically asymptomatic at time of donation and are not routinely screened for HEV infection. However, there have been reports of HEV infections in transfused patients, leading to investigations that identified transfused patients positive for antibodies or RNA from HEV infections [96–98]. Endemic areas such as India are at increased risk of transfusion transmission [99]. HEV infected transmission have also been reported in Japan [100], China [101], Germany [102], England [13], Netherlands [103], Scotland, and Austria [104]. Transfusion-transmitted HEV infections range in their clinical outcomes from short viremias to chronic infections, as seen with cases from England [13]. The infectious dose necessary for transfusion transmission is unknown, but it is believed to be a low dose and is at the limit of detection by PCR [105]. As a non-enveloped virus, HEV poses extra challenges to demostrate complete inactivation. A report from Hauser et al described two cases of HEV transmission by blood products treated by the psoralen+UVA based PRT method [106]. HEV emphasizes the need for effective strategies to mitigate blood transfusion transmission globally for emerging viruses.

These emerging viral pathogens underscore the potential impact on blood transfusion medicine. This in turn has significant short-term and long-term consequences on blood safety and life-saving treatments. It also emphasizes the importance of continuing to develop effective strategies to maintain the safety and quality of blood transfusion to prevent the spread of emerging infectious diseases.

4. Riboflavin+ UV Light Pathogen Reduction Technology

The effectiveness of the Mirasol PRT System against a broad range of pathogens has been previously described for multiple blood product types. Designed to be a pathogen-agnostic system, the technology has a demonstrated ability to reduce the infectious pathogen load of viruses, bacteria and parasites in plasma, platelet and whole blood products, including against emerging diseases for which the development of diagnostic tests may lag behind the emergence of the pathogen. Of importance, the Mirasol PRT System has been demonstrated to be effective against mpox, SARS-CoV-2, Ebola, and HEV (Table 1.)

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Table 1. Blood product types used to evaluate PRT efficacy against viruses of interest.

Viral Pathogen	Platelets	Plasma	Whole Blood	Reference
Hepatitis E	ü	ü	Not tested	[107]
Ebola	Not tested	ü	ü	[108]
SARS-CoV-2	ü	ü	ü	[109–111]
Mpox	Not tested	ü	ü	[112]

4.1. Monkeypox

To evaluate the effectiveness of the Mirasol PRT System against the mpox virus that emerged in 2022, plasma and whole blood products (n=3 of each) were inoculated with the mpox virus (USA_2003), with pre-treatment titers of 3.50 and 3.08 log10 pfu/mL, respectively. These pre-treatment viral titers were clinically relevant based on the amount of virus detected in patients infected with the mpox virus. All products were treated with the Mirasol System per manufacturer's instructions for each product type, and for all products the post-treatment titer was below the limit of detection.

4.2. SARS-CoV-2

Before it was known whether SARS-CoV-2 could be transmitted via blood, several studies were performed to assess the ability of the Mirasol PRT System to reduce the viral load in blood products. In one study, plasma and whole blood products were inoculated with 3-4 log10 pfu/mL of SARS-CoV-2 virus (USA-WA1/2020). The rate of viral inactivation was evaluated in the plasma products, with energy doses of 30, 60 and 100% of the target dose delivered and post-treatment titers measured. Whole blood products were treated per manufacturer's instructions with 100% of the target UV dose. Viral titers reached the limit of detection at 60% of the target energy dose in plasma products, while treatment of whole blood products yielded an average viral reduction of 3.30 log10, demonstrating a high level of efficacy against this strain of coronavirus.

This data was further bolstered in a second study that reported results from Mirasol treatment of both plasma and platelet products in plasma. Pre-treatment titers for all products were greater than 4.3 log10 pfu/mL, and as in the first study, treatment resulted in no detectable virus plaques, meaning that remaining infectious titers were below the limit of detection of the standard plaque assay.

Because convalescent plasma collected from patients who had recovered from SARS-CoV-2 infection was utilized in the early days of the pandemic to treat patients with active disease, a third study was performed to evaluate whether the neutralizing antibodies present in SARS-CoV-2 convalescent plasma products would be preserved following Mirasol PRT treatment. Plasma products collected from known SARS-CoV-2 convalescent donors were collected and pre-treatment neutralizing antibody titers were determined by both a plaque reduction neutralization test against live SARS-CoV-2 virus, as well as a pseudovirus reporter viral particle neutralization (RVPN) assay. Spike protein receptor binding domain (RBD) and subunits S1 and S2 were also evaluated using an enzyme-linked immunosorbent assay (ELISA). Minimal effects to the measured antibodies were demonstrated in all assays, suggesting that the Mirasol System is effective in reducing viral burden in blood products while simultaneously conserving therapeutic benefits of convalescent plasma components.

4.3. Ebola

The Ebola epidemic that originated in Guinea, West Africa in 2013 lasted for over two years and claimed over 10,000 lives, spreading not only within Africa but to other continents as well, as health care workers working on the front lines traveled back to their home countries and then tested positive for infection. At the time, there was no approved vaccine for EBOV, and the use of convalescent plasma was one of the only effective treatments to combat the disease, but came with the risk of transmitting pathogens to plasma recipients including other strains of EBOV.

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Cap et al.(2016) evaluated the effectiveness of Mirasol PRT treatment of plasma and whole blood for inactivation of Ebola virus. The investigators reported that UV+ Riboflavin treatment reduced EBOV titers to non-detectable levels in both nonhuman primate serum (≥ 2.8- to ≥3.2-log reduction) and human whole blood (≥ 3.0-log reduction) without decreasing protective antibody titers in human plasma [108].

4.4. Hepatitis E

Initially believed to be transmitted orally, HEV is now understood to be transmitted by blood transfusion and can cause sever hepatitis disease. HEV is classified into four genotypes (G1-G4), with G3 the most widely distributed globally. In order to evaluate the ability of the Mirasol System to be used as one tool to prevent transfusion-transmission of HEV, Owada et al. (2014) reported that they used plasma and serum specimens collected and cultured from HEV RNA-positive patients to produce the JRC-HE3 strain for G3 and a UA1 strain for G4 [107]. These authors further observed that the Mirasol PRT system achieved > 3 log inactivation for the JRC-HE3 strain and > 2 log inactivation for the UA1 strain of HEV. They concluded that the Mirasol PRT system "inactivated greater than 2 to 3 logs of live HEV in PLTs and can potentially be used to lower the possibility of bloodborne HEV transmission".

5. Discussion

Over the last two decades, the world has experienced how changes in the environment, society and human behavior resulted in the emergence or re-emergence of infectious agents. Some of these pathogens were able to be transmitted by blood transfusion and represented an unknown risk at the time of their appearance. The standard safety measures in place, such as donor selection and donation screening, were not immediately effective in reducing the risk of transfusion. Moreover, a continuing strategy of additional screening and donor deferral for microbial safety is unlikely to be sustainable in the future and in some cases this approach has proven to be extremely costly, due to very low positive detection rate of regional infections [18,113]. Introducing new tests at a time when transfusion transmission is uncertain and unknown also has the potential to introduce costs into already financially strained services that later prove to be unwarranted and unnecessary.

Pathogen reduction technologies for labile blood components, especially for platelet concentrates, have been shown to decrease the risk of bacterial transmission in countries where these technologies have been nationally applied [114]. A milestone trial that investigated PRT capability to decrease malaria transmission by blood in a malaria-endemic country, showed a significant reduction (87%) of transmission events in the patient group that received Riboflavin + UV light treated whole blood [19].

Pathogen reduction technologies for labile components are in their first-generation release and cannot completely eliminate infectious risks, as seen by some transmission cases despite PI/PRT treatment [106]. Pathogen reduction performance varies due to physical/structural/genetic composition of the pathogen. Some technologies are unable to inactivate non-enveloped viruses while some are more effective against these agents [106,115,116]. Nevertheless, the treatment adds a new layer of safety that might contribute to close the window period of detection of tested viruses like HIV, HBV and HCV and reduce transmission risk as compared to untreated components [117,118].

Unquestionably the success of this blood transfusion intervention will depend on the ability of manufacturers to develop the technologies further to treat whole blood for componentization. The proof of this concept has been delivered in a pilot study in Russia, where pediatric patients have been transfused with red cell concentrates produced by fractionation of Riboflavin + UV light treated whole blood, showing the performance of these components remained clinically acceptable [21]. Moreover, two patients in this group also received plasma and platelet concentrates also treated with the same PR technology, showing after each transfusion the positive therapeutic effect of these interventions [24]. This is the first documented case of universal component pathogen reduction being employed in a clinical setting.

As changes in climate, transportation and social dynamics continue to drive emergence of new diseases into human populations, so must innovation and technology advances drive our ability to respond to and address infectious disease threats. The interdependence of blood safety and availability with general human population health is based on the fact that transfusion products are derived from human donors. Their susceptibility to emerging disease threats which may alter the integrity of those products and pose a risk for transfusion recipients will continue to be a factor driving blood availability for patients who require transfusion support. New methods designed to reduce or eliminate infectivity in blood products through proactive pathogen reduction methods have been developed and are being implemented globally for blood components including plasma, platelets, red cells and whole blood. The ability of these processes to address emerging disease threats has been tested in real time as these agents are emerging and even before the full threat of transfusion transmission is known. Given the likelihood that diseases will continue to emerge, investment in the exploration of new ways to implement these methods in logistically practical and cost-effective ways for all components of blood seems both prudent and warranted.

Author Contributions: Conceptualization, MC, IR, LH, RG.; methodology, MC, IR, LH, RG.; formal analysis, MC, IR, LH, RG.; investigation, MC,IR,LH, RG..; data curation, IR, LH.; writing—original draft preparation, MC,IR,LH,RG.; writing—review and editing, MC,IR,LH,RG.; visualization, MC, IR, LH; supervision, MC,RG; project administration, LH.; All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: All data utilized in this review was obtained from publicly available records and published data which are included in the reference section of the manuscript with citations.

Conflicts of Interest: MC is an employee of Terumo BCT, the manufacturer of the Mirasol PRT system. RG is the inventor of the Mirasol PRT system and has received speaker's fees from Terumo BCT. IR and LH have no conflicts to declare.

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