The Canadian Massive Transfusion Consensus Conference Proceedings

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The Canadian Consensus conference on Massive Transfusion was held in Toronto in June of 2011. The panel report is published[1] but the following is a summation of the presentations leading to that report. The audience comments and Section 7 Going Beyond Trauma are provided as supplementary content (SC 1 & SC 2) at the end of this document.

Session 1 BACKGROUND

Epidemiology of civilian trauma in Canada

Dr. Carolyn Snider

Traumatic injuries are the leading cause of death among those aged 1-44 and the third highest cause of death overall at 9% of the world's deaths. Motor vehicle collisions are the leading cause of traumatic injuries up to age 65.[2]

However the trauma room is not representative of the true burden of injury. While blunt injuries account for 93% of trauma hospitalizations, penetrating injuries require urgent surgical repair, extensive amounts of blood[3] and are more likely to be fatal. For those that make it to hospital, there is a survival benefit to being treated at a trauma center.[4] This is not a result of more rapid assessment and intervention alone, but to complex factors,[5] one of which is the distance to a trauma center. Simons et al. demonstrated that mortality is significantly higher in rural areas. As only 77.5% of Canadians are within 1 hour of a trauma center[6], the majority of deaths occurred in the pre-hospital phase.[7]

Early trauma related versus dilutional coagulopathy

Dr. Karim Brohi

The rapid delivery of blood products is central to the care of trauma-related hemorrhage. The amount of RBC transfused in the first 24 hours correlates with mortality.[8] Patients who receive > 10 units of RBC have a 1:3 chance of dying, usually within the first 6 hours. Even patients who need only 4-7 units have a remarkably high mortality rate (18%).

Until recently we had a single philosophy regarding trauma induced coagulopathy: trauma patients developed coagulopathy from dilution diagnosed by laboratory tests late in the clinical course. A retrospective study of severely injured trauma patients illustrates this is too little, too late.[9] The paradigm has changed due to the discovery of acute traumatic coagulopathy.[10] A study of 1,088 patients found that one-quarter had coagulopathy on arrival to hospital (INR>1.5). The chance of death was four-fold higher for patients with early coagulopathy (46% versus 11%, P<0.001).[8,11]

In a multi-center study of over 3000 trauma patients, the mortality rate increased in patients from 8% to 17% when the baseline INR increased from 0.8 - 1.2 to 1.3 - 1.4. It further increased to 27% once the INR rose above 1.5. In 21% of patients, the INR was above the traditional cut-off of 1.5 and 36% had INRs above a clinically derived cut off of 1.3[8]. Hence there are 15% more trauma patients who might benefit from better coagulation management.

There is a strong association between INR and injury severity score (ISS); and between INR and the degree of shock. There are some patients with traumatic injury, shock and normal INR/PTT test results, but clear coagulation derangements are detected by thromboelastography (TEG). In a study of 300 trauma patients, the acute traumatic coagulopathy was a problem of clot strength not detected with routine laboratory testing.[12] An EXTEM clot amplitude of less than 36 mm at 5 minutes predicted patients with acute traumatic coagulopathy. The EXTEM clot amplitude was

not affected by hemodilution or temperature; evidence against hemodilution as the primary cause of the coaguloapthy.

We have also observed hyperfibrinolysis in these patients. The more thrombin you generate, the more t-PA you produce; activating plasmin to breakdown fibrin. If one uses thromboelastometry (ROTEM) to determine percent maximal clot lysis, less than 3 to 5% of patients have hyperfibrinolysis. However if use plasmin activation levels (plasmin-antiplasmin >7000 ug/L), 60% of patients in shock would have hyperfibrinolysis.

There appears a perfect storm in acute traumatic coagulopathy: poor fibrinogen utilization due to thrombomodulin generation, anticoagulation due to activated protein C and clot breakdown by hyperfibrinolysis. Each of these is associated with increased mortality. Also, during the resuscitation we see the further effect of dilution caused by RBC only protocols.

The term 'massive transfusion' is an old concept so the use of the term 'massive transfusion protocols' (MTPs) based on this definition should be avoided. The term 'major hemorrhage protocols' should be used instead; activated on the suspicion of hemorrhage when there is poor response to fluids in a patient with shock rather than waiting for a specific number of RBCs to be transfused.

Can we identify trauma patients at risk using on baseline characteristics?

Dr. Bryan Cotton

We need to answer two questions: Can we identify patients at risk for massive transfusion (MT)? and Is it important to identify these patients early?. In 1,088 trauma patients, one-quarter arrived with coagulopathy (PT, aPTT, or thrombin time (TT) > 1.5 times normal) which was associated with higher mortality rates (46% vs. 11%)[10]. Another series of 243 MT Iraq casualties demonstrated that arrival with an INR > 1.5 had a mortality rate of 30%, compared to 5% for

those < 1.5.[13] Seventy percent of 211 MT patients demonstrated coagulopathy and a mortality of 67% compared to 42% in non-coagulopathic patients.[14]

Does early activation matter? A 2009 publication showed that when the clinical team is compliant with the MTP, there is a survival benefit at 24 hours (88 vs. 61%).[15] Failure to activate quickly increases the risk of death 3-fold, so location of activation matters.[16] At Dr. Cotton's center, there was activation in the emergency department in only 60% of cases. Several scoring systems designed to predict the need for massive transfusion have been developed to improve early identification. Some are not practical in real time as they are weighted scores relying on laboratory values and/or injury severity score calculations. [3, 17, 18, 19, 20, 21, 22, 23, 24] The simplest is the ABC score: it has 4 components, each one equal to 0 (absent) or 1 (present) with a score of $\geq$ 2 considered predictive of MT. This score is 84-87% accurate.[3] It results in an over-triage rate of 47% and an under triage rate of 5%. The use of uncrossmatched RBCs has also shown to be a predictor of massive transfusion.[23,24] The ABC combined with uncrossmatched RBCs resulted in the development of the ABC+ score. The presence of two or more variables has a sensitivity of 87%, specificity of 82% with a positive predictive value of 51%, and a negative predictive value of 97%. In summary, we can detect early onset of coagulopathy by laboratory testing and there are several scores currently used to assist with the prediction of risk of MT but all have limitations.

Session 2 LIMITATIONS OF MASSIVE TRANSFUSION PROTOCOLS.

Dr. Gwen Clarke

Massive transfusion protocols (MTPs) are not new. In 1998, the United Kingdom's National Blood Service (NBS) held a MT symposium resulting in a template for clinical implementation. Then the priorities for treatment were: restoration of blood volume to maintain tissue perfusion

and oxygenation; and, achievement of hemostasis by treating surgical sources of bleeding and correcting coagulopathy by judicious use of blood components. Optimal care requires prompt action and good communication.[25] The AABB published their MT document in 2005. Both focus on a multidisciplinary approach to patients requiring MT. The AABB guideline specifically states "medical considerations (and) the laboratory aspects of massive transfusion are enhanced through collaborative efforts of professionals involved in patient care".[26]

There are studies that address the evidence of benefit of a MTP separately from evidence supporting high ratios of plasma to RBCs.[27] One demonstrated that only 27% of MTP activations were fully compliant but compliance was associated with better survival.[15] This suggests that protocols may improve survival; alternatively, less complex patients who were easier to "fit" into the protocol were more likely to survive. It also highlights one of the major limitations to protocols – how do you achieve compliance? There are many studies that suggest enhanced outcomes with the use of pathways, protocols or checklists.[28-30] Barriers to high quality care include unnecessary variation in care; gaps between knowledge and practice; and failure to recognize the complexity of care, with interdisciplinary interactions and a number of care providers. These barriers can be addressed by using clinical pathways but the pathway must be based on solid evidence of best or most cost-effective processes.[31]

Everyone should have a plan for dealing with the massively bleeding patients, the format depends on the clinical support capability, inventory capacity and patient population. Due to limitations in inventory diversity and quantity, treatment goals for non-tertiary facilities may need to focus on stabilization and supply for transport rather than definitive management of the patient. (Table SDC 3)

Session 3 LABORATORY TESTS

The ideal laboratory test in the face of a massive hemorrhage (MH) would provide an accurate, rapid assessment of the patient's current in vivo hemostatic capacity. There are two broad categories of laboratory tests that are useful: The first 'static' category includes the complete blood cell count (CBC), prothrombin time (PT), activated partial thromboplastin time (aPTT), thrombin time (TT) and fibrinogen. The second 'dynamic' category includes thromboelastography (TEG) and rotational thromboelastometry (ROTEM).

How do coagulation laboratory tests help with management?

Dr. Mark Crowther

There is a lack of evidence regarding utility of conventional laboratory tests (PT, aPTT, TT and fibrinogen) in patients with MH. These tests have been developed for static not dynamic monitoring. The PT is effective at determining the amount of Warfarin present in steady state; the aPTT is attuned to measure a single coagulation factor defect of less than 30% allowing screening for inherited hemophilia. In the context of MH, the utility of these tests has been extrapolated from stable clinical settings and the values obtained may not correlate with in vivo bleeding risk. There is also a fixed delay in the performance of laboratory tests that negatively affect clinical relevance in the acute setting. Current point–of-care clot based assays which may correct for the delay, are however wrought with the same issues as conventional tests and may not be the ideal solution.

Despite the paucity of evidence for routine coagulation studies in this setting, some practical conclusions may be drawn. Trends may be more clinically meaningful than a single test result (control for inherent variability between patients). Also, a normal coagulation screen indicates

that there is no significant factor defect. Future research is necessary to further evaluate the utility of dynamic and static tests in this setting.

Strategies to reduce turn-around-time for laboratory results.

Dr. Wayne Chandler

Speed is critical in the case of MH. The focus should be on accuracy sufficient to make clinical decisions within the shortest time frame. The development of strategies to reduce testing turn-around time is integral to the promotion of goal-directed resuscitation. An emergency hemorrhage panel -Hemoglobin, PT, fibrinogen, platelet count - can address this.

The PT was chosen over the aPTT for its rapidity; good correlation with factor concentrations (II, V, VII, X and fibrinogen) and response to plasma; and a lack of interference from non-specific inhibitors, heparin contamination and elevated FVIII (acute phase reactant).[32] Furthermore, these 4 parameters correlate to the need for the commonly transfused components (rbcs, plasma, cryoprecipitate, platelets).[33]

Once a MTP is triggered, the emergency hemorrhage panel should be priority tested above routine work. A rapid fibrinogen assay with the analyzer reprogrammed to a modified calibration curve allows fibrinogen results between 50-1100 mg/dL without the need for time consuming dilution studies.[34] Hemolyzed samples should not be rejected due to the lack of significant interference,[33] nor should there be repeats for confirmation. These alterations can lead to results within 10-20 minutes of sample accrual (historic 25 -75 minutes)[33] demonstrating effectiveness of reducing the timeframe of coagulation testing.

What does ROTEM® add to management?

Dr. Herbert Schöchl

It is necessary to understand why the patient is currently bleeding: is it coagulopathic or surgical in nature? The theranostic concept (individualized, patient centered) cannot be captured by routine laboratory tests, but is central to the clinical application of TEG and ROTEM. These tests provide dynamic information on the development, stabilization and dissolution of a clot reflective of in vivo hemostasis. Citrated, re-calcified, whole blood is added to a cuvette, maintained at 37°C and an activator is added to hasten clot formation. Movement of the pin is initiated and as clotting begins the impedance of pin movement by fibrin strands is detected and a trace is generated.

In Salzburg, ROTEM is used on a routine basis. ROTEM provides a similar trace pattern to TEG with clotting time and maximum clot firmness (MCF). The clotting time is a function of coagulation factor and inhibitor levels. The MCF measures the strength of the platelet-fibrin-factor XIII network. A reduction in MCF has been shown to be associated with increased transfusion requirements[35-37]; which were not predicted by PT/aPTT prolongation.[37] There are also modifications that provide additional information: EXTEM contains tissue factor as an activator akin to the PT; APTEM contains aprotinin to inhibit fibrinolysis; and FIBTEM adds a platelet inhibitor to block the platelet contribution, facilitating analysis of the functional fibrinogen component alone.

Primary hyperfibrinolysis in trauma is likely under recognized (reported incidence of 2.5-7.2%) and is associated with hemorrhage-related death exceeding trauma and injury severity score predictions.[35,36,39] The FIBTEM may be the most useful analysis of the hyperfibrinolytic

contribution to bleeding to allow early prediction of patients requiring MT.[40,41] Once identified, it can be addressed with fibrinogen containing products and/or antifibrinolytic agents.

A retrospective study of ROTEM in 131 trauma patients guiding fibrinogen and prothrombin complex concentrate (PCC) administration showed that 119 (91%) of these patients were managed with factor concentrates and no components.[42] The observed mortality compared with the predictions of trauma injury severity (TRISS) and revised injury severity classification (RISC) scores. ROTEM guidance leads to less plasma, PCC, RBC and platelet use.[42,43] ROTEM-guided hemostasis with first line fibrinogen concentrates has a favorable survival effect. However, it is unclear what specifically leads to decreased blood product transfusion: early detection of coagulopathy with ROTEM?, coagulation therapy ? or both?[36] so prospective evaluation is essential.

What does TEG® add to management?

Dr. Jeffry Kashuk

There are many stages of coagulopathy in massively bleeding patients; an acute stage due to tissue injury, hypoperfusion, hypothermia and metabolic acidosis, followed by a progressive systemic phase occurring due to large volume resuscitation and hyperfibrinolysis. Approximately 30% of trauma patients have plasma resistant coagulopathy due to coagulopathy of trauma compared to the plasma sensitive systemic coagulopathy developing as part of the resuscitation process.[44]

The recognition that various coagulopathic stages exist and that coagulation is a cell based phenomenon necessitated the development of a reliable, reproducible test rapidly clarifying the timing and contribution of these hemostatic shifts while incorporating the cellular components. [45]

TEG addresses relational hemostasis including: enzymatic ability of all coagulation factors in the clot and thrombin generation; fibrinogen contribution to clot kinetics; clot strength (G value) measured in units of force (dynes/cm2); functional platelet impact; and thrombolytic influence on clot stability. A study to determine TEG based transfusion triggers used the INR compared to TEG in anticipation that TEG would result in decreased transfusion.[46] Upon analysis of TEG parameters in 34 MT patients, normalization of the G value and restoration of thrombin generation within 3 hours was associated with improved survival. Also, a thrombin generation of >9.2 mm/min was associated with less blood product administration.[47] However, the concept of primary hyperfibrinolysis provides the strongest argument for the use of TEG. A review of 61 MT patients found that 18% had evidence of primary hyperfibrinolysis with a statistically significant association for mortality. With every unit of clot strength lost during the first hour of presentation, the risk of hyperfibrinolysis increased by 30% and death increased by 10%.[35] Logistic regression models for prediction of primary hyperfibrinolysis identified clot strength (G value) as a significant variable.[35] In the cohort, primary hyperfibrinolysis occurred early (< 1 hour) post injury and was associated with MT requirements, coagulopathy and hemorrhage-related death.

In conclusion, the lack of accurate monitoring of coagulation function is a limitation in the current MTPs. TEG provides insight into the etiology of acute coagulopathy of trauma. TEG could help establish uniformity to massive transfusion by helping to improve an algorithm-driven transfusion approach.

Session 4 RATIO BASED RESUSCITATION IN TRAUMA PATIENTS

Summary of the evidence in civilian trauma patients.

Dr. Philip Spinella

It is important to clarify that we are describing transfusion at a ratio of at least 1:2 (FFP: RBC), as achieving a 1:1 ratio early in resuscitation is very difficult. Use of the terms "high" versus "low" ratio may be more appropriate. Also need to clarify is what we are comparing these strategies to: the ATLS-advocated[48] crystalloid administration with laboratory guided component therapy; an empiric approach of >1:3, or a TEG/ROTEM guided approach?

Damage Control Resuscitation (DCR) is a comprehensive approach incorporating a 1:1:1 transfusion strategy limiting crystalloid. DCR is not meant for the majority but intended only for massively bleeding patients (3-5% of all patients). These select patients are at high risk of early hemorrhagic death (20-50% mortality) and may benefit from aggressive infusion of components. There is increasing literature suggesting that high ratios are associated with improved survival, [49-59] with only a few studies showing no association.[60-63] A systematic review and meta-analysis performed prior to more recent reports of increased quality[64-66] concluded that "very-low-quality evidence suggests that plasma infusion in the setting of MT for trauma patients may be associated with a reduction in the risk of death and multi-organ failure".[67] When taken in context with the literature on alternative resuscitation strategies, the data on high ratios is of superior quality.

Since all the existing evidence is retrospective, the data is methodologically suboptimal. The characteristics of an optimal study include: large sample size; multicenter; inclusion of time-dependent covariate adjustment; exclusion of early deaths; use of propensity analysis; adjustment

for known confounders; and reporting of causes of death. There is currently no study incorporating all of these characteristics so all studies should be interpreted with caution.

The most methodologically sound of all studies, uses a 24 hour mortality outcome and a thorough statistical analysis[53] but it is a single center study that did not adjust for shock or coagulopathy, nor did it report cause of death. A recent analysis,[65] excluded early deaths, adjusted for shock and coagulopathy and performed a time covariate analysis and Cox regression to adjust for survival bias and confounders with mortality, indicated that a ratio >1:1.5 was associated with improved survival. This study contradicts Snyder's [63] which reported that survival bias was responsible for the association between high ratios and improved outcomes.

The effect of transfusion ratios was examined in patients grouped according to the presence or absence of traumatic brain injury (TBI), although no time covariate analysis was done.[66] The study found a mortality benefit for high plasma transfusion ratios in patients *without* TBI and high platelet ratios in patients *with* TBI. The results in non-TBI patients were maintained even with exclusion of early deaths.

The mechanisms by which plasma may improve survival includes: reversal of consumptive coagulopathy, prevention of dilutional coagulopathy, and repair of endothelial dysfunction.[68,69] However, potential benefits must be weighed against potential risks. Plasma may be associated with a higher risk of multiple organ failure (MOF) and acute respiratory distress syndrome (ARDS).[70] This is controversial since not all reports indicate increased risk of MOF/ARDS and for the reports that do [71] there is still improved survival associated with high ratios.[70]

In conclusion, a large amount of low to moderate level evidence exists supporting the use of high ratios for life-threatening traumatic bleeding. Future studies, such as the PROPPR study,[72] will provide much-needed higher quality evidence.

To what extent is the evidence affected by survivorship bias?

Dr. Christopher Snyde

Survival bias is a form of selection bias that arises when death is a competing risk for receiving the treatment of interest.[73] In ATLS resuscitation, RBCs are given first, then plasma, so the ratio of blood components is a time-dependent variable that starts at zero and increases over time. In trauma patients, most deaths occur early, before plasma or platelets are transfused to significantly increase the ratio. These patients did not survive long enough to receive the treatment being studied; they died *with* a low ratio, not *because* of it.

When it is present, survivorship bias will favor the time-dependent intervention. The importance of recognizing the effect of this bias is clearly outlined by Austin et al: "*Ignoring the time-dependent nature of treatment results in overly optimistic estimates of treatment effects. Depending on the period required for patients to initiate therapy, treatment with no effect on survival can appear to be strongly associated with improved survival*."[74] When evaluating the methodology of the pertinent studies [50-52,54,57-59,61,63,75], only those by Snyder[63] and Magnotti[75] included time-dependent analysis, showing no effect of ratios on mortality.

The ideal method for addressing survival bias is to conduct a study randomly allocating the intervention of interest. In the absence of randomized data, there exist a number of techniques to adjust for survival bias Exclusion of early deaths; although easy to apply, disadvantages include an arbitrary exclusion period, a loss of external validity, inability to observe effect during the initial exclusion period, the loss of study information (i.e. outcome data), and the possible introduction of new biases. Distribution matching (calculating the time to treatment initiation for each treated subject) maintains the subject information but ignores the possible effect during the

early period where treated subjects are being defined. It requires labor-intensive data collection with variables that are not found in trauma registries.

Time-dependent analysis is the preferred method to adjust for survivorship bias and is key to negating its effects in retrospective studies. This analysis calculates the ratio over time for each subject and is included in the model as a time-dependent covariate. The advantage of this is maximization of statistical efficiency with the best external validity. Alternately, it requires labor-intensive data collection. In summary, survivorship bias is likely to affect most existing civilian studies.

A critical appraisal of ratios and outcomes in massive transfusion.

*Dr. Ryan Zarychansk*i

After Borgman's publication in 2007[76] describing a mortality benefit associated with high ratios, the use of AB plasma in Canada increased by 50%. To evaluate the evidence underlying this change, a systematic review including 11 non-randomized studies totaling 3107 patients was performed[77]. It concluded "*there is insufficient evidence to support the use of a fixed 1:1 ratio of plasma to RBC units in massively transfused trauma patients. The majority of studies failed to account for known or potential variables known or thought to be related to survival in massive transfusion, and only 3 of 11 studies attempted to account for survival bias which is evident in each study*." If the mortality benefit from high ratios is not as robust as initially reported, then the potential harms from such a transfusion strategy have greater importance. Some studies have demonstrated an increased rate of septic complications, ventilator days, ICU length of stay, and organ failure.[50, 54] Zarychanski is leading a retrospective multicenter review of all MT events. Data collection allows for time-dependent analysis and adjustment for factors known or believed

to be associated with survival. A total of 218 MT events (2004-2010) have been identified with trauma cases comprising 15%. Although still in progress, preliminary analysis suggests that survival is not improved in patients receiving a high ratio. This study will be the first to systematically address many of the methodological and statistical weaknesses of currently published studies pertaining to MT.

A critical appraisal of the 1:1:1 trial methodologies.

Dr. Damon Scales

The current evidence base informing transfusion ratios in MT is limited. The systematic review by Rajasekhar [77] included 11 studies with heterogeneous patient populations and variable thresholds for classifying high versus low ratios. Three studies found survival benefits with 1:1 compared to higher or lower ratios, six concluded higher ratios were better than lower ratios, and two found no difference. The research in this area is limited by relatively small sample sizes, lack of clinical trials, and the observational nature of all the studies with non-random treatment allocations and the high potential for confounding.

The main threats to internal validity of existing studies include secular trends in practice patterns, selection biases, survivorship bias, and measured and unmeasured confounders. When evaluating these threats, it is especially important to consider the *direction* of the bias in light of each study's results; the results may be given greater credence if the existing biases would have acted to diminish the positive signal as opposed to augment it.

Secular trends in practice patterns are common threats to observational studies, introducing selection bias if different patients are enrolled in before versus after groups. Changes in practice are especially problematic if the practice being studied has changed, along with other changes

that may impact outcomes. Overall, transfusion rates are increasing[58] and mortality rates are decreasing.[78-81]

Survivorship bias is the greatest threat to the validity of existing studies. In many,[52, 59, 82] the majority of the clinical benefit appears early with minimal differences seen later in the survival curves further suggesting possible survivorship bias. Options to account for survival bias in analyses, by excluding outcomes during the potential exposure period or performing analyses with time-dependent covariates, can be problematic. Time-dependent adjustment works well if the risk of dying is stable during the time of the study but this is not the case for trauma patients—their risk of dying is extremely high initially, diminishing dramatically over time. Excluding early deaths (the patients at highest risk for competing with delivery of blood products) will remove many patients *and* outcomes, but excludes the group that is being targeted. Unmeasured confounders cannot be adjusted for despite sophisticated analytical techniques. Such confounders include: the quality of the physicians/surgeons, availability of blood products, resuscitation quality, and competing clinical volume during resuscitation. When evaluating the effect of transfusion ratios, it is important to consider that if a mortality benefit does not exist or is minimal, then careful attention should be paid to other outcomes—number of units of blood used, incidence of ARDS, incidence of MODS/MOF and cost.[77]

Although a future RCT may improve the quality of evidence, there are a number of important challenges. Given the small proportion of trauma patients requiring MT, strategies are needed to minimize the enrolment of patients at low risk for massive hemorrhage that could dilute any study signal. Analyses must also be done as intention-to-treat to minimize survivorship bias. Ideally, blinding would be used to account for any co-interventions, but is seldom possible in such a setting, so alternatives are needed. These could include: blinded outcome assessments, non-subjective outcomes (e.g. mortality), measurement of all co-interventions and potential

confounders, and protocols to standardize use of potential co-interventions. An appropriate end-point must be chosen, and although a mortality outcome is favored, it typically requires a very large sample size for clear delineation.

In summary, the existing literature is comprised of small observational retrospective and before-after studies vulnerable to secular trends, survival bias, and unmeasured confounding, all of which might favor higher ratios. As such it does not establish causality. There appears to be a signal towards benefit, but should be viewed with a great degree of skepticism until further research is available.

Session 5 ROLE OF NON-PLASMA COAGULATION PRODUCTS.

Tranexamic acid (TxA)

Dr. Ian Roberts

Tranexamic acid's antifibrinolytic action is mediated by a reversible blockade of lysine binding sites on plasminogen, preventing binding of plasmin to fibrin. It is a well-established therapy for minimizing bleeding and has an excellent safety record. In elective surgery, it reduces the chance of RBC transfusion (odds ratio 0.61; 95% CI 0.53-0.70).[83] To determine if antifibrinolytics would be effective therapy for patients with traumatic injury, the CRASH-2 investigators performed a multicenter, randomized, placebo-controlled trial in 20,211 patients.[84] The primary research question was to determine if TxA reduced the risk of death without increasing risk of thromboembolic complications. TxA was administered as 1 gram over 10 minutes, followed by a maintenance infusion of 1 gram over 8 hours.

Patients allocated to TxA had a 15% reduction in death from bleeding (OR 0.85, 95% CI 0.76-0.96) and a 9% reduction in risk of death from all causes (OR 0.91, 95% CI 0.85-0.97). The

therapy was not associated with an increase in risk of death from vascular occlusion (OR 0.69, 95% CI 0.44-1.07, p=0.096). These results are important: this therapy is safe, cheap and widely available. In subgroup analysis, the effect was similar whether the patient had blunt or penetrating injury, presented with hypotension, or with a low Glasgow Coma Scale. The only subgroup analysis that found a difference between outcomes was related to the time from injury to the administration of the therapy. Patients administered TxA within 1 hour had a remarkable 32% reduction in risk of death from hemorrhage (OR 0.68, 95% CI 0.54-0.86). If administered between 1 - 3 hours there was a 21% reduction. Surprisingly, if administered after 3 hours, risk of *bleeding deaths* was increased (OR 1.44, 95% CI 1.04-1.99), but not risk of all-cause mortality (OR 1.00, 95% CI 0.86-1.17). There is no plausible explanation for this unexpected result; it may be an erroneous finding.

A subgroup analysis was done to evaluate the effect of geographical location on the effect of treatment, due to prior criticism that the study was primarily conducted in low/middle income countries so results were not applicable to high income countries. There was no effect of geographical location on the effectiveness of TxA. It was just as effective in European countries, compared to other regions.

In another subgroup analysis, patients were analyzed based on their risk of death due to bleeding, stratified by baseline characteristics. Overall, 81.5% of the CRASH-2 patients had a 0-10% chance of a bleeding death, 8.5% with a 10-20% risk, and 10% of patients with > 20% risk. There is tendency to focus attention on the small patient subgroup with a very high chance of death and MT, but this is inappropriate. The absolute number of deaths in the low risk group is still quite high; they represent the most common type of patient. In the CRASH-2 study, there were 126 deaths in the low risk group, 119 in the medium risk group and 188 in the high risk group. By just focusing attention on the highest risk group, 57% of all deaths are ignored.

Overall, of the deaths that could be prevented by the use of TxA, the majority will be in low and medium risk patients. There is no evidence that the benefit of TxA was different when the three groups were compared. There was also no evidence that the risk of vascular occlusive events were different. Therefore, there is no reason to restrict the use of TxA to only high risk patients. In summary, TxA safely reduces mortality in all bleeding trauma patients. It should be given as soon as possible (within 3 hours of injury) and to all bleeding trauma patients, not just those at risk for massive hemorrhage. In the CRASH-2 study, only half of the patients were transfused, suggesting that this therapy needs to be more broadly applied in trauma protocols, not just in massive hemorrhage situations.

Fibrinogen concentrates and Cryopreciptate

Dr. Herbert Schöchl, Dr. Harry Stinger and Dr. Samuel Tisherman

Fibrinogen functions as a ligand between the glycoprotein IIb/IIIa molecules on activated platelets in primary hemostasis. It is also critical in secondary hemostasis for fibrin formation. Hippala showed that fibrinogen was the first factor to drop in trauma patients. Fibrinogen reaches a set 'critical level' of < 1.0 g/L when 142% of total blood volume (TBV) is lost but platelets hit a critical level (50 x 10^9/L) at 230% of TBV loss.[85] In porcine models, as blood loss continues there is a near linear drop in fibrinogen level, in contrast to a stabilization of the platelet count.[86] The patient's baseline fibrinogen level is critical in determining at what estimated blood loss the patient will develop hypofibrinogenemia.[87]

Consumption of fibrinogen is thought to occur with activation of the coagulation system from exposure of tissue factor at sites of injury. Consumption of fibrinogen with marked tissue injury has raised the question of the optimal fibrinogen level in the injured. In work by Schöchl

(unpublished), patients with ISS greater than 30 had a higher than 50% chance of having a baseline fibrinogen below 1.0 g/L. This inverse relationship between the ISS and fibrinogen was also demonstrated in 45 French trauma patients.[14] Other factors to consider include: colloid volume expanders contribute via dilution,[88] hypothermia reduces the synthesis of fibrinogen and acidosis increases the degradation of fibrinogen.[89], [90]

Hyperfibrinolysis can contribute due to enhanced breakdown of the fibrin clot. There are several forms of hyperfibrinolysis: fulminant - occurring very early after injury (<30 minutes), intermediate - occurring between 30-60 minutes, and delayed - occurring more than 60 minutes after injury. In addition, hyperfibrinolysis becomes increasingly more common as the ISS increases in patients with severe blunt trauma. Non-survivors with hyperfibrinolysis had lower platelet counts and poorer measurements by ROTEM for clot formation time and maximum clot firmness, when compared to survivors with hyperfibrinolysis.[39]

Stinger [92] looked at the effect of the ratios of fibrinogen to RBCs on patient outcomes in Iraq war patients between 2003 and 2005. They showed that a high fibrinogen to RBC ratio was associated with a reduced mortality. The fibrinogen administered was calculated: plasma (400 mg), platelets (300 mg), cryoprecipitate (2500 mg), whole blood (700 mg), and red cells (80 mg).[60] An expanded analysis of 450 Iraq patients injured between 2003 and 2006 with exclusion of 8 patients who died with 1 hour was performed.[76] The mortality rate was highest in the patients with the lowest ratio of fibrinogen to RBC, this ratio was significantly ($p<0.001$) associated with mortality. The mortality rate for patients with a fibrinogen: red cell ratio of less than 0.3 was 46%, compared to 23% for those patients who received more than 0.3. Patients in the higher ratio group had received more fresh whole blood (1.87 vs. 0.21 units, $p<0.001$), dramatically more plasma (13.74 vs. 4.45 units, $p<0.001$), more cryoprecipitate (10.18 vs. 0.99

units, p<0.001) and more rVIIa (10.81 vs. 7.44 mg, p<0.001). Overall, 91% of all patients who died in the low ratio group succumbed to hemorrhage, compared to 59% of deaths in the high group. However, there are numerous limitations to this analysis. The retrospective nature identifies association not proof of causation. The high ratio group received more rFVIIa and there were no baseline fibrinogen levels to determine if the groups were similar. Most of the fibrinogen came in the form of plasma which administers a wide range of clotting factors making it difficult to isolate the impact of fibrinogen alone. As the source, plasma contributed twice as much as fibrinogen compared to cryoprecipitate, suggesting that the mortality difference may not be fibrinogen alone.

Are fibrinogen concentrates the 'magic bullet' for trauma patients?[91] In Austria, ROTEM is used to assist in the timing of fibrinogen concentrate administration (FIBTEM MCF <10 mm). If ROTEM is unavailable, a target fibrinogen level of 1.5-2.0 g/L is used, with fibrinogen concentrates as the primary fibrinogen replacement. Using a dose of 25-50 mg/kg of fibrinogen concentrates does not appear to further increase the fibrinogen level in the days following injury when it becomes progressively elevated due to its role as an acute phase reactant (Schöchl et al, unpublished).

In traumatic injury models, the administration of fibrinogen, as compared to saline, decreased blood loss and reversed abnormalities seen on TEG.[93,94] A cohort study of 43 patients receiving fibrinogen concentrates for a wide range of hemorrhagic conditions[95] (all had fibrinogens below 2 g/L and received a mean of 2 grams (range 1-5)) showed dramatic reduction in the transfusion needs (12 units RBC versus 2 units RBC). However, they are unable to implicate the product as the true cause of the reduction in blood loss, as it is possible that by the time the product was administered the physicians were able to obtain hemostasis through other measures.

In summary, fibrinogen plays a central role in hemostasis. The fibrinogen level falls early in trauma patients due to blood loss, consumption, hyperfibrinolysis, dilution, acidosis and hypothermia. It is unlikely that a fibrinogen level of 1 g/L is sufficient to curtail ongoing blood loss but there needs to be more data to guide dosing and the type of product used.

Factor XIII

Dr. Herbert Schöchl

Factor XIII is a transglutaminase which is converted by thrombin into factor XIIIa to crosslink fibrin forming an insoluble clot. On analysis of factor XIII levels in trauma patients, Schöchl et. al. (unpublished data) found the level to progressively drop to approximately 25% by day 4, with little recovery by day 8. In addition, they found that patients with higher ISS had lower factor XIII levels, but that the level was maintained above 50% (normal range) until the injury severity score exceeded 45. However, the role of factor XIII as potential therapy for the bleeding in trauma patients is unclear.

Prothrombin complex concentrates (PCCs) and recombinant activated factor VIIa (rVIIa)

Dr. Yulia Lin

PCCs contain the coagulation factors II, VII, IX, and X, plus the natural anticoagulants, protein C and S with or without antithrombin. These products are currently licensed for the treatment of bleeding (or perioperative prophylaxis) in acquired deficiency of these factors (i.e. Warfarin). The advantages of PCCs over plasma include: viral inactivation, shorter preparation times, smaller volumes, rapid infusion rates and no requirement for ABO typing. The main advantage of plasma over PCCs is that it contains all of the coagulation factors.

What is the evidence for the use of PCCs in trauma? There are no prospective RCTs and evidence is limited to two retrospective case series. The first had 131 trauma patients who received 5 or more units RBCs 24 hours after injury.[42] Although only 3 patients had a licensed indication, 101 of 131 patients received both PCCs and fibrinogen concentrates. The mortality was lower than expected but there was no concurrent control group.

The second series compared the patients above to those in the Germany trauma registry.[43] The groups were not well matched. The Austrian group had lower blood pressure and higher heart rate while the German group had worse head and thorax injuries, higher TASH scores, and lower Glasgow coma scores. RBC and platelet use was markedly lower in the Austrian group in comparison to the Germans with 23% of Austrian patients receiving only PCC and fibrinogen[43]. It is difficult to draw conclusions from these studies where not all patients received MT and a well-matched control group was not available. In conclusion, there is insufficient data to support the routine use of PCC in the setting of trauma, exception for trauma patients on vitamin K antagonists.

Up until 2008, there had been a marked increase in the off-label use of rVIIa (18% trauma) [96]. It would be overly simplistic to think that rVIIa alone would be able to form a hemostatic clot, as clotting factors, platelets, the thrombin burst, thrombin-activatable fibrinolysis inhibitor (TAFI), and factor XIII are also required.

There are two prospective, randomized, placebo-controlled trials of rVIIa in trauma patients.[97,98] One randomized 277 patients, with the first dose given after the 8th unit of RBC.[97] The second randomized 573 patients, with the first dose given between the 4th and 8th unit of RBC.[98] The second trial was terminated early due to interim analysis showing a high probability of a negative study due to no difference in mortality. When these trials were combined in a meta-analysis, there was no difference in mortality when the treatment and control groups were compared (risk

difference 0.00, 95% CI -0.05 to 0.05).[99] Both suggested that the use of RBC was less (2.0 units[101] and 1.3 units[102]) with rVIIa. This may be due to hemostatic properties, however, an alternative possibility is that rVIIa may reduce plasma use by improving the INR result, resulting in less hemodilution, and fewer RBCs transfused. There was no evidence that rVIIa increased the risk of thromboembolic events in trauma patients.[99] In contrast, a meta-analysis of randomized rVIIa trials in a wide variety of clinical settings found a significant increase in the risk of arterial thromboembolic events (OR 168, 95% CI 1.20-2.36).[100] In conclusion, there is insufficient evidence to support the use of rVIIa in trauma patients.

Session 6 RISK-BENEFIT

Is there evidence to suggest that formula driven resuscitation may harm patients?

Dr. Kenji Inaba

Any discussion about transfusion must include the risks. Is there in fact evidence that formula driven resuscitation may harm patients who receive less than 10 units RBCs? There is currently very little data available to answer this question and guide practice in this patient subset.

One of the primary problems underlying this question is the difficulty in predicting who will receive MT. Plasma is being transfused earlier and earlier, facilitated by the increasing availability of thawed plasma and the fear of "falling behind". The majority of 1:1:1 transfusion studies examined patients that received > 10 units RBC in the first 6-24 hours but few studies evaluate patients who received < 10 units RBC. There is no clear evidence that a 1:1:1 ratio in non-MT patients improves survival.

Reviewing the risks of instituting these protocols must include an analysis of cost and supply; and the infectious and inflammatory complications associated with plasma. An intensive care unit (ICU) trial showed the administration of plasma was associated with an increased risk of infection and death, with a cumulative risk for every unit transfused.[101] Another retrospective ICU based study demonstrated exposure to plasma was associated with an increase in the number of infectious complications.[102]

In a retrospective study, it was shown that there was no survival advantage associated with giving plasma to non-MT patients. This demonstrated that patients receiving > 6 units plasma had a 4-fold increase in pneumonia and sepsis, a 6-fold increase in MOF and a 12-fold increase in ARDS,[103] suggesting that there is no benefit to transfusing plasma to these patients, and it may be harmful.

A contributing factor may also be exposure to non-identical plasma. A retrospective study comparing ABO compatible non-identical to ABO identical plasma transfusions in 568 trauma patients showed an increase in complications as the volume of compatible non-identical plasma transfusions increased[104]. The bulk of what is known about the use of plasma comes from MT trauma patients and the benefit, if any, of giving plasma to those who do not require MT is unknown.

What is the cost associated with formula-driven resuscitation?

Jeffrey S. Hoch, PhD

This is an attempt to provide a health economist's view of the practice of 1:1:1 transfusion as there is a complete lack of literature on this topic.

A budget impact analysis can be used to determine if 1:1:1 MTPs are affordable. Consider cost effective analysis and a cost utility analysis as tools to evaluate practice. It is also important to assess these values in quality adjusted life years (QALY) and incremental cost effectiveness ratios (ICER). These can be plotted on a cost-effectiveness plane; cost of a treatment versus its effectiveness. The effectiveness of a treatment also includes the values in society and the medical system. There are many difficulties in implementing the results of a cost effective analysis and cost utility analysis in transfusion medicine, due to many legal and societal values that are also involved in decision-making. In one of our papers we stated "*mechanical barriers to prevent transfusion of the wrong blood type with an estimated cost-effectiveness of $197,000/QALY have never been adopted, whereas the current approach to WNV screening in North America is at least $500,000/QALY, if not substantially more*."[105] Transfusion medicine is not solely driven by clinical and economic outcomes, but core problems are legal (blood suppliers are legally accountable for blood safety). This accountability is absolute and based on avoidance of all possible risks, regardless of costs. This strategy leads to inefficiencies in health care - (i) blood safety management is guided by available rather than cost-effective technology, and (ii) private insurance premiums for civil liability are sharply increasing, and are not related to the expected returns or the high and increasing cost of blood safety.[105]

There are alternative models of value judgments - "*the UK, with a single-payer system (National Health Service), requires that health interventions not only produce increased health but do so in a way that is economically supportable. The blood system has to justify the proportion of the health care budget it receives. The willingness to use economic evidence in health care decision making, including blood safety, is demonstrated by the UK's unwillingness to adopt technologies used in other developed countries because the new technologies… do not generate sufficient*

health gains in relation to the costs when compared to other available health care interventions".[105]

Perhaps the main value of doing an economic evaluation of 1:1:1 transfusion would be the process of thinking about treatment and not the actual results. Physicians should consider how strong the evidence is for and the objective of 1:1:1 transfusion. The putative goals could be decreasing costs, conserving blood products, increasing survival, avoiding exposures and infections.

Blood is a finite resource with an opportunity cost. The opportunity cost is that blood used for one purpose might not be available for another. Refrain from thinking about 1:1:1 transfusion in dollars, but the opportunities to do something else. In conclusion, blood is in us to give – wisely. More research is required in this field to determine the actual economic costs of this treatment.

Session 7 GOING BEYOND TRAUMA – see SC #2

Session 8 FUTURE STUDIES

Dr. Bartolomeu Nascimento

Implementing a MTP is a complex intervention for a heterogeneous population. Implementing a trial is difficult due to wide variation in the current standard of care. Some centers consider 1:1:1 a proven therapy and may be reluctant to participate in an RCT. However, not all trauma centers in the United Kingdom, Canada and the United States even have MTPs. Observational data indicates that in most the current standard of care is close to 1FFP:1PLT:2RBC ratio for transfusion support.

In addition to blood delivery and the initiation timing for MTPs, differences in accessibility to interventional radiology and local differences in mechanisms of injury could challenge a multicenter study. Another challenge is the difficulty in predicting which patients are at risk of MT. Since 80% of all transfusions in this patient population occur within the first 6 hours post injury, it may be prudent to change the cut off to 6 hours rather than 24 hours. In addition, 35% of patients are pronounced dead within the first 15 minutes limiting the ability to recruit patients.[106] Since only 0.7-3% of all trauma patients receive MT and 30 day mortality rate is estimated at 40%; a study of 356 patients per arm would be needed to demonstrate a 10% difference in survival. Since trauma centres in North America have only 30 to 40 massively transfused patients annually, an extremely large multicentre study would be needed to detect small mortality differences.

There will be a need to: standardize the intervention; stratify according to both mechanism of injury and participating site; and clearly define both physiological and mortality endpoints. Both 24 hour and 30 day survivals are important. The 1:1:1 protocols may reduce early mortality, but may come at the expense of an increase in later deaths due to ALI and MOF. A clear definition of the control group is also needed: laboratory-guided (goal-directed) component therapy or other?

Do 1:1:1 transfusion strategies save lives? To answer this, there are three ongoing research studies: PRospective, Observational, Multicenter, Massive Transfusion sTudy (PROMMTT), the Trauma – Formula-driven vs. Lab-guided study (TR-FL), and the Prospective Randomized Optimum Platelet and Plasma Ratios (PROPPR) trial. PROMMTT will evaluate the natural history of MT, assess the timing and utilization of blood products; outcomes; effect of having a transfusion protocols on survival; and, the role of TEG in evaluating coagulation. The PROPPR study is a multi-center trial comparing two ratios of component therapy in massively bleeding

trauma patients (1:1:1 vs. 1:1:2). It will have a 90% power to detect a 10% difference in 24 hour and 30 day mortality.

Table 1. Process steps in delivery of care to massively haemorrhaging patients.

Process Step	**Definition & Benefits**	**Potential Limitations**
Definition	A common definition for both clinical and laboratory staff is a necessary starting point.	Literature based definitions may not be applicable to the clinical setting. Lack of awareness can lead to either early activation or failure to activate.
Notification	Standardizes the lines of communication and ensures that the right personnel are informed. Need direct and efficient communication links – ideally one individual is responsible for all communication on the clinical side and one on the laboratory side.	Patient location may change requiring a change in communication personnel. Notification sometimes precedes clinical information. Too much communication may be intrusive.
Patient Identification	Consistent processes for specimen identification are especially important when dealing with chaotic situations and "unidentified" patients to ensure safe vein to vein ID process.	If trauma or alternate ID is delayed, may prolong and deplete the use of unmatched stock.
Selection of blood products	Allows a standardized approach to provision of products prior to completion of testing and maximizing available inventory by establishing criteria for switching blood groups. May result in a "loosening" of concurrent audit criteria to expedite release of products.	If the protocol requires a large amount of product, it may deplete stock in centers with limited inventory.
Issue of blood products	Supplying a "package" of products streamlines the issuing process. The "near patient" storage of blood products allows movement of patient and product from one clinical area to another.	Issue of multiple products can result in inappropriate use. Use of remote storage / transport containers adds complexity and may result in incorrect storage of certain products (i.e., platelets). There is an increased complexity of blood bank processes with inventory re-entry requirements and formal product acceptance criteria needed.
Monitoring Coagulation Status	The inclusion of haematology and coagulation laboratory staff in the notification process enhances turnaround times and reporting of results.	With conventional testing, data used for informing decisions may be "historical".
Inventory Resupply	Ensures that processes are in place to allow ongoing inventory monitoring and resupply planning.	Lengthy process. Problematic for geographically isolated facilities. Some components not available at all locations.
Stand Down & Debrief	Notification of all parties when the acute event is over. Evaluation of compliance with key indicators allows for learning and continual improvement of plan.	Notification to stand down is often the most neglected step in protocol and may result in wasted time/ product. Debriefing is labour intensive.

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Supplementary Content #1 - Massive Transfusion Consensus Conference Audience Questions and Comments

SESSION 1: EPIDEMIOLOGY AND BACKGROUND

Dr. Jacob Pendergrast (Toronto, Canada): In the CV surgery patients, there is significant bleeding and massive transfusion—is there any work in nontrauma?

Dr. Karim Brohi (London, United Kingdom): The coagulopathy associated with bypass has always been attributed to activation of intrinsic factor pathway. But fibrinolysis and other aspects have not been fully investigated.

Dr. Elianna Saidenburg (Ottawa, Canada): We need to recognize the importance of having a single massive transfusion protocol for all bleeding patients. It is too complicated to have separate protocols for each different patient population (obstetrics, cardiac surgery, etc.) There is also a need for close communication with blood bank throughout the protocol. I am skeptical about a cut-off of an INR of 1.3, as there is considerable variation between laboratories.

Dr. Bryan Cotton (Houston, USA): The blood bank should be involved in the protocol development. We have extended the use of ABC score for non-trauma patients, such as in liver surgery, obstetrics, and cardiac surgery.

Dr. Karim Brohi (London, United Kingdom): Coordination must be done not only for transfusion MDs, but ER MDs, anaesthesia, etc. Everybody needs to know in advance, and have a single protocol for all hemorrhages. There is insufficient data for use ratio 1:1:1 in different settings. Regarding the INR cut-off, once you increase this threshold, you increase the chance of having a coagulopathic patient left untreated.

Dr. Morris Blajchman (Hamilton, Canada): The most important factor appears to be hyperfibrinolysis and lack of fibrinogen. In England, do they concentrate efforts in formula driven replacement or focus on fibrinolysis and fibrinogen replacement?

Dr. Karim Brohi (London, United Kingdom): Tranexamic acid has been used as first line for massive bleeding, according to CRASH 2 guidelines, and can be activated by prehospital team. Also, TEG can be used, but still empirical replacement is provided. Cryoprecipitate can be used later on our protocol.

Dr. Morris Blajchman (Hamilton, Canada): If you were to design a randomized control trial in massively bleeding patients, would you use the current approach that is being utilized in North America (comparing different formulas) or would you add other modalities to your treatment arm?

Dr. Karim Brohi (London, United Kingdom): Anti fibrinolytics have already been dealt on CRASH-2 trial and no one could do it better. Plasma is a suboptimal replacement product and we are interested in utilizing factor concentrates as an alternative therapies.

Dr. Bryan Cotton (Houston, USA): It seem counterintuitive to apply pre-emptive use of tranexamic acid for all trauma patients, when only under 5% of trauma patients have evidence of fibrinolysis, especially when used after 3 hours may increase the risk of bleeding deaths.

Dr. Karim Brohi (London, United Kingdom): We use it early and pre-emptively. CRASH-2 is a robust trial. Only 5% of patients arrive hyperfibrinolytic on TEG or ROTEM, but

60% of patients will have laboratory signs of hyperfibrinolysis by other testing modalities. There is also preliminary data from the military in the UK documenting a survival advantage from the use of tranexamic acid.

Dr. Sarvesh Logsetty (Winnipeg, Canada): Should we have two different protocols – one for pre-hospital and one for after patient arrival? Should massive transfusion be redefined as 4 or 6 units?

Dr. Carolyn Snider (Winnipeg, Canada): We need develop prehospital protocols. Better communication between the referring physician and the trauma team leader of trauma centre would also be helpful.

Dr. Bryan Cotton (Houston, USA): There is activation of massive transfusion protocol when fridge is open at his trauma centre with the first uncrossmatched RBC.

Dr. Karim Brohi (London, United Kingdom): Speed and responsiveness are critical for early coagulation factor replacement.

Dr. Louise Phillips (Melbourne, Australia): Do you treat patients differently if they are not coagulopathic on baseline testing?

Dr. Karim Brohi (London, United Kingdom): There is no need for plasma replacement if not the patient is not coagulopathic. On the other hand, if not replaced at all, patients will become hemodilute over time. I am not a fan of prediction tools. They have a tendency to overtiage patients. I prefer clinical bedside gestalt.

Dr. Pang Shek (Ottawa, Canada) We believe there is utility in TEG/ROTEM even if you start with 1:1:1. It enables you to guide component therapy during resuscitation.

Dr. Karim Brohi (London, United Kingdom): I believe there is huge educational value to having TEG. It is similar to the anesthesia monitor for vital signs. It gives you real time information. It also provides awareness and educational value to the clinical team about the important of coagulation management.

SESSION 3: THE USEFULNESS OF LABORATORY TESTS FOR THE MANAGEMENT OF MASSIVELY BLEEDING PATIENTS

Dr. Elianna Saidenburg (Ottawa, Canada): Part of the reason that I am wary about TEG performed outside of the laboratory is that machine is not subject to the same quality control as other lab tests and the results are not reported in the laboratory information system. Information about the presence of anticoagulants should be included in the massive transfusion protocol. The protocol needs a separate arm for those on anticoagulants as they should be managed differently.

Dr. Wayne Chandler (Houston, USA): With ROTEM or TEG, they do not check for hemolysis as they are using whole blood. It would be interesting to know if ROTEM/TEG has similar error statistics to the emergency hemorrhage panel.

Dr. Herbert Schöchl (Salzberg, Austria): When using colloids, one can obtain false positive results when quantifying fibrinogen, however TEG is a functional test and describes fibrinogen stability and is therefore not liable to similar false positives.

[Question]: Is there any data to support the use of TEG or ROTEM in the pediatric population?

Dr. Philip Spinella (Saint Louis, USA): There are been studies looking at TEG in

pediatrics. There is a similar incidence of shock and coagulopathy in children. We are behind the curve in pediatrics but the physiology is similar. Our group has published a weight based massive transfusion protocol.

Dr. Yulia Lin (Toronto, Canada): For the patients in your study who did not require red cell nor platelet transfusions, did they actually need the coagulation factor concentrates?

Dr. Herbert Schöchl (Salzberg, Austria): The idea was to save platelets and red cells by improving clot quality with the use of fibrinogen. Can we save platelets by increasing fibrinogen? – is a topic for the future. We do not transfuse platelets even if platelet count is less than $50x10^9$/L.

Dr. Charles MacAdams (Calgary, Canada): Are there any tips as to how to inspire laboratories to change process and improve turnaround time?

Dr. Wayne Chandler (Houston, USA): Faster centrifuges cost a few thousand dollars. Little details make the difference. They should inspect ever step that may be causing a delay as I do not believe that it is a staffing issue. Everything in the lab stops to facilitate the running of the emergency hemorrhage panel.

Dr. Sarvesh Logsetty (Winnipeg, Canada): Where is your TEG located and who is responsible for reading it?

Dr. Jeffry Kashuk (Denver, USA): The machine is located in the laboratory but real time tracings are available in the emergency room, operating room and intensive care on computer screens.

Dr. Damien Paton-Guy (Edmonton, Canada): What kinds of statements with regards to the impact of tissue hypoperfusion on the coagulopathy of trauma can the panel make?

Dr. Jeffry Kashuk (Denver, USA): Greater than 30% of patients have acute coagulopathy of trauma, thus this necessitates early monitoring of coagulation function. The only way we will better understand the hemostatic shifts is with frequent monitoring. In Denver, we use a 1:3 replacement ratio, but it is unclear if we know when to stop giving plasma.

Dr. Charles MacAdams (Calgary, Canada): What are some of the practicalities of initiating a TEG program?

Dr. Jeffry Kashuk (Denver, USA): There is certainly a learning curve. There needs to be an extensive educational program before implementation.

SESSION 4: IS THERE SUFFICIENT PUBLISHED EVIDENCE TO JUSTIFY 1:1:1 FORMULA-DRIVEN RESUSCITATION AS THE STANDARD OF CARE FOR BLEEDING TRAUMA PATIENTS?

Dr. Bryan Cotton (Houston, USA): Although trauma-associated mortality has decreased, hemorrhage-related mortality as a contribution to trauma deaths has been stable over the past 30 years.

Dr. Damon Scales (Toronto, Canada): This is true, but system changes may also be contributing to improvements in outcome.

Dr. Bryan Cotton (Houston, USA): You can't give what you don't have-in your study the mean time to plasma was 90 minutes, which introduces an "availability bias" of blood product transfusion. The ATLS approach to resuscitation is outdated and such an approach will also introduce survival bias. The way to deal with this is to have blood products readily available for transfusion in the emergency room.

Dr. Christopher Snyder (Birmingham, USA): Those limitations are duly acknowledged. Nevertheless, the decision to place thawed plasma in your emergency room is based on retrospective data extrapolated from a time period of conventional resuscitation.

Dr. Philip Spinella (Saint Louis, USA): A delay of 90 minutes for thawed plasma administration in patients who require massive transfusion is not "conventional resuscitation" and is even outside the norm for ATLS.

SESSION 5: IN ADDITION TO PLASMA, IS THERE A ROLE FOR OTHER BLOOD COMPONENTS AND PRODUCTS IN THE RESUSCITATION OF MASSIVELY BLEEDING PATIENTS?

Dr. John Freedman (Toronto, Canada): Were seizures seen in the tranexamic acid treated patients and is there any evidence in trauma for topical use of tranexamic acid?

Dr. Ian Roberts (London, United Kingdom): No seizures were seen in the tranexamic acid treated patients, likely because the dose used was only 2 grams, compared to higher doses in other settings (6-10 grams) that have reported seizures. There is data supporting topical use in both orthopedic and cardiac surgery, but no reported studies in trauma. Topical use in the field may be very useful to the paramedics and should be explored in randomized trials.

Dr. Mark MacKenzie (Edmonton, Canada): As an emergency medicine service medical director we have been having a lot of discussion about moving the tranexamic acid to the pre-hospital phase due to long pre-hospital transport time in Canada (can be more than an hour) and we hope the panel will discuss in their deliberations.

Dr. Sandro Rizoli (Toronto, Canada): When setting up a protocol for tranexamic acid which patients would you include and not include? Any concerns about patients with hematuria or subarachnoid hemorrhage?

Dr. Ian Roberts (London, United Kingdom): It is unlikely to cause any harm to a patient with tranexamic acid, so we should be less concerned about use in less severely injured patients. In our analysis, 95% of deaths of deaths could be captured by including patients with systolic blood pressure of less than 100 or pulse rate greater than 100. I would not treat patients beyond 3 hours from injury as they are less likely to benefit. Hematuria is a theoretical contraindication and the mortality benefit likely trumps the risk of thrombosis in the urinary tract. Randomized controlled trials in subarachnoid hemorrhage showed that tranexamic reduced the risk of re-bleeding, but increased the risk of cerebral infarction. These trials used high dose and prolonged courses (3-6 weeks), compared to 8 hours in the CRASH-2 study. In a subgroup of the CRASH-2 patients with traumatic brain injury, there was a non-significant trend towards less hematoma expansion and less cerebral ischemia on imaging. If you combine these results with the only other randomized trial in traumatic brain injury, there is a significant reduction in both hematoma expansion and mortality. And, certainly, there is no suggestion of any harm.

SESSION 6: RISK–BENEFIT

Dr. Bartolomeu Nascimento (Toronto, Canada): What is your definition of a massive transfusion and how do you predict the patient that will need it? Can you identify patients who might be harmed by a massive transfusion?

Dr. Kenji Inaba (Los Angeles, USA): There is no consensus on the number of red blood cells that represents massive transfusion. Furthermore, using a number to define massive transfusion is faulty. It is not a yes or no question – it is a continuous variable. Also, we are looking at a variable that is determined by its treatment. Determining which patient will require a massive transfusion is the million-dollar question. We still have no idea what the optimal trigger is for starting a massive transfusion protocol in a trauma patient.

Dr. John Freedman (Toronto, Canada): Who are the stakeholders who should decide about the economics in blood transfusion?

Dr. Jeffrey Hoch (London, Canada): Society should decide on how to spend the resources, but is society well equipped to make this decision? Should these types of medical decisions be left to doctors? In Ontario, these types of decisions go to a committee, and then a decision is made by one person in government. The best way would be that the society chooses on the value and cost of treatment, with broad group consensus of all stakeholders.

SESSION 8: FUTURE STUDIES

Dr. Katerina Pavenski (Toronto, Canada): You have identified that blood sample and blood product transportation is a problem. In addition, many times we cannot locate the patient, resulting in delay in delivery to the patient. How are you going to address these?

Dr.Bartolomeu Nascimento (Toronto, Canada): We saw delays in all parts of the protocol: delays in requesting plasma, delays due to time required to thaw plasma, and delays due to unknown location of patient. We have even seen delays in transfusion, even when the blood cooler is in the room, because the anesthesiologist did not know it was there. Communication is the key in managing massively bleeding patients.

Dr. Elianna Saidenburg (Ottawa, Canada): During the course of the study did you need to change your order to Canadian Blood Services in order to have sufficient products to be able to activate the protocol? Did you record delayed complications of massive transfusion? Did you see any delays related to the delivery of type specific blood, as compared to uncrossmatched RBC between the groups? How frequently are the pack delivered – at the discretion of the physician or at a set time period?

Dr. Bartolomeu Nascimento (Toronto, Canada): We did not change our blood bank inventory for the study purposes. Delayed complications are being tracked as part of our secondary outcomes. We generally use uncrossmatched blood until emergency issue uncrossmatched group-specific blood is available. The packs are delivered as demanded by the clinicians and the blood bank keeps one pack ahead at all times.

Supplementary Content #2

Section 7 GOING BEYOND TRAUMA.

What is the level of evidence and biological rationale supporting the adoption of 1:1:1 formula driven resuscitation in cardiac surgery?

Dr. Gurmeet Singh, University of Alberta /Mazankowski Heart Institute, Edmonton, Canada

The coagulopathy associated with cardiopulmonary bypass (CPB) is complex and secondary to hemodilution, activation and consumption of coagulation factors[1] in the setting of a prothrombotic and proinflammatory milieu. Approximately 9% of patients will have massive hemorrhage with CPB increasing their mortality rate by 8-fold.[2] Although multiple coagulation factors can be decreased by up to 50%,[3] one of the most important and well understood aspects of CPB coagulopathy is platelet destruction and dysfunction.[1,4]

Although the Cochrane collaboration states that there is no RCT evidence for decreased morbidity and mortality with the use of TEG in massive transfusion,[5] there is recent evidence in cardiovascular surgery. Girdausksa et. al. demonstrated a decrease in RBC and plasma transfusion and a decrease in the risk of massive transfusion in 56 patients[6] using TEG to guide patient management (aortic dissection repair). Studies evaluating TEG in cardiac surgery demonstrate the ability to predict massive transfusion leading to decreased plasma/platelet utilization.[7,8] Implementation and adherence to a laboratory-based transfusion algorithm decreases all transfusion by 57% and RBCs by up to 47%.[9]

Although there is no direct evidence for the benefit of 1:1:1 transfusion for the treatment of massive hemorrhage in cardiovascular surgical bleeding, there is some intuitive biologic plausibility. The dynamic and complex nature of patients with post CPB coagulopathy requires employment of lab driven and protocolized strategies. These strategies should not be mutually exclusive; both approaches should form a continuum of care. Regardless of the ratio of products, a massive hemorrhage protocol allows for rapid access to products while laboratory testing is pending, standardization of care, and clearer communication between surgery, anaesthesia, and blood bank.

What is the level of evidence and biological rationale supporting the adoption of 1:1:1 formula driven resuscitation in other specialties?

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Upper gastrointestinal bleeding: Acute upper gastrointestinal bleeding (AUGIB) is associated with a mortality rate of 5-14%.[10] Other predictors of poor outcome in AUGIB include shock, malignancy, > 65 years age, number of co-morbidities and INR > 1.5 at presentation.[11 -13] Perhaps, coagulopathy at presentation provides a biologic rationale for 1:1 resuscitation.[11 -13] The author of one study on predictors in AUGIB argues that an INR > 1.5 in these patients was neither a causative factor for bleeding nor a target for resuscitation, but served as a marker of co-morbid burden.[12]

Most patients who present with AUGIB have neither exsanguinating hemorrhage nor features of hemodynamic compromise[13] suggesting that a standard requirement for 1:1 transfusion is not necessary. Studies in management of AUGIB appropriately focus on endoscopic, surgical and pharmacological therapy and there is a paucity of studies on transfusion management. The many guidelines on the management of AUGIB do not address transfusion management, except to comment on the need to reverse Warfarin.[13,14] Although Baradarian et. al. claim a mortality benefit when the INR was corrected to < 1.8 as part of an intensive resuscitation strategy, the authors failed to mention how this was achieved. The intensive resuscitation arm was confounded by earlier endoscopy, hemodynamic monitoring, and hemodynamic support, in addition to transfusion. Despite a reported mortality benefit, the patients with more aggressive resuscitation had longer ICU stays.[14] A retrospective observational study of 4441 patients with AUGIB to assess outcomes according to early (within 12 hours) or late initiation of transfusion support demonstrated that patients transfused early had consistently worse outcomes including an increase in mortality.[15] These studies raise the possibility that the use of 1:1 transfusion in this patient population may be inappropriate, and perhaps harmful.

There have been many studies in the past demonstrating that protocolized care for the resuscitation, transfusion and interventional management of patients with AUGIB leads to improved outcomes and mortality.[16-18] However, the contribution of the protocolized transfusion management to improvement in outcomes in this patient population remains unknown.

Post partum hemorrhage (PPH): Physiology suggests that women with PPH may be ideal candidates for 1:1 transfusion protocols due to the rapidity and nature of their bleeding. At parturition, the uterine blood flow at term is 500-800 mL/min. For an average 60 kg female with an estimated blood volume of 5400 mL[19] at term, bleeding at this rate would result in a loss of entire blood volume in 7 minutes.

The hemostatic challenges of PPH include those experienced by all massively hemorrhaging patients (i.e. dilution, hypothermia and acidosis) but may also include vascular injury from uterine artery rupture; disseminated intravascular coagulation due to preeclampsia, abruption, or amniotic fluid embolism; and a higher risk of fibrinolysis due to extensive tissue trauma. There are no studies looking at the use of TEG in PPH but there are two studies that suggest routine laboratory tests may be informative in assessing hemostatic derangements. [20],[21] The PT and aPTT may remain in the normal range despite large (>1500 mL) bleeds; however, fibrinogen level correlates well with developing hemostatic impairment and severity of hemorrhage.[21]

Most studies on management of PPH appropriately concentrate on obstetrical, surgical and radiological therapies. Although there are trials and registries, that explore red cell transfusion triggers (WOMB [22]), use of tranexamic acid (EXADELI[23], WOMAN), and use of rVIIa (Northern European Registry), there are no trials evaluating the use of plasma or cryoprecipitate in this population. Despite this, Bonnet et al.[24] hypothesize in a review of 38 maternal deaths that a low FFP:RBC ratio may have contributed to the poor outcome of these patients. The patients reviewed received a median of 9 units RBC and 9 units FFP (median FFP: RBC ratio of 0.6). More striking is that < 50% of patients received platelets or fibrinogen replacement and a median delay in starting any transfusion was 82 minutes. Three women did not receive any blood products; suggesting that the majority of deaths were due to the lack of recognition of hemorrhage and/or delay in resuscitation, and may not be attributable to the ratio alone.

The recent UK Royal College of Obstetricians and Gynaecologists guideline recommends transfusion of 4 units plasma for every 6 units red cells, or to maintain a PT/ aPTT < 1.5-times normal, with greater than 1000 mL blood loss and ongoing bleeding and/or shock. It also suggests that if > 80% of blood volume is lost with ongoing bleeding, the physician should give empirically 1 L plasma and 10 units cryoprecipitate.[25]

A few studies have suggested that a protocol for stepwise active management of PPH improves outcomes.[26,136] Perhaps, it is more important to have a PPH pathway and/or a rapid response team facilitating early diagnosis and management rather than a specific ratio of blood products. In conclusion, despite no direct evidence, there appears to be a biological rationale for the adoption of MTP that includes early resuscitation with plasma products in severe post partum hemorrhage.

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