Development of a nationwide out-of-hospital transfusion protocol: A modified RAND Delphi study

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Abstract

Background

Early resuscitation with blood components or products is emerging as best practice in select trauma and medical patients. As a result, out-of-hospital transfusion (OHT) programs are being developed based on limited and often conflicting evidence. This study aims to provide guidance on the development of OHT protocols to Canadian Critical Care Transport Organizations (CCTOs).

Methods

We used a modified RAND Delphi process to achieve consensus on statements guiding various aspects of OHT in the context of critical care transport. Purposive sampling assured a representative distribution of participants in regards to geography and relevant clinical specialties. We conducted two written survey Delphi rounds, followed by a virtual panel discussion. Statements which did not achieve consensus in the first two rounds, defined as a median score of at least six on a seven-point Likert scale, were discussed and voted on during the panel discussion.

Results

Seventeen subject experts participated in this study. After the study process was completed, a total of 39 statements were agreed upon, covering the following domains: general oversight and clinical governance, storage and transport of blood components and products, initiation of OHT, types of blood components and products, delivery and monitoring of OHT, indications for and use of hemostatic adjuncts, and resuscitation targets of OHT.

Interpretation

This guidance document is the first of its kind to provide guidance on OHT best practices. We present a range of consensus statements which we hope will support efficient and safe OHT in CCTOs in Canada and other countries around the world.

Background

The transfusion of blood components such as red blood cells (RBCs) or plasma is increasingly common in prehospital and transport medicine.[1-3] In addition, the potential benefits of administering whole blood or blood products such as fibrinogen or prothrombin complex concentrate (PCC) in select patients are being investigated. In this manuscript, we will use the umbrella term out-of-hospital transfusion (OHT) to refer to the transfusion of whole blood, blood components such as red blood cells (RBCs) and plasma, or blood products such as fibrinogen and prothrombin complex concentrate (PCC). While the increasing practice of OHT suggests general consensus on a likely clinical benefit, evidence regarding the effect of OHT on morbidity and mortality is limited and conflicting.[2] A recent randomized controlled trial (RCT) of RBC and lyophilized plasma transfusion in prehospital helicopter emergency medical services (HEMS) in the United Kingdom (RePHILL) showed no difference in the composite outcome of mortality or impaired lactate clearance in patients with traumatic hemorrhagic shock.[4] A randomized cluster trial of thawed plasma in a similar patient population in the United States (PAMPer trial) demonstrated a significant and important improvement in 30-day mortality in trauma patients receiving plasma when compared to standard care alone.[5] On the other hand, an RCT from the United States (COMBAT trial) did not find a mortality benefit from transfusing thawed plasma in trauma patients in an urban ground emergency medical service (EMS).[6] The generalizability of this limited evidence is further complicated by the fact that feasibility and potential benefit of OHT is dependent on multiple regional factors such as geography, patient factors, and healthcare configuration. For example, two secondary analyses of the PAMPer and COMBAT data sets suggest that OHT was beneficial if transport times were greater than 20 minutes and that a benefit present in blunt trauma does not translate to a benefit in penetrating trauma.[7, 8] It also worth noting that out-of-hospital management of acute hemorrhage extends beyond OHT and includes factors such as administration of tranexamic acid (TXA), avoidance of hypothermia and physical means of hemorrhage control where possible, among others.[9, 10] Efficient and effective implementation of OHT requires a combination of medical and logistic considerations which span multiple specialties. This is particularly relevant in countries like Canada with long transport times to tertiary care centres, and remote communities that have limited or no access to physicians or blood components and products at their local healthcare facilities.[11] We invited an expert panel to review the current evidence examining out-of-hospital hemorrhage management and in particular OHT, to developed a national consensus recommendations to guide OHT practice and to begin to optimize the effectiveness and safety of OHT.

Methods

We used a modified RAND Delphi process to create an expert consensus document on the development of OHT protocols by CCTOs.

Participant recruitment

The study team created a list of subject experts for study participation with the following inclusion criteria: senior clinician in a critical care transport organization, or in-hospital trauma care with an interest in transfusion, or in a transfusion service involved in OHT, and current clinical practice in Canada. In addition, potential participants on this list were given the option to nominate further experts for potential participation in the study. From this list of subject experts, purposive sampling of participants was used to ensure a diverse group of experts with respect to professional background, clinical specialty, and location of practice. Given the relatively small pool of eligible experts in Canada, we sought a sample size of 15 to 20 participants to achieve good representation.[12] Potential participants were contacted via email, with two further follow up emails in two-week intervals. The recruitment email contained a short summary of the study objective and design, and participants completed a written consent form for participation. There was no financial remuneration. Co-authorship was offered to participants who completed all rounds of the Delphi study and reviewed the final manuscript.

Modified Delphi process

A modified RAND Delphi process was used to establish recommendations for the development of local or regional OHT protocols. The Delphi technique is deemed a relevant source of evidence in health care research and is particularly important if randomized controlled trials are unavailable to set health care policies.[13]. The Delphi technique is a systematic, interactive method that relies on a panel of experts to converge on consensus statements following a series of iterative written surveys.[14] We modified the original technique by adding a panel discussion to the written survey rounds, to allow an exchange of information and opinions between the participants of different backgrounds and expertise. We also chose a RAND/UCLA Appropriateness Method in which the participants were encouraged to edit the list of recommendations during the written survey rounds as well as add further recommendations. The final modified RAND Delphi structure used in this study therefore consisted of three rounds: two written surveys of recommendation statements followed by a panel discussion. Due to the considerable geographical distance between participants, we used an online survey tool for written survey rounds of the Delphi study and an online meeting platform for the panel discussion. A similar Delphi process was successfully utilized recently to create a regional massive hemorrhage protocol in Ontario, covering in-hospital practice.[15]

At the start of the process, the study team created a list of statements relating to OHT, covering the following domains:

1. General oversight and clinical governance
2. Storage and transport of blood components and products
3. Initiation of OHT
4. Types of blood components and products
5. Delivery and monitoring of OHT
6. Indications for and use of transfusion adjuncts
7. Resuscitation targets to guide transfusion

In Round 1, participants were asked to score each of the recommendation statements on a Likert scale of 1 to 7, representing "definitely should not include" to "definitely should include". Participants were also asked to propose wording changes to existing statements, add comments, or to add additional statements they considered important. Participants were blinded to other participants' responses. Once all participants submitted their ratings and comments, the research team calculated median Likert scores for each statement and reviewed all comments. The research team was blinded to the identity of the participants during this phase of the Delphi process. The following outcomes were possible after Round 1:

- Median score 6 to 7 – statement included as written, or with minor adjustments based on participants' comments if these changes did not alter the meaning of the statement. These statements were excluded from further rounds.
- Median score 6 to 7 with critical commentary – if one or more participants suggested relevant changes to a statement which changed some or all of the original meaning, these changes were incorporated, and the revised statement included in the following round.
- Median score 3 to 5 – the research team reviewed participants' comments and updated these statements accordingly. All statements were included in the following round.
- Median score 1 to 2 – unless there were participants' comments clearly in favor of these statements, these were considered as rejected by the panel and removed from the process.
- Merging of one or more existing statements – if participants' comments suggested a significant improvement of statements by merging them into one item, the resulting merged statement was then included in the following round.
- New statements – new statements suggested by participants were added in their respective domain and included in the following round.

The above process was repeated in Round 2. Statements requiring further review to achieve consensus (median Likert scale score 6 to 7 with critical commentary or median score 3 to 5) were then included in Round 3. Round 3 was an online meeting of participants which allowed discussion and clarification of statements. The meeting was recorded and transcribed by an automatic transcription service and the recording and transcription was made available to all participants. All participants (including those who were unable to attend the virtual meeting) were then asked via email if the statements crafted during the meeting should be included in the document. Consensus in Round 3 was defined as all responding participants agreeing to include a given statement. Finally, all participants were given the opportunity to review the recommendation statements in their final form prior to completion of the data analysis phase of the study.

Ethical considerations and consent

Research ethics board review and approval was provided by the Research Ethics Office, Unity Health Toronto on 15th July 2021, REB 21-155.

Results

We invited 29 subject experts, of which 17 agreed to participate in the study. Table 1 provides an overview of participants' backgrounds.

Table 1. Characteristics of study participants

Participants	**n (17)**	**%**
Profession		
Physician	14	82%
Critical Care Paramedic	2	12%
Registered Nurse	1	6%
Specialty		
Transfusion medicine	77	41%
Emergency medicine	4	24%
Trauma surgery	3	18%
Prehospital/Transport	3	18%
Province		
Ontario	88	47%
British Columbia	4	24%
Manitoba	2	12%
Alberta	1	6%
Saskatchewan	1	6%
Quebec	1	6%

All participants completed Round 1 and Round 2 of the modified Delphi process, and 13 (76.5%) participants attended the virtual panel meeting (Round 3). All participants who were unable to attend the meeting reviewed the recording and/or transcript and provided further commentary if required. All 17 participants reviewed the final list of statements. Figure 1 shows the progression towards consensus for all statements.

Figure 1. List of statement and progress towards consensus over the 3 Delphi rounds

Statement	Round 1: median score (range; abstaining vote if applicable)	Round 2: median score (range; abstaining vote if applicable)	Round 3: panel discussion results
1. General oversight and clinical governance			
1.1	7 (5 - 7)		
1.2	7 (2 - 7)		
1.3	7 (3 - 7; 1)		
1.4	7 (2 - 7)		
1.5	7 (2 - 7)	7 (5 - 7)	
1.6	7 (2 - 7)		
1.7	6 (2 - 7; 1)		
1.8	6 (2 - 7; 2)	7 (4 - 7)	Consensus achieved
1.9	7 (5 - 7)	6 (4 - 7)	Consensus achieved
1.10	7 (3 - 7)	7 (5 - 7)	
1.11	6 (2 - 7)	7 (5 - 7; 1)	Consensus achieved
1.12	New statement	6 (1 - 7)	
1.13	New statement	7 (4 - 7)	
1.14	7 (2 - 7)		
2. Storage and transport of blood components and products			
2.1	7 (1- 7; 2)		
2.2	7 (2 - 7)		
2.3	New statement	6 (1 - 7)	Consensus achieved
2.4	New statement	7 (4 - 7)	
3. Initiation of out-of-hospital transfusion			
3.1	6 (3 - 6; 1)	6 (1 - 7)	Consensus achieved
3.2	6 (2 - 7; 1)		
3.3	6 (1 - 7; 1)	6 (3 - 7; 1)	Consensus achieved
3.4	7 (6 - 7)		
3.5	4 (1 - 7)	5 (2 - 7)	Consensus achieved
3.6	7 (1 - 7; 1)		
3.7	6 (1 - 7)	6 (4 - 7)	
3.8	4 (1 - 7; 2)	4 (1 - 7)	
4. Types of blood components and products			
4.1	6 (1 - 7)		
4.2	6 (1 - 7; 3)	6 (3 - 7)	
4.3	5 (1 - 7; 1)	5 (1 - 7)	Consensus achieved
4.4	New statement	6 (5 - 7)	
4.5	5 (1 - 7; 1)	5 (1 - 7)	Consensus achieved
4.6	5 (1 - 7)	5 (1 - 7)	No consensus
4.7	6 (2 - 7)		
4.8	6 (1 - 7)		
5. Delivery and monitoring of out-of-hospital transfusion			
5.1	7 (5 - 7)	7 (5 - 7)	
5.2	7 (1 - 7; 1)		
5.3	7 (1 - 7)		
5.4	7 (5 - 7)		
5.5	6 (1 - 7; 1)		
5.6	New statement	7 (4 - 7)	
5.7	7 (2 - 7)		
6. Indications for and use of transfusion adjuncts			
6.1	7 (5 - 7)		
6.2	7 (5 - 7)		
6.3	6 (4 - 7)		
6.4	7 (5 - 7; 1)		
7. Resuscitation targets to guide transfusion			
7.1	6 (4 - 7)		
7.2	6 (4 - 7)		
7.3	New statement	5 (2 - 7; 1)	No consensus

Legend for outcomes from rounds

Accept as written	Round 2 (critical commentary)	Merged with other statement
Accept revised version	Round 2 (score)	New statement

Of the 41 initial statements, 21 were accepted with no or only minor changes after Round 1. Five statements were merged with others. The remaining 15 statements were modified according to participants' comments and included in Round 2, together with an additional 7 new statements which were suggested by participants. In Round 2, a further nine statements were accepted, and two statements merged with other. The remaining 11 statements were discussed in the virtual panel meeting. During the panel meeting (including feedback from participants who were unable to attend), consensus was achieved on all but two statements. Table 2 and Box 1 contain a comprehensive list of all 39 final consensus statements and their rationales. Table 3 shows the two statements for which no consensus was achieved.

Table 2. Consensus statements on the development of out-of-hospital transfusion protocols

	Statement	Rationale
1. General oversight and clinical governance		
1.1	All critical care transport organizations (CCTOs) shall have a protocol to guide out-of-hospital transfusion (OHT).	The panel agreed on the importance of standardization of OHT within CCTOs. For the purpose of this document, CCTOs should be viewed as organizations that provide a critical care level of stabilisation and transport of severely ill or injured patients, whether by ground or air ambulance.[16] This includes scene calls and inter-facility transfers. Most Canadian local and regional Emergency Medical Services (EMS) ground ambulances will probably not be dispatched to sufficient numbers of critically ill patients to warrant the addition of OHT to such services.[17] However, some EMS might create smaller units for second-tier dispatch to select patient groups (for example major trauma), and such units should be considered CCTOs in the context of this document.[1]
1.2	The protocol shall be developed by a multidisciplinary team, be approved by the participating transfusion service, and comply with best practices and local and national transfusion guidelines.	A OHT protocol requires support from multiple organizations and individuals. This includes, but is not limited to, prehospital providers, aviation safety experts in some cases, blood transport personnel, communication services and laboratory personnel.[18] The protocol should be reviewed and approved by the hospital transfusion committee and the CCTOs medical advisory committee.
1.3	The protocol shall incorporate principles of damage-control resuscitation, including appropriate treatment of ongoing hemorrhage, and careful selection of a receiving hospital that can provide appropriate definite hemorrhage control.	Damage-control resuscitation principles in prehospital trauma care include control of external hemorrhage, application of pelvic binders (if indicated), correction of deranged physiologic measures with particular focus on avoiding hypothermia and acidosis, and the early administration of tranexamic acid (TXA).[9] Extensive crystalloid administration should be avoided if possible.[19] New technologies such as partial resuscitative endovascular balloon occlusion of the aorta (p-REBOA) might play a role in internal hemorrhage control in the future.[10] Many damage-control resuscitation principles can be applied to non-traumatic causes of hemorrhagic shock but the panel acknowledges the lack of clear evidence. Notwithstanding the increasing number of therapeutic options outlined above, timely transfer to a receiving hospital with the resources required for definite hemorrhage control remains a key component of care for patients in hemorrhagic shock.
1.4	The protocol shall reflect the types and amounts of blood components and products which can be stored and transported by the CCTO, as well as additional components and products which might be available from sending facilities.	The panel anticipated that the quantity and variety of blood components and products which CCTOs will be able to access is likely going to evolve with the publication of numerous prehospital trials currently underway. [15] Optimal care for patients with major hemorrhage might require a combination of the CCTOs stock and further blood components and products which might be available from sending facilities, and protocols should provide guidance for such situations.
1.5	The protocol should be reviewed at specified regular intervals, when the CCTO adopts new relevant products or procedures, or if new practice-changing evidence emerges.	The panel acknowledge the pace of ongoing research in this area, with a number of relevant randomised controlled trials expected over the coming years.[4, 20] In addition, changes in blood transfusion services might make new products available in the near future based on needs and logistics, for example, lyophilised plasma or whole blood.

1.6	A single protocol for all patients is preferred in order to ensure compliance; there should be specific guidance provided for selected patient populations.	Previous research has demonstrated poor compliance with major hemorrhage protocols during in-hospital transfusions and a potential detrimental effect on patient outcomes.[21] To optimise compliance with OHT protocols, the panel recommended a single protocol for patients with active, major bleeding. This single protocol should include or reference considerations for specific situations such as trauma, obstetrical hemorrhage, GI bleeding, acquired coagulopathy, or pediatric hemorrhage.
1.7	Each CCTO shall have named lead(s) and contact person(s) for any issues related to OHT.	Due to the inherently unpredictable nature of the critical care transport environment, situations will arise which are not directly addressed by protocols already in place.[16] It is imperative that CCTOs have a responsive and accountable system to deal with any queries and issues in a safe and timely fashion.
1.8	All OHTs should be reviewed by a designated individual (for example the named lead for OHT, see statement 1.9) or committee for quality assurance.	Adherence to major hemorrhage protocols in regards to safety measures, indication for transfusion, and damage-control resuscitation is a critical aspect of assuring patient benefit and efficient use of blood products during in-hospital care.[21, 22] While no direct evidence exists for protocols guiding transfusion in prehospital and retrieval settings, it is likely that the in-hospital evidence is transferrable, and many CCTOs routinely review all cases involving OHT.[23] CCTOs should have a mechanism to review all cases of OHT, including feedback to care providers and shared learning across the CCTO.
1.9	In addition to the minimal regional and national training requirements for competence in blood product transfusion, prehospital care providers shall have formal training specific to blood transfusion in the prehospital or transport medicine setting.	Standards of training exist for all healthcare providers performing transfusion of blood products, and CCTOs must assure their clinicians have received initial training and are compliant with ongoing standard requirements.[24] Provision of multi-modal training has been shown to improve relevant knowledge of and adherence to best practice in blood product transfusions in hospital settings.[25] Transfusion in the critical care transport setting poses additional logistical and clinical challenges. Additional training, taking these aspects into account, is important to ensure safe and efficient practice.[18]
1.10	Any clinical or administrative adverse events, errors or near-misses shall be documented and reported through the CCTO's incident report system. This shall trigger a notification of the named lead(s) of the CCTO and the participating transfusion service.	A timely information cascade after errors or near-misses will allow for the preservation of information and materials required for a thorough investigation.[26] Importantly, errors or near-misses with a high probability of recurrence can be addressed quickly and further harm avoided. A transparent and just culture in regard to errors is paramount to support such a reporting system.[27] Adverse event reporting systems will also be required to comply with regulatory safety requirements.
1.11	The quality metrics in Box 1 should be tracked on all OHTs and the data reviewed quarterly at the CCTO's medical advisory committee with representation from the participating transfusion service.	Safety, efficiency and clinical effectiveness in OHT requires cooperation and procedural compliance, from the blood transfusion service to the blood delivery and storage system, to the transfusion at the patient's side, and post transfusion documentation and tracing.[18] Audit of quality indicators is an important tool for measuring and improving compliance with protocols and must be undertaken regularly.[28] The panel agreed that some flexibility should be included in the choice of quality metrics, Box A contains a list of (strongly) recommended metrics.

1.12	If the patient (or a substitute decision maker) is unable to consent to OHT, this should be documented in the CCTO's patient's records. If consent can be obtained, documentation of consent should include an explanation of the risks and alternatives to OHT.	Obtaining consent is a crucial step before commencing transfusion of blood products.[29] The panel anticipated that many patients requiring OHT will not be able to consent due to the severity of their underlying illness or injury.[18, 30] Nevertheless, in such cases, there should be documentation of the reason why consent could not be obtained. The panel strongly recommended a structured and standardised documentation approach for consent, refusal or inability to obtain consent.[31, 32]
1.13	CCTOs shall comply with all Health Canada Blood Regulations and applicable Canadian Standards Association and provincial standards which govern OHT.	While storage and transfusion of blood components and products will occur outside of traditional hospital settings, the same standards as for in-hospital practice apply.[33]
2. Storage and transport of blood components and products		
2.1	Blood components and products shall be stored in validated storage containers in accordance with national and regional accreditation standards of the participating transfusion service.	One of the main logistical challenges of OHT is the storage of blood components and products outside of blood transfusion services' labs. As per many transfusion standards, the use of validated containers is required to reduce the risk of transfusion complications and wastage.[18, 32]
2.2	Containers shall be closely inspected/monitored for any compromise or defects at defined times (i.e. start and end of shift, prior to initiation of OHTs, on return to the participating transfusion service).	Containers will be frequently moved between different storage areas at CCTO's bases, aircrafts, and vehicles, and also be transported to the patient's side at scene or sending facility. The frequent movement and storage in compartments shared with other equipment in aircrafts or vehicles introduces a risk of damage to containers, with the subsequent risk of wastage of blood components and products if not recognised and mitigated.
2.3	If a temperature monitoring device is included in the storage container, it shall be inspected for temperature range violations prior to initiation of OHT.	Depending on local practices, such as choice of storage containers and frequency of exchange of blood components and products, temperature monitoring devices will be included in the storage containers.[18] If present, identifying temperature violations prior to initiation of OHT is a critical step in avoiding transfusion complications.
2.4	All prehospital providers handling blood components and products shall receive training regarding the safe storage and handling of the containers, as well as the procedures for receiving and returning blood components and products from/to the transfusion service.	Training in the clinical aspects of OHT is addressed in statement 1.12. However, the panel agreed that specific training and instructions regarding the storage, handling, and exchange procedures for blood products and components was important to reduce the risk of wastage.

3. Initiation of out-of-hospital transfusion		
3.1	The indication for OHT is confirmed or suspected hemorrhagic shock secondary to traumatic or non-traumatic hemorrhage AND TWO or more of: • Systolic blood pressure <90mmHg • Heart rate >110/min • Clinical signs of end organ dysfunction • Lactate >4mmol/L • Hb <90g/L • Base excess <-6	While the panel expected that trauma would be the main cause for OHTs, it is important to also consider OHT in non-traumatic causes of hemorrhagic shock such as obstetrical, gastrointestinal, peri- or post-operative, or aneurysmal hemorrhage.[18, 30] Previous research in trauma patient has shown that clinician gestalt alone is a poor predictor of the need for massive transfusion, suggesting the need for standardised transfusion protocol triggers.[34] The combination of clinical and laboratory parameters to trigger OHT in this statement aims to provide guidance but also some flexibility to the healthcare provider. For unstable patients in need of urgent transfusion (two of hypotension, tachycardia, and/or end organ dysfunction), OHT can be commenced without the need for laboratory testing.[35] In patients with no or only one of these clinical signs of hemorrhagic shock, OHT might still be beneficial, and the decision can be augmented by obtaining point-of-care laboratory values, if possible.[36, 37] In trauma patients, additional factors such as injury patterns (amputation, pelvic fractures, penetrating trauma) or positive Focused Assessment with Sonography in Trauma (FAST) scan findings can be used to determine the indication for transfusion.[36, 38]
3.2	In addition to acute hemorrhagic shock, OHT may be initiated in other cases where a transport physician considers the benefits to outweigh the risks.	While statement 3.2 aims to provide a comprehensive trigger for OHT, there might be situations which do not fulfil the above criteria in which OHT might be considered. As these cases are likely going to have a less time sensitive nature and more marginal benefit to risk ratios, the panel agreed that these decisions should be made by a CCTO transport physician.[36]
3.3	OHT may be commenced without physician authorisation within the boundaries of a clearly defined medical directive, or if the anticipated delay would result in significant harm to the patient (e.g. severe hemodynamic compromise).	Transfusion of blood products typically requires physician orders. However, the panel agreed that critically ill or injured patients might come to harm if initiation of PHPB transfusion is delayed due to the need to obtain remote physician authorization.[39] Protocols should therefore include mechanisms for autonomous initiation of OHT within clearly defined boundaries (see statement 3.2, for example).
3.4	The indication for commencing OHT should be clearly documented in the patient's records.	Blood components and products are scarce resources.[40] Additionally, the risk to benefit ratio of OHT needs to be carefully considered for individual patients.[41] Documentation of indications for OHTs is necessary to demonstrate the consideration of risk to benefit and for auditing protocol adherence.
3.5	If feasible, a pre-transfusion blood sample should be obtained by the prehospital provider to be used by the hospital transfusion service for ABO and Rh investigations.	Pre-transfusion samples, while not immediately beneficial in the context of OHT, can be valuable for blood transfusion services when further transfusions are required, can reduce downstream use of group O RBC, and support eligibility for organ donation if indicated.[42] The panel had some concerns regarding the increased work load for prehospital providers and accurate sample labelling. Nevertheless, a number of CCTOs currently obtain pre-transfusion samples when feasible and this option should be considered in the development of OHT protocols.[23, 43]

4. Types of blood components and products		
4.1	At a minimum, OHT stocks of CCTOs shall include 2 units of O Rh D-negative red blood cells (RBCs).	The panel agreed that, pending availability of whole blood and further evidence for other blood components and products, RBCs are the central component of OHT.[2, 18, 43] The panel considered that a large number of patients could safely receive O Rh D-positive RBCs.[44, 45] However, for the patients truly requiring O Rh D-negative, the CCTO's stock of RBCs might be the only blood component or product available, and as such, CCTOs should stock O Rh D-negative RBCs whenever possible. In addition, logistical considerations favour CCTOs carrying one type of RBCs consistently, rather than a mix of RBC Rh types.[18] Finally, administration of Rh D-positive blood without a pre-transfusion sample can significantly delay Rh-group determination following OHT.[46]
4.2	If blood group is unknown, O Rh D-negative RBCs shall be the preferred RBC for patients of child-bearing potential. CCTOs may consider use of O Rh D-positive RBC for all other patients.	In addition to the CCTO's O Rh D-negative RBCs (statement 4.1), further blood products might be available through the CCTO and/or sending healthcare facilities.[15] The Ontario MHP guideline suggests using O Rh D-positive RBCs for all patients with the exception of patients of child-bearing potential, in order to maintain sufficient O Rh D-negative stocks.[15] O Rh D-positive RBCs should be used in these circumstances, if this is possible without delay.[47]
4.3	Depending on local availability, feasibility, and clinical requirements, CCTOs may consider including plasma in addition to RBCs.	Correction and/or prevention of coagulopathy is an important aspect of damage-control resuscitation for hemorrhagic shock. Many CCTOs internationally stock plasma in addition or instead of RBCs.[5-7, 48] The Ontario MHP guidelines suggest a ratio of RBCs to plasma of 2:1 in massive transfusion[15] and there is evidence that prehospital administration of plasma might improve survival in trauma patients with longer transfer times.[7] While availability of group AB plasma is limited in Canada,[40, 49] CCTOs should consider including plasma if availability and logistics allow this.
4.4	CCTOs may consider storing and transporting 2000 IU of PCC and 4 g of fibrinogen concentrate as an alternative to thawed plasma.	The recent Ontario MHP guidelines recommended PCC and Fibrinogen as an alternative to plasma for healthcare facilities where plasma is not immediately available for logistic reasons.[15] CCTOs are similar to such facilities in their limited storage capabilities of blood components and products, and therefore could consider the addition of PCC and Fibrinogen to their OHT stocks, as an alternative to plasma.
4.5	Additional blood components and products, such as larger volumes of RBCs or thawed plasma, platelets, or specific clotting factor concentrates may be requested from the sending healthcare facility as required. The benefits of obtaining these additional products need to be balanced against the risks of delaying transfer of the patient.	Frequently in hemorrhagic shock, and particularly with longer transport times to definite care, the CCTO's stock of blood components and products will be insufficient to meet the patient's needs.[18, 30, 43] The options of obtaining further blood products either from a sending healthcare facility or one on route to definitive care should be explored. The potential benefits of releasing these limited stocks from the sending facility need to be weighed up against the risk of depleting local resources, to the potential detriment of other patients requiring care at the sending facility. Importantly, this process should occur with no or minimal delay in transport to definite care, and thus should be initiated early on, if appropriate.

5. Delivery and monitoring of out-of-hospital transfusion		
5.1	Prehospital providers should have access to a standard operating procedure which includes the indication, administration, and monitoring of OHT, and the management of adverse reactions.	OHT might be an infrequent event for prehospital providers working in Canadian CCTOs.[18, 30] Access to relevant standard operation procedures, electronically or in print, is essential to assure protocol adherence,[23] and their use has been shown to improve quality of care in other aspects of prehospital or retrieval medicine.[50]
5.2	RBCs and plasma shall be given through a commercial, portable, and approved warming device.	Avoidance of hypothermia is an important aspect of damage-control resuscitation.[51] Blood components and products that are stored at low temperatures (RBCs and plasma) should therefore be given through a warming device. Multiple portable devices for the use in the critical care transport environment are commercially available.[18, 23]
5.3	All patients receiving OHTs should have a temperature measured within 30 minutes of provider assessment, and then at a minimum of every 30 minutes (or continuously where available) until arrival at the receiving hospital.	In both traumatic injury and postpartum hemorrhage, temperature monitoring is infrequently performed, and, when the temperature is measured, hypothermia is common.[51, 52] Hypothermia in traumatic injury is associated with worse outcomes,[51] although prospective trials have not confirmed whether aggressive warming protocols would alter outcomes.[52] Warming of patients improves their comfort, and, therefore, even in the absence of a confirmed survival benefit, it should be a core part of every OHT.
5.4	All patients should receive interventions to prevent hypothermia and achieve normothermia (≥ 36°C)	See rationale for statement 5.4.
5.5	Point-of-care hemoglobin, lactate and/or base excess may be used to guide OHT (see statements 3.2 and 7.2) but should not delay initiation of transfusion in critically ill or injured patients.	During in-hospital MHPs, regular laboratory testing is used to direct management.[15] A number of commercially available point-of-care testing devices are now small and light enough that they have been successfully incorporated into the critical care transport environment.[16, 53] The panel encouraged the use of point-of-care testing with the caveat that it should not impede or delay OHT in critically ill or injured patients.
5.6	Monitoring for transfusion reactions and clinical management of transfusion reactions should follow the same standards as in-hospital blood transfusions.	Transfusion reactions range from relatively common and benign febrile non-hemolytic reactions to rare and severe haemolytic transfusion reactions.[54] The monitoring for and management of such transfusion reactions should be clearly outlined in standard operation procedures and closely mirror established protocols of in-hospital practice. Since the vast majority of RBCs administered during OHT will be uncrossmatched, patients should be closely monitored for signs and symptoms of delayed hemolytic transfusion reactions.
6. Indications for and use of transfusion adjuncts		
6.1	Tranexamic Acid (TXA) should be given as soon as possible with any OHT for hemorrhagic shock due to trauma within 3hrs.	Early administration of TXA has been shown to reduce mortality from traumatic hemorrhage with the effect gradually decreasing over time.[55] Administration of TXA later than 3hrs after initial injury is associated with increased mortality.[56] Current recommendations include a 1g bolus followed by a either a further 1g of TXA as bolus or infusion, or a single 2g bolus.[57, 58]
6.2	TXA should be given as soon as possible with any OHT for hypovolemic shock due to post-partum hemorrhage.	Early administration of TXA has been shown to reduce mortality from post-partum hemorrhage, with earlier administration more beneficial than later administration.[56, 59]

6.3	Consideration of calcium gluconate or calcium chloride should be prompted by OHT protocols at defined intervals (eg. after 2 units and then every 4 units thereafter).	Hypocalcemia is common in trauma patients and is associated with increased mortality. [60] RBCs are preserved using citrate, which could cause or exacerbate hypocalcemia, particularly during OHT with large volumes of RBCs. Calcium plays an important role in the clotting cascade and as an inotrope.[60] The panel considered there to be insufficient evidence for routine calcium administration during OHT, however, a prompt to consider empirical administration or point-of-care testing (if feasible) was considered beneficial.
6.4	Prothrombin complex concentrate (PCC) 2000 IU should be given empirically for adult patients requiring OHT due to hemorrhage and taking warfarin or a direct Xa inhibitor (e.g. rivaroxaban, apixaban, edoxaban).	The Canadian National Advisory Committee on Blood and Blood Products recommends the empirical administration of 2000 IU of PCC in patients taking warfarin with major bleeding and an unknown INR.[61] The same dose is recommended for the management of severe bleeding in patients taking a direct Xa inhibitor.
7. Resuscitation targets to halt ongoing transfusion		
7.1	OHT should be re-evaluated if the following systolic blood pressure (SBP) has been achieved in acute traumatic hemorrhagic shock • SBP ≥90mmHg if blunt trauma • SBP ≥110 if suspected or confirmed traumatic brain injury • SBP >=80 in penetrating trauma	Permissive hypotension has become an established concept in early damage-control resuscitation for trauma, however, much uncertainty remains over what the ideal blood pressure targets are and after what time period more aggressive restoration of perfusion might be beneficial.[62] This statement reflects commonly utilised systolic blood pressure targets.[63, 64] These values should be seen as a trigger to review the current situation and OHT, rather than an automatic stop of an ongoing transfusion. Factors outlined in statement 7.2 can be used to supplement decision making.
7.2	For longer transfers, particularly inter-facility transfers, or patients where active bleeding has stopped, the factors below can be used to guide the amount and speed of OHT, in addition to systolic blood pressure: heart rate, lactate, hemoglobin, base excess, signs of organ dysfunction (urine output, signs of cardiac ischemia, level of consciousness).	See also rationale for statement 7.1. There is considerable uncertainty regarding when to stop or reduce an ongoing OHT.[15] The decision should be supported by multiple data point as outlined in statement 7.2 and statement 3.2, in addition to factors such as the volume of remaining blood components and products and length of transport to definite care.

Box 1. Suggested quality metrics for quarterly at the critical care transport organization's medical advisory committee, see Statement 1.11

Strongly recommended

1. Number of wasted blood components and products (absolute number and proportion of total blood components and products)
2. Transfusion-related errors (ie. ABO/Rh incompatibility, compromised blood products)
3. Independent double checks of blood components and products
4. Proportion of patients receiving OHT who met protocol indications
5. Proportion of blood components and products successfully traced to final disposition (i.e. transfused, returned to transfusion services, wasted).

Recommended

1. Proportion of patients with OHT where receiving facilities were notified of need for further in-hospital transfusion, prior to arrival (pre-alert).
2. Proportion of patients who received tranexamic acid within 1 hour of first contact with CCTO (if within 3 hours of injury or acute post-partum hemorrhage)
3. Proportion of patients who had temperature of >35C by time of arrival at receiving hospital
4. Proportion of patients of child-bearing potential that received O Rh-D negative RBCs

OHT: Out-of-hospital transfusion, CCTO: Critical care transport organization, RBC: Red blood cells

Table 3. Statements for which consensus was not achieved

	Statement	Rationale
4.6	In suspected or confirmed hemorrhagic shock secondary to trauma, balanced transfusion with plasma, red blood cells (RBCs) and platelets in a ratio of 1:1:1 to 1:1:2 is ideal. As hospital major hemorrhage protocols usually lead with RBCs, prehospital providers should consider prioritising plasma transfusion as well as communicating the need for early plasma and platelets to the receiving hospital, to achieve a balanced transfusion over the patient's journey.	The panel considered there to be insufficient evidence to make strong recommendations on balanced transfusion and the use of plasma in the prehospital and retrieval setting. While there was general agreement that a balanced transfusion approach as outlined by the Ontario consensus document on in-hospital major hemorrhage protocols[15] is likely beneficial, the panel agreed that an attempt to standardise such an approach in the prehospital and retrieval setting was beyond the scope of this document. The panel considered the results of the PROPPR trial to show no difference in outcomes between a 1:1 and 2:1 ratio of RBCs to plasma.[65]
7.3	Crystalloids and vasopressor/inotrope infusions should only be used to treat hemorrhagic shock if there is diagnosed or suspected concurrent cardiac impairment or neurogenic shock, or in a peri-arrest situation, or where blood components and products are not available or have been depleted.	Similarly to the rationale for statement 4.6 above, the panel largely agreed with the clinical arguments supporting this statement,[62] but considered it to be beyond the scope of this document.

Interpretation

Through a modified RAND Delphi process, we present 39 expert consensus statements and nine quality metrics on the transfusion of blood components and products in the prehospital and retrieval setting. This guidance document is the first of its kind to specifically address OHT and the CCTOs responsible for implementation and quality assurance of OHT. While some of the guidance in this document is specific to the Canadian setting, to the best of our knowledge, this is one of the very few documents providing guidance on OHT internationally.[66] We hope it will prove useful to CCTOs in Canada and other countries around the world. The consensus statements cover various aspects of OHT, from logistics to clinical aspect and quality assurance measures. As such, we consider the multi-disciplinary makeup of the expert panel participating in the study to be an important strength of this research.

Of note, the two domains where gaining consensus were more challenging were the initiation of blood transfusion in the out-of-hospital environment and the types of blood components or products to be used (Figure 1). This slower, and in two statements failed, progress towards consensus in these domains likely reflects the lack of clear evidence and considerable variations in practice in these areas.[67] From our experience during this modified RAND Delphi process we would like to stress the benefit of an exchange of information between the subject experts, particularly between patient-facing clinicians and transfusion specialists, as well as the importance of striking a balance between specific and flexible guidance statements.

The importance of dialogue between subject experts is reflected in a number of statements that only found consensus after panel discussion in Round 3. In particular statements in domain *4. Types of blood components and products* only achieved consensus (or in one case rejection) after Round 3. Transfusion medicine experts were able to outline the current estimates for the risk of Rh-D sensitization which were considerably lower than many patient-facing clinicians had assumed.[44] On the other hand, logistical considerations, the higher proportion of patients of childbearing potential receiving OHT in some participants' CCTOs, and the higher risk of errors in the critical care transport setting when compared to in-hospital practice resulted in an agreement to primarily recommend O Rh-D negative RBCs for CCTOs. Other important discussion points during the panel meeting were the limited availability of plasma[49] which contrasted with a desire by many patient-facing clinicians to stock blood components and products which could provide clotting factors and volume,[7] and the consideration of alternatives to plasma, such as PCC and Fibrinogen.[15]

Statement 3.1, regarding the indication to commence OHT, can be seen as a representative example of the attempt to balance specific guidance with flexibility. While there are multiple scores or algorithms to predict the requirement for massive transfusion for trauma patients in the emergency department, none of the current methods to decide on which patients benefit from early transfusion in trauma achieve particularly high specificity or sensitivity.[38] In addition, most of these scores have not been validated in the prehospital setting or non-traumatic causes of major hemorrhage. The authors of a recent systematic review on the topic concluded that the process to trigger major hemorrhage protocols should be *'individualized to hospital resources and skill set to aid clinical judgment'*.[38] This conclusion holds particular truth in the context of OHT in the setting of the unique geographical challenges faced by CCTOs in Canada. The patient population requiring OHT might be as diverse as a trauma patient transported from scene of the accident to the nearest trauma centre through a 30-minute flight, a patient with a peri-operative major hemorrhage in a smaller hospital requiring a 90-minute inter-facility transfer to the nearest tertiary care centre, or a patient with post-partum hemorrhage in a remote nursing station with no access to blood products or laboratory testing, and transport time exceeding 2 hours.[11, 30] We believe that this expert consensus document on OHT can help to overcome these challenges through a nationwide approach that provides specific guidance while also taking into account the variability in geography, patient factors, in-hospital and prehospital blood product availability, and other available resources.

Importantly, we consider this document a starting point, rather than an end product in the process of ensuring consistent and equitable access to blood components and products for all patients, irrespective of geography. While outside the scope of this project, we have created a national collaboration and OHT working group with all Canadian CCTOs to assure processes are aligned as much as possible across the Canadian provinces, emerging evidence and new technology is reviewed in a timely and efficient manner, and quality improvement measures are shared across organizations. This collaboration will also ideally include a pan-Canadian OHT registry with consistent data entry from all participating CCTOs for quality assurance and future research projects.

Limitations

Our modified RAND Delphi study achieved good representation across relevant clinical specialties and a wide geographical distribution. However, we must acknowledge that we were not able to recruit clinicians from every Canadian province and that there was a lack of representation from obstetricians

as well as patient representatives. An important aspect to acknowledge is that many of the consensus statements lack strong supporting evidence. At the same time, multiple relevant trials are currently recruiting, and the evidence is likely going to evolve and change over the coming years. While we attempted to incorporate a level of flexibility to accommodate these developments, this guidance document will need to be reviewed and updated in the future. Finally, we did not provide any specific guidance on the pediatric population. While many of the principles can be applied to pediatric patients, we recommend involving local pediatric specialists when creating OHT guidelines for this population.

Conclusions

This nationwide consensus document covers a wide range of important domains in the development of OHT protocols. We anticipate that this document will support CCTOs in establishing and standardizing OHT, to assure efficient and equitable use of this valuable resource.

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Data sharing

Anonymized data can be shared upon reasonable request by contacting the corresponding author.

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