The American Red Cross
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Hepatitis E Virus (HEV) Infection in Blood Donors and Risk to Patients in the United States and Canada

HEV is one of the most common causes of acute hepatitis worldwide. The virus is most prevalent in developing countries and is primarily transmitted through consumption of undercooked meat and contact with fecal-contaminated water. To date the United States doesn’t routinely test blood donations for HEV.

This non-enveloped RNA virus has four unique genotypes comprising a single serotype including two responsible for food- and water-borne epidemic outbreaks in developing countries (genotypes 1/2) and two (genotypes 3/4) responsible for food-borne infections and all transfusion transmissions. To date, over 30 transfusion-transmissions have been reported, most from Japan, England and France. Those at risk for severe clinical outcomes (chronic HEV-infection, liver failure and death) are those who are immunosuppressed including solid-organ transplant and stem-cell transplant recipients. The transfusion-transmission rate from an infected donor (HEV-RNA-positive) to a recipient was 42% in England with immunosuppression delaying or preventing seroconversion and viral clearance.

HEV-RNA in blood donors was reported as high as 1:600 to 1:800 donations in Germany and The Netherlands; and antibody positivity, documenting prior exposure, as high as 52% in Southwestern France. HEV-RNA testing is the only effective mitigation to prevent transfusion-transmission. Risk factor questioning is not effective, since most donors are considered at risk due to dietary factors (ingestion of undercooked pork and game), and HEV is resistant to pathogen inactivation.

In response to high donation frequencies and transfusion transmission, several countries including the United Kingdom, Ireland, The Netherlands, and Japan have

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implemented HEV-NAT either universally or initially for patient subsets deemed at higher risk; other European countries are in the process of implementing (Austria, Germany and Switzerland). HEV-NAT is performed on each donation or in small pools (24-96) using NAT assays approved by the European Union. However, because HEV transmission is more common through food sources, the efficacy of blood donor screening alone may be limited.

In the United States and Canada, small studies have shown low HEV-RNA frequencies and no transfusion transmissions. Thus, a larger study was undertaken testing over 100,000 donations by individual-donation HEV-NAT in the US (American Red Cross) and Canada (Héma-Québec and Canadian Blood Services) using the Roche HEV Assay on the Cobas 8800 platform performed at the American Red Cross Scientific Support Office. The assay has a 95% lower detection limit of 18.6 International Units (IU)/mL.

A risk-based decision-making (RBDM) framework was used to evaluate the quantitative risks and cost-benefit of HEV-blood donation screening in Canada that would also apply to the US. The RBDM compared three scenarios: no screening, screening blood for all transfused patients or screening blood for only those at greatest risk (i.e., selective screening).

The positive HEV-RNA rate in the US was 1:16,908 (95% confidence interval [CI], 1:5786-1:81,987), whereas Canadian HEV-RNA prevalence was 1:4615 (95% CI, 1:2579-1:9244). Although 4-fold greater, the Canadian HEV-RNA rate was not significantly higher than in the US. Viral loads for the 11 positive donations ranged from 20 to 3080 IU/mL; all successfully typed infections were genotype 3. These viral loads are considered low and below the assumed minimum infectious dose of 10,000 IU (dose dependent on viral load and component volume).

No HEV-RNA false-positive donations were identified for 100% specificity. The median estimated transfusion-transmitted-HEV infection risk predicted to lead to severe liver disease ranged from 1:47 million for pooled buffy coat platelets to 1:6 million for plasma.

Without donation screening, heart and lung transplant recipients had the greatest HEV-infection risk (1:366,962) versus kidney transplant recipients with the lowest (1:2.8 million) at calculated costs of $225,546 to $561,810 per quality-adjusted life-year (QALY) gained for partial (selective) or universal screening, respectively. Higher costs per QALY would be expected in the US because of lower HEV-RNA positivity. Thus, the rate of HEV positivity in North America is lower than in countries performing routine blood donation screening with screening costly under any scenario.

For additional information, please contact Susan Stramer at susan.stramer@redcross.org or refer to the published paper in Transfusion Medicine Reviews (June 20, 2019) https://doi.org/10.1016/j.tmrv.2019.05.017

Susan L. Stramer, PhD is currently the Vice President of Scientific Affairs in Biomedical Services at the American Red Cross where she has been for the past 24 years. Her primary interests are infectious diseases of blood, their epidemiology and interventions. She has authored over 150 peer-reviewed papers and received numerous awards including those from the Red Cross, the AABB, the Centers for Disease Control and Prevention, and the National Institutes of Health. She is a past president of the AABB and currently she is the immediate past chair of the Transfusion Transmitted Diseases Committee of the AABB.
Many of us are familiar with the applications of drones (also known as unmanned aerial vehicles or remotely piloted aircraft) for photography in the service of the military, media, geographic mapping, and personal entertainment. Now these flying robots are being put to a new use: providing life-saving blood and other medical supplies in remote areas and/or where conventional delivery methods pose a challenge.

The use of drones was first conceived in World War I as a remote-controlled airplane, but it would be several more decades before advancement in technology allowed for military implementation of this device. It was during the Vietnam Conflict, that these unmanned vehicles were exploited for surveillance purposes as well as outfitted to perform rescue operations. The first reported case of such an event was the use of a QH-50 Drone Anti-Submarine Helicopter programmed to airlift a stranded combat marine, who grabbed the skids of the aircraft to be carried off to safety. In more recent years we have seen drones pressed into service during humanitarian disasters including

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Hurricane Katrina in 2005 and the 2010 Haiti earthquake, for both of which medical supplies were delivered and for reconnaissance of inaccessible areas to assess the extent of damage and locate signs of human life.

Since then several international companies have become involved in the development of drones for the distribution of medical supplies, including blood. Zipline, an American based company, is at the industrial forefront having already implemented use of drones in Rwanda for more than three years. This country served as the test site due to its challenging geography, which is mountainous with an inadequate transportation infrastructure. The company has provided more than 7,000 units of blood on over 4,000 flights, representing more than 20% of the blood provided outside Kigali, the country’s capital. It is of interest to note that payload of these drones has been increasing: currently Zipline’s drones can carry almost four pounds, equivalent to 3 units of red cells. The drones carry their packages within a 80 km radius travel distance (160 km round trip) and do so without stopping—simply releasing its payload at its destination before returning to home base. In this manner blood has been able to be transported to awaiting medical facilities within 30 minutes rather than the hours to days of normal travel.

America’s regulations regarding drones for medical use are restrictive. However, the US Department of Transportation and Federal Aviation Administration (FAA) have taken steps to develop rules, with the establishment of the Unmanned Aircraft System Integration Program (UAS) in 2017. In the year prior, the Australian-founded Flirtey drone service partnered with John Hopkins School of Medicine and the FAA to test the transportation of medical supplies to Cape May, New Jersey, as well as a vessel off the coast of New Jersey. In 2019, the FAA certified United Parcel Service to deliver health care supplies by drone.

These early results are encouraging and the use of these pilotless aircraft in the US to deliver blood and other medications is only expected to grow.

Ling G and Draghic N Aerial drones for blood delivery Transfusion. 2019; 59:1608-11
Jackson T and Hance D Fortune. 2019; https://fortune.com/2019/01/07
Effectively remove the risk of transfusable infectious diseases with pathogen-reduced platelets (PR PLT). PR PLT are produced with safe, effective technology to diminish the impact of life-threatening agents.

Pathogen-Reduced Platelets: Patient Safety Comes First

Bacteria | Viruses | Fungi | and more

Get further information at Success.redcross.org or contact your American Red Cross hospital account representative.
Despite numerous advances in preventive and diagnostic methods in reducing the risk of sepsis resulting from transfusion of contaminated platelets the potential danger to patients persists. In September 2019 the Food and Drug Administration (FDA) issued final Guidance outlining measures that blood collectors and transfusion services should take to further enhance the safety of the platelet supply.

There are three main approaches, particularly pertaining to apheresis platelet units: Pathogen Reduced Platelets (1); Large Volume, Delayed Sampling (LVDS) at two time intervals (2a and 2b) and Two-Step strategies combining different mitigation methodologies (3). The table below summarizes the main points for each strategy.

Red Cross believes that pathogen-reduced platelets are the most effective way to ensure the safety of the platelet supply and is committed to increasing the availability of this product for the hospitals and patients we serve. To learn more about the Guidance and its implementation please visit our educational portal success.redcross.org and search ‘FDA’.

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**Mitigation Strategy**

### For Consideration

<table>
<thead>
<tr>
<th>Mitigation Strategy</th>
<th>For Consideration</th>
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<tbody>
<tr>
<td><strong>1. Pathogen Reduced Platelets</strong></td>
<td>• Currently restricted to apheresis platelets</td>
</tr>
<tr>
<td>5 Days Storage</td>
<td>• Protection beyond bacteria with mitigation of multiple pathogens including viruses (e.g., CMV and Zika).</td>
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<tr>
<td></td>
<td>• No additional testing needed</td>
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<tr>
<td><strong>2a. LVDS no sooner than 36 hrs</strong></td>
<td>• Extra security and confidence with assurance that lag time for slow-growing bacteria is addressed</td>
</tr>
<tr>
<td>5 Days Storage</td>
<td>• Refer to ‘Mitigation Strategy 3(1b) – LVDS ≥ than 36 hours’ can be used to extend product shelf life to 7 days</td>
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<td></td>
<td>• Due to required hold of an additional 12 hours prior to release product shelf life</td>
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<tr>
<td></td>
<td>• Sampling ≥ 16 ml, for aerobic and anaerobic culture testing, from each split product may reduce final product volume and shelf life may be shortened</td>
</tr>
<tr>
<td><strong>2b. LVDS no sooner than 48 hrs</strong></td>
<td>• Currently restricted to apheresis platelets</td>
</tr>
<tr>
<td>5 to 7 Days Storage</td>
<td>• Extra security and confidence with assurance that lag time for slow-growing bacteria is addressed</td>
</tr>
<tr>
<td></td>
<td>• Sampling ≥ 16 ml, for aerobic and anaerobic culture testing, from each split product may reduce final product volume</td>
</tr>
<tr>
<td></td>
<td>• Due to required hold of an additional 12 hours prior to release product shelf life may be shortened</td>
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<tr>
<td></td>
<td>• FDA approval for 7 days storage pending</td>
</tr>
<tr>
<td><strong>3. Two-Step strategies</strong></td>
<td>• Bacteria might have a lag time for growth; checking again at point of transfusion should add an extra measure of safety</td>
</tr>
<tr>
<td><strong>STEP 1</strong></td>
<td>• Performance of secondary culture or rapid testing (e.g., Verax testing) adds additional labor, cost to the transfusion service, and reduces final product volume</td>
</tr>
<tr>
<td><strong>a) Primary culture ≥ 24 hours</strong></td>
<td>• Duration of secondary culture has not been standardized, but a minimum of 12 hours is recommended.</td>
</tr>
<tr>
<td><strong>b) LVDS ≥ than 36 hours</strong></td>
<td>• Due to required hold of ≥ 12 hours prior to release, usable shelf life may be shortened</td>
</tr>
<tr>
<td><strong>STEP 2</strong></td>
<td>• Requires local SOP development to meet minimum incubation period and process to control products during secondary testing phase</td>
</tr>
<tr>
<td><strong>a) Secondary aerobic testing (8 ml) ≥ day 3</strong></td>
<td>• Mitigation Strategy 3(1b) – LVDS ≥ than 36 hours can be used to extend product shelf life for 7 days</td>
</tr>
<tr>
<td><strong>5 days storage OR</strong></td>
<td>• Mitigation Strategy 3(2b) – secondary testing on day 4 applies only to apheresis platelets</td>
</tr>
<tr>
<td><strong>b) Secondary aerobic + anaerobic testing (16ml) ≥ day 4</strong></td>
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<tr>
<td>7 days storage OR</td>
<td></td>
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<tr>
<td><strong>c) Secondary rapid testing (e.g., the Verax®)</strong></td>
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<tr>
<td>5 – 7 days storage</td>
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Citrate has been the anticoagulant of choice during the collection and storage of blood components since 1914 because of its ability to bind calcium ions, which can cause the blood to clot, and because of its clinical safety profile. However, there remains a question, as it relates to apheresis platelets, whether citrate is required or even beneficial for platelet storage after most calcium ions have been chelated during the collection phase. Recent studies have even demonstrated that blood cell lines undergo cell death following 16-72 hours incubation with 5-10 mM citrate.\textsuperscript{1-3}

With the aim to determine whether platelet storage could be improved by the removal of citrate from platelet additive solution, Dr. Getz and coworkers from the American Red Cross Holland Laboratory Transfusion Innovation Department followed several storage properties of platelets suspended in 35% plasma and 65% modified Platelet Additive Solution-3 [PAS-3] which contains 10 mM of citrate. The study evaluated platelets aliquots that were stored in PAS-3 modified to have varying citrate levels, 0–10 mM, for 7 days of platelet storage.

Results demonstrated changes in platelet quality parameters that were directly related to citrate dose. Higher citrate exposure led to increased levels of platelet activation as shown by greater energy consumption, glycolysis; increased release of reactive oxygen species; and increased detection of a protein marker of platelet activation, p-selectin, on Day 5 of storage. In addition,
platelets were more likely to show changes associated with cell death, as shown by higher levels of another intracellular protein called annexin V, by Days 5 and 7 of storage.

A second study compared platelets units suspended in 35% plasma/65% PAS-3 with those suspended in 35% plasma/65% PAS-3 lacking citrate (called Fixsol). Results confirmed those observed in the first, aliquot, platelet study, with the Fixsol platelets not as readily activated during storage and yet retaining greater levels of functionality, as shown by increased aggregation response to collagen, TRAP6, or a combination of collagen + ADP than those of platelets suspended in PAS-3.

These results were replicated with another solution, Tyrodes buffer, which also lacks citrate, to replace plasma as the platelet suspension media. In contrast to plasma-based platelets, those in Tyrodes demonstrated greater levels of aggregation when exposed to collagen, TRAP6 or collagen + ADP than platelets.

If 65% of the Tyrodes media was replaced with Fixsol a similar enhanced aggregation response was observed when compared to platelets stored in 35% plasma/65% PAS-3 solutions. This would again suggest a potential to improve platelet function during in vivo storage with unenhanced citrated plasma

Unlike apheresis platelets suspended in plasma, current platelet additive solutions are licensed for only 5 days of storage because platelets stored in PAS containing citrate fail to meet regulatory requirements following 7-day storage. Optimization of additive solution may enable 7-day platelet storage and may improve the storage characteristics and function of pathogen reduced platelets as well.


Dr. Wagner received his Ph.D. in BioPhysics from Penn State University and has been a researcher with the American Red Cross over 30 years in the Department of Transfusion Innovation. He has over 125 publications and 8 patents in the areas of pathogen reduction, bacterial growth and detection in platelets, and platelet preparation and storage. Dr Wagner has received two American Red Cross Presidential awards for technical and managerial excellence; he is a coauthor of a National Academy of Sciences report on alternatives to CsCl irradiators, including the use of x-ray devices for blood irradiation. Dr. Wagner is on the editorial boards of Transfusion, Transfusion Medical Reviews and Transfusion and Apheresis Science and is an internationally recognized scientist.
A Question for Treatment of the Smallest of Patients: “Do I hear an ECMO round here?”

Few things are more distressing to families than watching their child struggle to breathe. In settings in which the heart or lung function are compromised, a patient can rely on the life-saving machine called Extracorporeal Membrane Oxygenation (ECMO) to provide supportive treatment.

This device draws blood from the patient, removes the carbon dioxide, oxygenates it, and then returns the blood in a continuous circuitous process. In this way the device replaces the function of the patient’s heart and lung. ECMO cannot cure the underlying condition but can give enough time, hours to weeks, for the medical team to treat the disease, repair the injury, and/or find a transplant. But is it a front-line treatment for pediatric respiratory failure?

ECMO has been around since the 1960s and continues to evolve. Successful ECMO treatments were initially demonstrated in neonates and, dependent on the cause for the respiratory failure, use of the device improved survival rates by as much as 67–91.1%. In contrast, the data from studies performed with older pediatric patients are primarily based on observations and find that mortality rates were either comparable or worse than for non-ECMO patients.

The most common condition that ECMO is used to treat in the pediatric patient is Acute Respiratory Distress Syndrome (ARDS), which occurs when the lungs fail to oxygenate due to the airways becoming obstructed by fluid, usually from infection or trauma. Pediatric ARDS account for as much as 4% of ICU admissions; with a mortality rate of up to 35%. Reports of ECMO being successful, but only in observational studies, include children awaiting a liver transplant, severe asthmatic events, trauma, diffuse alveolar hemorrhage, and even poisoning that directly damaged the airways.

A review article by John Lin and published in the journal Respiratory Care outlines those factors that would define the pediatric patient population most suitable for ECMO support. Not surprisingly, fatality is notably higher, when presented with one or more of the following: immunocompromised state, severity of alveolar involvement, multiple organ dysfunction syndrome, or whose dependence on mechanical ventilation exceeds more than 14 days.

Moving forward with ECMO requires consideration of the patient’s probability of survival to the underlying disease as well as the potential complications of the use of ECMO which include (1) mechanical induced hemolysis; (2) bleeding; (2) infection; and (4) non-pulmonary organ dysfunction, such as renal failure and neurologic impairment. Other factors for consideration and which have been observed to guide improved outcomes are the use of ambulatory ECMO to preserve physical conditioning, and a shorter, < 2 weeks, duration of ECMO use.

For the time being the decision to proceed or not with ECMO rests upon a discussion among the family and the medical caregivers who can provide this potentially life-saving treatment. For more about ECMO the reader is invited to explore the online self-paced learning course on this topic at www.success.redcross.org


Platelets are tiny cellular fragments whose functional role is to maintain integrity of the blood vessel walls through formation of clots at sites of injury. In certain situations, the patient’s platelet count may not increase as expected in response to the platelet transfusion. If the increment is less than expected after two to three consecutive transfusions, the patient is suspected of having a condition known as platelet refractoriness.

Approximately 80% of platelet refractory cases are due to underlying clinical conditions including on-going active bleed, fever, infection, disseminated intravascular coagulation (DIC), splenomegaly, and/or a side-effect to any of many medications (e.g., Penicillin, Rituximab, and Heparin). The remaining 20% of cases are associated with immune-mediated causes with the patient developing alloantibodies after contact with antigens on the surface of donor-sourced platelets: primarily the Human Leukocyte Antigens (HLA), namely Class I and, less common, the Human Platelet Antigens (HPA). These antigenic exposures are generally from prior blood product transfusion, pregnancy, and/or transplantation.

A common method for determining whether the transfusion is effective is to calculate the Corrected Count Increment (CCI): post- minus pre-transfusion platelet count divided by the number of platelets, multiplied by the body surface area. Patients with platelet refractoriness due to immune cause will show repeated low CCIs: (1) one-hour post transfusion, the platelet counts will be less than 5,000/microliter; and (2) 24 hours post transfusion, the platelet counts will be less than 2,500/microliter.

Two possible strategies to manage platelet refractory patients due to HLA alloimmunization are to (1) find donors whose HLA phenotype matches that of the patient; or (2) through the performance of serologic platelet cross-matching (testing the patient’s plasma to donor platelets for alloimmunization reactivity). Both of these approaches require time for testing as well as a sufficient number of blood donors to test. Also, it is important to consider the time required to schedule and collect from donors who are a match.

When there is an immediate need, it may be preferable to use either a pooled platelet derived from 4 - 6 whole blood donations, or a random apheresis platelet unit from a single donor. The decision as to which is the preferable product remains controversial. Many clinicians believe that using the pooled platelet would mean a chance that one of the donors in the pool will be a match. Others consider it a risk for further alloimmunization due to exposure to several donors at once and would instead find the use of the randomly selected apheresis platelet preferable.

A recent retrospective study from the journal Transfusion evaluated the responses of 94 platelet refractory patients after receiving one of three different type of products: pooled platelets vs randomly selected apheresis platelet units vs HLA matched apheresis platelets. The results indicated that HLA matched platelets, serving as a control indicator, were superior to either pooled or random apheresis platelets. The latter two did not have any statistically significant difference in terms of CCI response post-transfusion. Unfortunately, hemorrhagic control was not assessed by the investigators of the study and therefore clinical effectiveness among the tested products could not be determined, with further studies needed. The authors conclude that based on their data, randomly selected apheresis platelets and pooled platelets can be considered equivalent, pending the results of further research.


March serves as the official month for the American Red Cross to support and fundraise for the non-profit organization’s humanitarian objectives. The celebration commences with the current President of the United States of America issuing a proclamation to the citizens of our country. In the statement, the President asks all to recognize and honor the dedication of American Red Cross employees and volunteers who contribute to the organization’s mission to make a positive and life-saving impact on people’s lives through five lines of service.

- Disaster Services: shelter, feed, and provide emotion support to victims of disasters
- Biomedical Services: provide ~40% of the nation’s blood supply
- Training Services: teach skills that save lives including swimming and CPR
- International Services: worldwide emergency health service and disaster response
- Services to the Armed Forces: humanitarian support to military members and families

This tradition began in 1943, during World War II, when President Franklin D. Roosevelt set out to raise awareness of the American Red Cross relief efforts as well as support for the Red Cross War Fund. During the war, the organization not only served as a chief distributor of international relief supplies to affected civilian victims, but also established a blood donor service, providing further aid to the wounded. This was performed to fulfill the duties mandated by the U.S. government’s 1905 congressional charter.

Red Cross Month serves to highlight the ongoing need for support of the American Red Cross, by asking the people across the country to consider giving blood, becoming a volunteer, or to make a financial donation.

Publications Corner

Recent publications by American Red Cross scientists and physicians:


**Therapeutic plasma exchange for neuromyelitis optica spectrum disorder:** A multicenter retrospective study by the ASFA neurologic diseases subcommittee.


**Bacterial safety of extended room temperature storage of thawed cryoprecipitate.** Wagner SJ, Hapip CA, Abel L. . 2019 Nov;59(11):3549-3550

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Remember these websites:

*Immunohematology Journal*
RedCrossBlood.org/biomedical-services/educational-resources/immunohematology

*Reimbursement*
RedCrossBlood.org/hospitals/educational-resources/reimbursement

SUCCESS®
success.redcross.org