BloodNet

The Pediatric Critical Care Blood Research Network

BloodNet Newsletter – Fall 2020

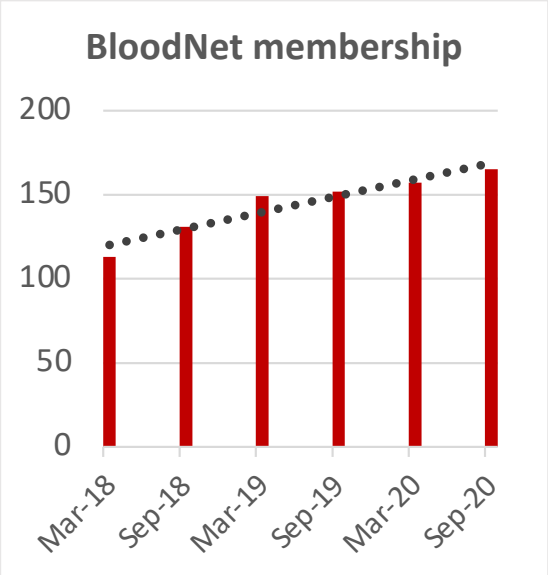
Key Numbers

165 members from **81** sites in **10** countries

37 publications in 2020, of which **3** with BloodNet as a co-author

3 manuscripts and **4** grants reviewed in the last six months

425 Twitter followers



Note from the Chair

What a year!!! I can't believe our last BloodNet meeting, in March of 2020, was the last time I talked to someone without a mask… The world around us has changed dramatically, probably not for the best. But there are some silver linings.

Six months into this, BloodNet's online-only fall meeting got twice as many attendees as any other BloodNet meeting! There were up to 64 attendees for our three-hour meeting. I am so grateful to all the presenters who made this possible! And although we all miss the in-person interactions, the chat option and live-discussions at the end of each presentation were precise, pertinent, pragmatic, and encouraging.

Finally, this was my last meeting as BloodNet's chair. These last three years were an incredible adventure. Building on to the foundations Phil Spinella had laid, BloodNet has continued to grow to a mature international research network with bylaws, elections, and a mentoring program (more details on page 5).

I am looking forward to the next three years; Jenn is a fantastic leader!

O. Karam

Oliver Karam, MD, PhD
Children's Hospital of Richmond

Pro-thrombotic Extracellular Vesicles Generated by Extracorporeal Blood Pumps

Cardiogenic shock following cardiopulmonary bypass surgery (CPB) is the most common cause of death in children with congenital heart disease (CHD). However, transient support with extracorporeal mechanical oxygenation (ECMO)is often limited because of frequent bleeding and thrombotic complications. Platelet transfusions and reduction of systemic heparinization have been shown to reduce ECMO-related bleeding. Nonetheless, current anticoagulant strategies using heparin, direct thrombin inhibitors, or surface coatings do not completely prevent ECMO-related thrombotic complications. ECMO thrombosis develops from exposure to its components, an artificial lung (i.e., oxygenator) and a mechanical pump that regulates blood flow activating circulating cells. Over 34% of patients supported on ECMO require an emergent exchange of an ECMO part due to thrombosis. Activated monocytes and platelets have been shown to promote ECMO thrombosis under controlled static and flow conditions. However, potentially increased prothrombotic biomarkers derived from other pro-thrombotic leukocyte populations (e.g., neutrophils and monocytes) associated with cardiac ECMO-related thrombosis are less well-studied.

Prolonged extracorporeal circulation is known to induce leukocytes to express tissue factor (TF), a potent initiator of thrombin generation. Our in vitro studies with human blood confirm and extend that increasing TF expression on leukocytes lead to thrombotic occlusion of an ECMO oxygenator. Additionally, circuit thrombosis was associated with increased generation of TF expression on leukocyte-derived extracellular vesicles (EVs), which are micron-sized membrane vesicles that can amplify initiation of thrombosis. As a biomarker, EVs have the advantage of being detectable in frozen plasma samples allowing multiple site studies. Studies with adults supported with a left ventricular device (LVAD) report that elevated pro-thrombotic EVs are strongly associated with an increase in thrombotic events. However, there are no pediatric studies on the association of generation of leukocyte EVs (LEVs)with thromboembolic events in post-operative congenital heart surgery patients or children supported with cardiac ECMO.

Our hypothesis is that length of time on CPB or ECMO increases the generation of TF-expressing LEVs that promote thrombin generation which can be identified in blood samples from children with congenital heart disease. Our proposed project will address this hypothesis with two specific aims (1) Define the increase in thrombin generation from LEVs in blood samples during and after pediatric CPB surgery. Hypothesis: CPB time greater than 60 minutes significantly increases pro-thrombotic LEVs and significantly elevates thrombin generation compared to under 60 minutes. (2) Define the thrombotic potential of LEVs in blood samples from children on ECMO support for cardiac failure. Hypothesis: Duration on ECMO increases pro-thrombotic LEVs increasing thrombin generation in plasma samples from children on cardiac ECMO support.

The purpose of this study is to develop a sensitive and specific biomarker that can be stored for later analysis that predicts leukocyte-derived thrombotic complications during extracorporeal support. Marie Steiner, MD, MS, and Andrew Meyer, MD, MS are looking for collaborators in submitting multi-center grants to collect plasma samples from post-cardiac surgery patients to define their effect on thrombin generation and clot formation. The research is significant because few if any biomarkers can predict thrombotic complications in children after CPB surgery or during ECMO support for cardiac failure. The studies are innovative because EVs are a novel biomarker for extracorporeal pump activation of leukocytes. Moreover, identification that leukocyte generation of EVs leads to coagulation complications will help develop therapies to prevent activation of leukocytes to generate EVs. Discoveries in this proposal will then lead to new clinical interventions that can safely reduce thrombosis associated with cardiopulmonary life support devices.

Andrew Meyer and Marie Steiner

Pediatric Convalescent Plasma Registry

The pediatric convalescent plasma registry is a multi-institutional project intended to characterize the pediatric population (<18 years of age) who received Covid-19 convalescent plasma (CCP) transfusions. It will be hosted by Children's National Hospital (CNH) using the REDCap secure software system. International centers are welcome to participate.

This retrospective and prospective data study will collect de-identified data from January 2020 (first reports of Covid-19 in the United States) up to May 2024 (after vaccine availability when convalescent plasma is no longer expected to be widely used). This end date may change depending on pandemic resolution. Any pediatric patient who received CCP, whether therapeutic, prophylactic, under compassionate use or as part of a clinical study, is eligible to be entered. Inclusion in the registry will not impact eligibility for other studies. Collected data include demographics, pre-existing conditions, Covid-19 symptoms, laboratory testing, CCP transfusion metrics, and outcomes. All data submitted will be anonymized so that patients cannot be identified from the study data set. The institutional review board at CNH has approved the registry as an exempt study.

Each participating site can have up to two co-investigators, who will be the main contact persons and future co-authors on manuscripts. Each site will have access to their data in the registry. If a site investigator wishes to use other sites' data, each site will have the option of including up to two authors on future manuscripts. At least one publication will include all entries to characterize the pediatric patient population who received CCP.

Please contact me if you are interested.

Cyril Jacquot
cjacquot@childrensnational.org

Dynamic platelets transfusion thresholds in pediatric ECMO

Patients with ECMO support have a significant risk of bleeding, for various reasons. In addition to coagulopathy, heparin use and SIRS, thrombocytopenia is extremely common in ECMO treated pediatric patients. Hence, most centers adhere to the AABB and ELSO guidelines that recommend platelet transfusion when count<100,000 cells/mm3. These guidelines' recommendations are based on centers' experience and not evidence-based medicine. Since the establishment of our ECMO program in 1999 we have used a dynamic approach to platelets transfusion threshold. The threshold is decreased gradually every day from 100,000 cells/mm3 to ~20,000 cells/mm3 in a nonbleeding patient.

To examine our platelets transfusion practice and hemorrhagic complications, we reviewed the charts of all consecutive patients supported by ECMO in our unit between 05/2010 to 05/2020. In order to capture as many hemorrhagic events as possible, we used a very broad definition of a major bleeding event.

Charts of 229 patients were reviewed. Median age at cannulation was 20.9 days with a median weight of 3.7 Kg. 54.% were males. The median ECMO run duration was 6.8 days. ECMO indications were cardiac (49.8%), respiratory (42.8%) or other (7.4%). 17.5% were cannulated during active CPR (ECPR). Survival rate to ICU discharge was 60.3%

Our median platelets count was 50,000-70,000 cells/mm3 during the 1st 15 days of the ECMO run with a minimal count of 4,000-15,000 cells/mm3. 58.1% of the patients had their lowest count below 30,000 and 97.4% below 100,000 cells/mm3. Platelets were transfused on 28.5% of the ECMO days with a median daily and total platelets transfusion dose of 8.7 cc/Kg/day and 70 cc/Kg/ECMO run, all lower than previously published. The fraction of bleeding days and the proportion of bleeding patients were similar or lower to the published literature.

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Dynamic platelets transfusion thresholds in pediatric ECMO (cont'd)

Our bleeding complications (chest drain, surgical site, cannulation site, intracranial, gastrointestinal, and pulmonary bleeding) within the range of previously published ELSO data and single centers experience.

In conclusion, we practice a patient-tailored, restrictive-dynamic approach to platelets transfusion in pediatric ECMO, resulting in less platelets transfusion with no additional blood transfusion or excess bleeding complications.

Ofer Schiller

BloodNet Elections

As Oliver Karam (chair) and Phil Spinella (past-chair) three-year mandates will end on December 31, 2020, new elections were organized over the summer.

We are pleased to announce that Jenn Muszynski was appointed chair. She will lead BloodNet as of January 1, 2021.

Marianne Nellis was elected Vice-Chair. As such, she will also be responsible of the Scientific Committee.

Ken Remy has just been elected to the Executive Committee.

BloodNet Mentoring Program

Purpose: Create Mentor and Mentee relationships to promote clinical and research interest in pediatric transfusion medicine, hemostasis, thrombosis and blood management

Elements of Mentoring Relationship:

-Determine expectations and goals together between mentor and mentee

- Communication can be in person, online, over the phone
- Meet regularly-frequency to be set by Mentor/Mentee

-Research

- Provide constructive feedback on mentees goals
- Discuss research ideas, project design
- Review manuscripts, research projects, grant applications
- Explore funding mechanisms

-Career Planning and Development

- Promotion, Long-term planning
- Sustainability, Work-Life Integration, Burnout Avoidance, Resilience
- Increase the diversity and inclusiveness of the field
- Exploring networking opportunities

Mentees: Fellows and Junior Faculty Interested in Pediatric transfusion medicine, hemostasis, thrombosis or blood management

- Interested mentees will complete a survey of needs and interests
- They will be matched with 2-3 potential mentors
- Introduction email to the mentor/mentees to facilitate the 'match'
- The mentees are free to choose the most appropriate fit
- Interested? Send your contact info to: BloodNetResearch [at] gmail.com

Mentors: BloodNet Members

- All BloodNet Members will receive a link to a mentor survey
- If interested, they will be matched with a potential mentee
- Introductory email will be sent to mentee/mentor pair to facilitate the 'match'

Mentor Survey: Watch for it in your email soon!

- Name, institution, position (level and field), email
- Areas of Mentoring interest: check all that you would be willing and able to participate in
- Feedback on goals
- Discuss and give feedback on research ideas
- Discuss and give feedback on project design
- Review manuscripts
- Review grant applications
- Explore funding mechanisms
- Provide guidance on promotion and long term career planning
- Discuss techniques to improve resilience, work-life integration
- Explore networking and opportunities to increase exposure in the field
- Increasing diversity and inclusion in the field
- Preferred communication frequency (weekly, monthly, quarterly, flexible)

-Research interest (Transfusion Medicine, Hemostasis, Thrombosis, ECMO, Blood Management, Immune Response

We are excited to expand our BloodNet experience of openness, partnership and collaboration to include a Mentoring Program. Share this opportunity to any interested fellows or junior faculty. And please sign up to mentor if you are interested- we all have something to teach others. Guiding others to avoid the pitfalls of learning is rewarding!

Sheila Hanson, on behalf of the Executive Committee

Prospective RCT comparing unfractionated heparin to bivalirudin for pediatric ECMO patients

Anticoagulation continues to be necessary for ECMO to prevent circuit clotting. Unfractionated heparin (UFH) remains the standard of care anticoagulant but has several clinically important complications and limitations including heparin-induced thrombocytopenia, heparin resistance, and difficulty in laboratory monitoring. In addition, UFH requires antithrombin to achieve its maximum therapeutic effect. Bivalirudin is a direct thrombin inhibitor with several potential advantages over UFH including a short half-life and thrombin inhibition that does not require antithrombin. There are no large prospective clinical trials that examine the safety and efficacy of UFH versus bivalirudin for pediatric ECMO anticoagulation.

We propose a multicenter randomized clinical trial comparing UFH to bivalirudin for neonatal and pediatric ECMO patients. To inform the trial, a pilot study of 30 neonatal and pediatric patients randomized to either UFH or bivalirudin is currently enrolling at Children's Health, Dallas. Preliminary analysis of the first 18 patients in the pilot study has been encouraging with patients in the bivalirudin arm receiving less red blood cell and platelet transfusions compared to patients receiving UFH.

We estimate that we will need at least 10 pediatric US ECMO centers to enroll 326 patients over a two-year period. One of the key challenges for the trial will be creating consensus and standardization of all sites including UFH titration, anticoagulation laboratory monitoring, and transfusion guidelines. The next step for the trial will focus on site recruitment and protocol development and consensus. If you are interested in joining the trial, please contact Ali McMichael (ali.mcmichael@utsouthwestern.edu).

Ali McMichael

Point-prevalence study of neonatal transfusions

Background: Every year, approximately 66,000 very premature babies in Europe receive one or more blood transfusions. Despite the high frequency of transfusions in this population, the evidence for the efficacy and safety of these transfusions is limited, as only a few high quality randomized trials have been performed to date. Importantly, some of these trials have shown that neonatal transfusions are often redundant and can be even harmful. The few neonatal transfusion guidelines emphasize that many areas of neonatal transfusion practice are not substantiated by robust high -quality data. Our group has recently initiated a first pan-European survey of neonatal transfusion practices to investigate this variation in Europe. As a next step, high quality, patient-level multinational epidemiologic data are needed to support quality improvement projects, inform national and international guidelines and implementation projects, and to design new studies with the ultimate goal of improving neonatal outcomes through optimizing neonatal transfusion practices. We therefore aim to perform a pan-European prospective neonatal transfusion point prevalence study.

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Point-prevalence study of neonatal transfusions (cont'd)

Design: This will be a prospective, observational, international, pan-European point prevalence study in tertiary level NICUs. We will include neonates with a gestational age less than 32 weeks. Neonates with major congenital malformations, alloimmune hematologic disorders, twin-twin transfusion syndrome and twin anemia-polycythemia sequence not treated with fetoscopic laser surgery and neonates on Extracorporeal Membrane Oxygenation (ECMO) will be excluded. The primary outcome will be the point prevalence of RBC, platelet and plasma transfusions. Secondary outcomes are variation of prevalence, indications and appropriateness of use as defined by recommendations in guidelines and a description of component specification. Each participating center will prospectively record transfusion data, relevant laboratory parameters, data on adverse events, baseline characteristics, and general NICU characteristics for a period of 6 weeks. Based on the confidence interval for proportions using normal approximation, we calculated that a sample size of 520 will allow us to determine the point prevalence for these three common types of transfusions while taking into account potential loss to follow up. We will need to recruit 62 NICUs to obtain this sample size.

Potential Impact: This study will identify suboptimal practices that can be improved, and areas with substantial clinical variation which can be targeted in future clinical trials. This study has the potential of leading to the reduction of unnecessary transfusions through increased awareness of the proper use of transfusions in this vulnerable patient population, ultimately resulting in better neonatal outcomes, lower risk of adverse events, lower costs and better allocation of donor blood.

Suzanne Fustolo-Gunnink

Next meeting

March 2021: Online only
September 2021: New York City

Connect with us

Find us on the web:
www.bloodnetresearch.org

Connect on Twitter:
@BloodNet_PALISI

Or email us:
bloodnetresearch [at] gmail.com

BloodNet Leadership

Executive Committee

Oliver Karam, Chair
Jenn Muszynski, Vice-Chair
Philip C. Spinella, Past Chair
Nicole Zantek
Sheila Hanson
Jill Cholette
Marianne Nellis

Scientific Committee

Jenn Muszynski, Chair
Ken Remy
Kate Steffen
Arianne Willems
Alison Nair

Subgroup leadership

Kenneth Remy
Alison Nair

Incoming BloodNet Executive (starting January 2021)

Jenn Muszynski, Chair
Marianne Nellis, Vice-Chair
Oliver Karam, Past -Chair
Nicole Zantek
Sheila Hanson
Jill Cholette
Ken Remy