An update on the ORBCoN Standardized Pediatric Massive Hemorrhage Protocol

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In children, massive hemorrhage is a leading cause of preventable death in trauma and in the operating room, massive hemorrhage is the leading cause for cardiac arrest.[1-4] Six per 10,000 live births result in an emergency blood product request for a neonate experiencing massive hemorrhage in utero or during birth from placental abruption/placenta previa with a mortality rate of 35%.[5] Similar to adults, the in-hospital event rates of simple red blood cell (RBC) transfusions or larger volume RBC transfusions are, approximately 15 and 3%, respectively.[6,8] The care provided to children experiencing massive hemorrhage is highly variable in part due to limited access to evidence-based massive hemorrhage protocols (MHPs), particularly in community settings.[9] Care provided to children experiencing massive hemorrhage needs to be improved. In response, an ORBCoN sponsored Ontario-wide roll-out of a standardized massive hemorrhage protocol (MHP) and associated tool-kit for adults and children is planned for 2021. Pediatric MHPs have demonstrated improved system resource utilization such as, speed of blood product delivery to the bedside and decreased exposure to blood products in trauma settings. However, in contrast to adults, evidence for outcome benefits for children in both pediatric trauma and surgical settings remain elusive.[10-14]

The aim of this article, the first of a two-part series, is to briefly highlight key updates contained within the soon to be released ORBCoN-sponsored standardized pediatric MHP. The second article will address the "value proposition" to implement a pediatric MHP, particularly in a community setting. The reader is encouraged to read the associated MHP tool-kit document for management of children (≤ 12 years and < 40 kg) to gain an in-depth understanding of the background and references associated with these and other key recommendations.

Key pediatric MHP updates

A standardized province-wide pediatric MHP is the first step towards removing unwanted variation in care towards improving patient outcomes in all Ontario hospitals. Pediatric MHP best practices were determined by an ORBCoN-sponsored interdisciplinary working group (WG) and MHP Steering Committee from both Ontario community and tertiary care settings. Treatment guidance is based on pediatric observational data or extrapolated from the adult literature as prospective data availability is limited.[15] Key recommendations by the pediatric WG are as follows:

Re-define massive hemorrhage triggers for activation in children: The majority of MHP are activated at physician discretion based on various factors. The most-widely accepted evidence-based definition of massive hemorrhage (40 ml/kg of blood products administered over 24 hours),[16] has been replaced with an anticipated 40 ml/kg estimated/actual administration of red blood cells (RBCs) within three hours, as

this time period is when most deaths occur.[17,18] In combination with other factors, this definition was suggested to facilitate early activation of the pediatric MHP and prevent substantial blood volume loss which can be difficult to detect in children,[19] hypotension being a late and an independent predictor of death in trauma.[20,21]

Administer blood products and crystalloids on a per kg basis to avoid fluid overload: Blood products should be administered in children on a ml/kg basis (RBCs, frozen plasma and platelets-20, 10-20 and 10 ml/kg, respectively) to avoid inadvertent volume overload. Crystalloids should be limited to 20 ml/kg prior to switching to RBCs to limit dilutional coagulopathy and exacerbation of any associated traumatic brain injury (TBI) common in children.[22-24]

Avoid premature administration of frozen plasma: It is recommended that the first box of blood product administered to children, as in adults, should contain only RBCs during initial formula (ratio) driven resuscitation. Adult literature suggests premature administration of frozen plasma (FP) increases morbidity (TACO, ARDS, multi-organ dysfunction and infections)[25,26] and may dilute RBCs, platelets and fibrinogen to the detriment of effective coagulation,[27-32] and thus far pediatric combat or civilian settings report no difference in outcomes based on RBC to FP ratios.[15,33-36,37] The timing and availability of blood components (see tables 1 and 2) lends itself to a 2:1 RBC to FP ratio in children, consistent with adult recommendations, given that FP and platelets may exacerbate TBI-associated coagulopathy in children and increase mortality.[38-42]

Table 1. MHP Cooler Delivery Sequence: Community Setting.

If FP available, adjust RBC: FP ratio 2:1 (weight-based dosing 20: 10 ml/kg); Transfuse PLTs (10 ml/kg) if < 50 x 10^9/L; Consider PLTs if on antiplatelet drugs or if a trauma patient, level unknown and administering contents of Cooler 3; PCCs 25 IU/kg (rounded to closest 500 IU) max 2000 IU or frozen plasma 10 ml/kg per dose; Fibrinogen concentrate 50 mg/kg max 4 g (max 2 g if <30 kg)

Weight	Cooler 1	Cooler 2+
>40 Kg	4 U RBC*	4 U RBC, 2000 IU PCC & 4 g FBGN
31-40 Kg	3U RBC*	3 U RBC, 2000 IU PCC & 4 g FBGN
10-30 Kg	2 U RBC*	2 U RBC, 2000 IU PCC & 2 g FBGN
<10 Kg	1 U RBC*	1 U RBC, 2000 IU PCC & 2 g FBGN

*Administer O Negative for females, otherwise O Positive RBC

Note: U=unit, IU=international unit, RBC=Red Blood Cell, FP=frozen plasma, PLT=platelet, PCC= Prothrombin complex concentrate, FBGN=Fibrinogen concentrate

Remember Platelet administration should be goal-based and not formula driven: Prophylactic administration of platelets to reduce bleeding risk is controversial in children.[33-35,43,44] Platelet and plasma administration may exacerbate fibrinolytic dysregulation associated with TBI.[38-42] Mortality benefit from platelets has not been reported in combat-injured children[36] and prophylactic platelet transfusion in

neonates with severe thrombocytopenia has been associated with increased major bleeding events and mortality.[45] Also, platelets are associated with the highest risk of adverse events of all allogenic blood products, bacterial sepsis being the second most common cause of transfusion related deaths.[46] While a balanced resuscitation with RBCs, plasma and platelets (1:1:1) has been recommended regardless of platelet count,[47-49] platelets (10 ml/kg) should be administered based on a goal-directed 50 x 10^9/L threshold and not as part of the initial formula driven resuscitation. In tertiary care settings platelets may be considered when the blood product contents of cooler #3 (see tables 1 and 2) are being administered for a trauma patient and the platelet count is unavailable, but their availability and the ability to perform aliquoting or centrifugation to remove incompatible plasma for smaller children in a community setting may be limited. Finally, blood products administered to emulate reconstituted whole blood is achieved with RBC: FP: PLT ratios of 20: 10: 3-5 ml/kg, respectively,[49] and is in keeping with our recommended reduced platelet dose compared with the often confusing and higher dosed 1: 1: 1 recommended ratio.

Table 2. MHP Cooler Delivery Sequence: Tertiary Care Setting. **For Coolers 2+ adjust RBC: FP ratio 1-2:1 (weight-based dosing 10-20: 10 ml/kg) as needed UNTIL lab directed dosing possible; Transfuse PLTs (10 ml/kg) if < 50 x 10^9/L; Consider PLTs if on antiplatelet drugs or if a trauma patient, level unknown and administering contents of Cooler 3**

Weight	Cooler 1	Cooler 2	Cooler 3	Cooler 4+
>40 Kg	4 U RBC*	4 U RBC 4 U FP	4 U RBC 2 U FP 4 g FBGN	4 U RBC 2 U FP
31-40 Kg	3U RBC*	3 U RBC 3 U FP	3 U RBC 2 U FP 4 g FBGN	3 U RBC 2 U FP
10-30 Kg	2 U RBC*	2 U RBC 2 U FP	2 U RBC 1 U FP 2 g FBGN	2 U RBC 1 U FP
<10 Kg	1 U RBC*	1 U RBC 1 U FP	1 U RBC 1 U FP 2 g FBGN	1 U RBC 1 U FP

*Administer O Negative for females, otherwise O Positive RBC
Note: U=unit, IU=international unit, RBC=Red Blood Cell, FP=frozen plasma, PLT=platelet, PCC= Prothrombin complex concentrate, FBGN=Fibrinogen concentrate

Adopt similar resuscitation targets in children and adults: Pediatric resuscitation target thresholds for hemoglobin (≥ 80 g/L), INR (< 1.8), fibrinogen (≥ 1.5 g/L) and platelets (≥ 50 x10^9/L) should be similar to adults in most children under 12 years old, given results of pediatric liberal versus restricted RBC transfusion trials and changes in the coagulation system being most marked in the first six-months of life.[50-56] However, there are certain pediatric populations (e.g. neonates, congenital heart disease or severe respiratory distress) that may require higher thresholds for RBC transfusion. Viscoelastic technology has demonstrated promise in pediatric massive hemorrhage in trauma, but is yet to report improved survival outcomes in children; its role in hemostatic resuscitation remains unclear.[11,57-59] Pediatric patients who are adult-sized (> 40 kg) and > 12 years of age should be managed using the adult-directed algorithm.

Avoid hypothermia: Considering the morbidity (i.e. increased risk of coagulopathy, arrhythmias, acidosis and transfusion) and mortality associated with hypothermia in massively bleeding children, they should receive interventions aimed to prevent hypothermia (goal >36°C).[60-63] Children have physiological differences from adults (e.g. less body fat, higher body surface area to volume ratio) which increase their susceptibility to hypothermia and warrant early initiation of multiple simultaneous passive and active warming strategies targeting both the child and environment.[64] Beyond the usual warming strategies including adult in-line intravenous fluid warming devices, children may benefit from placement of a head cover, applying a total-body clear plastic cover sheet, convective air blankets, overhead radiant heaters or hospital-grade exothermic chemical pads placed under the child. Therapeutic hypothermia has NOT been shown to improve outcomes in pediatric patients with TBI.

Monitor potassium, blood glucose and calcium in children: Hyperkalemia due to RBC transfusion is second only to hypovolemia from blood loss as the most common causes of cardiac arrest in the pediatric perioperative environment.[4] Blood sugar is recommended as an additional minimum lab test to be measured early and monitored closely in a pediatric MHP activation beyond the standard blood tests. Both hypo- and hyperglycemia can occur in pediatric trauma patients and is of particular concern in the presence of severe TBI,[66,67] but recommended target glucose concentrations are no lower than 8.3-10 mmol/L (150-180 mg/dl).[68,69] Hypocalcemia due to citrate binding from administered FP is common in children and should be anticipated.

Remember Tranexamic acid (TXA) administration in the pediatric trauma patient is not a standard of practice: Although prospective evidence of benefit or harm is not yet available for the use of anti-fibrinolytics such as TXA in children (< 16 years old) with trauma, there may be benefit (e.g. decreased blood loss) with little risk of harm (e.g. seizures) when administered within 3 hours of injury. TXA is currently being evaluated in pediatric clinical trials.[70,71] Retrospective evidence in pediatric combat casualties reports TXA to be independently associated with decreased mortality, while in the elective perioperative environment (cardiac surgery, craniosynostosis repair and posterior spinal instrumentation) a reduction in blood loss and transfusion requirements has been demonstrated.[72,73,74] TXA may not be indicated in the child with trauma induced coagulopathy and severe TBI (head abbreviated injury scale score ≥ 3) because it may exacerbate a state of fibrinolysis shutdown and is therefore not recommended at this time.[40]

Transport and handover to a definitive care setting should be initiated early: Infants and children (< 13 years old) subject to or are at risk of MHP activation should receive specialized care.[75,76] Children cared for in a community hospital setting should trigger early/urgent consultation with a specialized service using a "**S**ituation, **B**ackground, **A**ssessment and **R**ecommendation" (SBAR) hand-over tool.

Conclusion

Given the inherent variability in pediatric MHPs, there is an opportunity to optimize patient outcomes by standardizing their care. This is ideal in an often chaotic and high-stakes environment found in both low trauma-volume community and busy tertiary care hospital settings. The protocol has to account for a child's immature body habitus and smaller size, mechanistic differences in trauma, unique indications for a higher RBC transfusion trigger and a predisposition to hypothermia and hyperkalemia compared with adults. Surrogate adult evidence suggests that in addition to improved patient outcomes, a reduction in complications and a potential for cost savings are to be expected,[77] however, in the pediatric setting there remain unresolved issues. More robust pediatric specific evidence is required to determine evidence-

based triggers for MHP activation and appropriate blood product ratios and timing of plasma and platelets especially in the setting of TBI. Further, while TXA is beneficial in the elective perioperative setting, advantage in the pediatric trauma setting is still to be determined. Finally, investigation of appropriate fluid, vasoactive agent and pain management strategies and means to modulate the associated systemic inflammatory response towards improved patient outcomes are still needed.

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