Emergency Blood Administration and Massive Transfusion Protocol

Managing the Hemorrhage

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Here, it's different.™

Disclosure

Dr. Annen, faculty for this session, is a speaker for Terumo and QuidelOrtho.

All other planners, faculty, and others in control of content (either individually or as a group) have no relevant financial relationships with ineligible companies.

All of the relevant financial relationships listed have been mitigated.

OBJECTIVE

To provide an in-depth review of our Emergency Blood Administration Policy and Massive Transfusion Protocol (MTP)

Discussion and focus: How to manage hemorrhage in pediatric patients.

Topics

1. Define and discuss best practice guidelines for an MTP
2. Indications for an MTP
3. Purpose and key roles of different blood products
4. Potential complications and considerations
5. Post-infusion management of the patient
6. Steps to implement low-titer O whole blood (LTOBW) and the impact it may have on the blood supply


Hemorrhage remains one of the leading causes of preventable death for all patients, accounting for 20-40% of all early trauma mortality.
(Shroyer, M. & Griffin, 2017)

Research

Current management of the pediatric patient who has massive bleeding has evolved over the past few decades, shifting to early transfusion of products in a balanced ratio as part of MTPs.

Pediatric data on successful management of MTPs are limited and the optimal transfusion approach is currently unknown, leading to practice variability among institutions.

High Crystalloid Volume = High Mortality

Aggressive fluid resuscitation was the cornerstone of managing hemorrhagic shock in pediatric patients. Further studies and data suggest this strategy may be harmful. But how harmful? Can one 20 ml/kg IVF bolus tip the scale and increase a patient's mortality score?

A recent study found that receiving greater than 20 ml/kg of IVF in the first hour of presentation - compared with less than or equal to 20 ml/kg - was associated with increased mortality with a dose-response relationship. Patients receiving greater than or equal to 40 ml/kg of IVF were more likely to require PICU admission, longer PICU stays, longer hospital stays, longer NPO status, and increased need for mechanical ventilation.

Research Criteria

- Patients under 16 years of age with blunt or penetrating injuries (excluding burns) who met level 1 or 2 trauma criteria. Pulseless patients were excluded.
- Age, sex, and weight
- Initial ED vital signs, GCS score, injury mechanism, and injury severity score (ISS) on presentation
- The Shock Index (SI) was adjusted using age-based reference ranges. Cutoffs as follows: 2.7 for less than 12 mo, 2.1 for less than 24 mo, 1.9 for less than 60 mo, 1.5 for less than 144 mo, 1.1 less than 180 mo, and 0.9 for all other ages
- Amount of crystalloid IVFs received within the first hour of presentation
- RBCs given, including whether this occurred within 1 hr of presentation
- Data on emergency transport was available for less than 1% of patients, therefore not used as a data point

Table 1 – Characteristics of patients included in the retrospective cohort.

Characteristic	n (%) or mean ± SD				P-value
	Overall (n = 1285)	≤20 cc/kg (n = 994)	20-40 cc/kg (n = 249)	≥40 cc/kg (n = 42)	
Sex					0.69
Female	456 (35.5)	348 (35.0)	94 (37.8)	14 (33.3)	
Male	829 (64.5)	646 (65.0)	155 (62.2)	28 (66.7)	
Age (yr)	8.1 ± 5.5	8.1 ± 5.5	8.2 ± 5.3	9.4 ± 5.5	0.30
Weight (kg)	35.4 ± 24.4	36.0 ± 25.2	32.5 ± 20.8	38.0 ± 23.3	0.10
Mechanism of injury					<0.001
Blunt	1074 (83.6)	853 (85.8)	198 (79.5)	23 (54.8)	
Penetrating	211 (16.4)	141 (14.2)	51 (20.5)	19 (45.2)	
Initial GCS	14.0 ± 2.9	14.2 ± 2.6	13.6 ± 3.4	11.4 ± 4.8	<0.001
Injury severity score	7.8 ± 8.7	7.1 ± 7.8	8.9 ± 9.1	18.3 ± 15.4	<0.001
Adjusted shock index*	0.67 ± 0.20	0.66 ± 0.20	0.68 ± 0.18	0.77 ± 0.28	<0.001
First red blood cell transfusion					<0.001
None	1184 (92.7)	949 (96.2)	213 (85.9)	22 (52.4)	
Within first hour	28 (2.2)	10 (1.0)	8 (3.2)	10 (23.8)	
After first hour	73 (5.1)	35 (2.8)	28 (10.9)	10 (23.8)	

SD = standard deviation.
* Adjusted shock index = shock index/shock index age cutoff. Shock index = heart rate/systolic blood pressure.

Table 2 – Unadjusted outcomes for patients included in the retrospective cohort.

Outcome	n (%) or mean ± SD				P-value[†]
	Overall (n = 1285)	≤20 cc/kg (n = 994)	20-40 cc/kg (n = 249)	≥40 cc/kg (n = 42)	
Mortality	23 (1.8)	10 (1.0)	7 (2.8)	6 (14.3)	<0.001
Hospital admission	1018 (79.2)	764 (76.9)	216 (86.8)	38 (90.5)	<0.001
Total hospital LOS (d)[*]	3.6 ± 5.8	2.9 ± 4.0	4.5 ± 7.9	11.2 ± 11.4	<0.001
PICU admission	535 (41.6)	382 (38.4)	118 (47.4)	35 (83.3)	<0.001
PICU LOS (d)[*]	2.7 ± 4.8	2.2 ± 3.1	3.2 ± 6.7	6.5 ± 9.2	<0.001
Mechanical ventilator	133 (10.4)	73 (7.3)	41 (16.5)	19 (45.2)	<0.001
Ventilator days[*]	4.6 ± 6.7	3.7 ± 5.0	4.3 ± 6.1	8.5 ± 11.4	0.15
NPO at any time	989 (77.0)	739 (74.4)	213 (85.5)	37 (88.1)	<0.001
NPO days[*]	1.3 ± 2.4	1.1 ± 1.9	1.4 ± 2.4	4.7 ± 5.6	<0.001
Discharge disposition					<0.001[‡]
Home or self-care	1192 (92.6)	947 (95.3)	221 (88.1)	24 (57.1)	
Rehabilitation	72 (5.6)	37 (3.7)	21 (8.4)	12 (28.6)	
Morgue	23 (1.8)	10 (1.0)	7 (2.8)	6 (14.3)	

SD = standard deviation.
[*] Among those ever with the outcome.
[†] Calculated as P-value for trend in unadjusted logistic regression, except where specified.
[‡] By chi-squared test.

Table 3 – Multivariable analysis for the following dichotomous outcomes after adjusting for covariates: ISS, adjusted shock index, age, mechanism.

Outcome	IV crystalloid given in first hr in our ED, compared with reference ≤20 cc/kg (aOR; 95% CI; P-value)	
	20-40 cc/kg	≥40 cc/kg
Mortality, in-hospital	2.96; 1.02-8.55; P = 0.045	6.26; 1.79-21.83; P = 0.004
Hospital admission	1.94; 1.29-2.92; P = 0.001	2.08; 0.70-6.19; P = 0.187
PICU admission	1.21; 0.87-1.68; P = 0.259	4.03; 1.51-10.77; P = 0.005
Mechanical ventilation	2.11; 1.31-3.41; P = 0.002	3.79; 1.62-8.87; P = 0.002
NPO	2.03; 1.38-3.00; P < 0.001	2.00; 0.75-5.35; P = 0.168

Table 4 – Multivariable analysis for the following interval outcomes after adjusting for covariates: ISS, adjusted shock index, age, mechanism.

Outcome*:	IV crystalloid given in first hr in our ED, compared with reference ≤20 cc/kg (aOR; 95% CI; P-value)	
	20-40 cc/kg	≥40 cc/kg
Hospital LOS	1.36; 1.03-1.80; P = 0.033	4.62; 2.44-8.75; P < 0.001
PICU LOS	1.18; 0.77-1.80; P = 0.457	2.20; 1.05-4.61; P = 0.036
Ventilator days	0.99; 0.47-2.05; P = 0.968	2.22; 0.83-5.91; P = 0.111
NPO days	1.08; 0.83-1.40; P = 0.586	4.40; 2.25-8.59; P < 0.001

*Among those ever with the outcome.

Blood is Thicker than Water

Increased pre-hospital crystalloid volume replacement was associated with increased transfusion requirements, adversely affecting coagulation (defined by a prolonged PT), and a tendency towards increased mortality and multi organ failure (MOF) rates.

Besides containing fibrinogen, which is essential for clot formation, FFP is an excellent volume expander. Patients that require a massive transfusion should therefore be given RBCs and FFP as the gold standard for volume therapy to treat hypovolemia which is causing hypoperfusion rather than crystalloids

The use of higher plasma and platelet doses appear to be associated with improved outcomes.

Early Blood

- The early and timely delivery of higher balanced ratios of plasma and platelets allows for the achievement of damage control resuscitation. (University of Texas Houston, Radwan et al 2013)

- Delays in the activation of MTP as well as delays in the delivery of the first blood products were both associated with increased time to hemostasis and increased mortality. Every minute of delay between the activation of MTP and the arrival of the first units, *regardless of ratio*, resulted in a 5% increase in the odds of mortality.

- Compared 30 day mortality in MTP patients before and after instituting an initiative to maintain a supply of thawed plasma in the ED. This cut time to plasma administration by 50% and decreased the odds of mortality at 30 days by 60%. (Meyer et al 2017)

Accept a Lower Blood Pressure

Permissive hypotension is defined as *the acceptance of below normal systolic blood pressure to avoid exsanguination while maintaining perfusion of end organs and controlling sources of bleeding.*

- Palpable pulse
- Normal Glasgow Coma Scale (GCS)

Pediatric patients can maintain a normal systolic blood pressure despite a loss of almost 45% of blood. Consider the patient who is cool and tachycardic in shock, until proven otherwise. (Lee, 2023)

Give the Plasma

- Patients divided into three groups based on their FFP: RBC ratio at 24 hrs. Out of 123,836 patients, 583 were massively transfused (received greater than 40 ml/kg total blood products). Higher FFP ratios were associated with lower 24-hour mortality.

- Inpatients with combat-related trauma requiring massive transfusion, a high 1:1.4 plasma to RBC ratio is independently associated with improved survival to hospital discharge, primarily by decreasing death from hemorrhage. For practical purposes, massive transfusion protocols should utilize a 1:1 ratio of plasma to RBCs for all patients who are hypocoagulable with traumatic injuries. (J Trauma 2007; 63:805 –813)

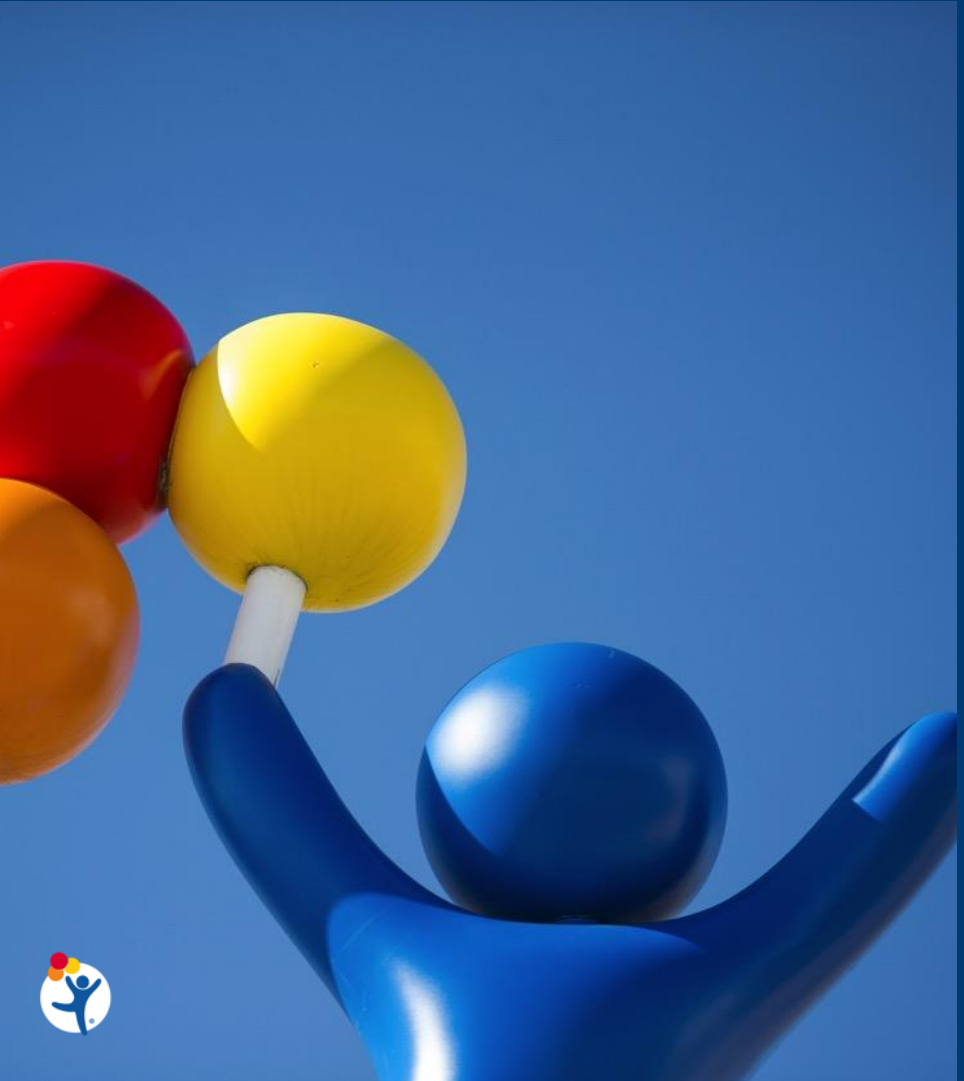
- In the first 6 hours, patients with ratios (plasma:prbc) less than 1:2 were 3 to 4 times more likely to expire than patients with ratios of greater than or equal to 1:1. (JAMA Surgery 2013)

Balanced Blood Administration

Massive Transfusion Protocols are designed to provide the right amount and balance of blood products, mimicking whole blood, for critically injured patients to prevent and treat hemorrhagic shock and coagulopathy.

What We Know

1. Minimal crystalloid use
2. Early blood component therapy
3. Balanced plasma: RBC ratios



CHCO Definitions

MTP - Active bleeding in which the patient has already received 40 ml/kg crystalloid or 20 ml/kg blood or a predicted blood loss of 50% of blood volume in three hours or less.

EMERGENCY RELEASE - Blood products that are released due to an emergency prior to the completion of patient testing and does not meet MTP criteria. Emergency release cross-match is incomplete.

MTP vs. Emergency Release

- The transfusion is started immediately on patient presentation with massive bleeding, before any laboratory testing is completed.
- An MTP provides a standardized response for the rapid delivery of blood components needed to prevent exsanguination and restore hemostasis.
- There are 4 weight categories: each will have a prescribed batch sent up from the Blood Bank.

- The emergency release of blood components is usually meant for red cell components. However, the form and process may be used for other components in emergent situations.
- Emergency Release products are prepared and sent out by the Blood Bank, according to the specific product ordered by the provider.
- The sequence of product infusion will be determined by the ordering provider and patient condition.

Thromboelastography (TEG)

- Provides data for goal-directed hemostatic resuscitation
- Can be beneficial to monitor post-injury coagulopathy
- Can help predict early transfusion, early life-saving interventions, and mortality

The true benefit of TEG may be its point of care (POC) availability and the ability to receive rapid, reliable, actionable data in the trauma bay. (J Ped Surg 2013)

Tranexamic Acid (TXA)

- Pediatric vs. adult
- Indications
- Timeframe of administration
- Dosing
- Patient history
- Risk vs. benefit

Post MTP

Once bleeding is controlled and the patient is hemodynamically stable, the issue changes to maintaining hematologic function.

Incorporate bedside laboratory results as a transfusion guide. Monitor labs closely for the first 24 hours post-stabilization. If no evidence of active bleeding, abnormal PT, PTT, and platelet counts, patient should not be treated with transfusion.

The most common complication of transfusion, *regardless of age*, is metabolic disturbances. Among these, post-transfusion hypocalcemia predominates due to the citrate preservatives in PRBCs. While important for all children, this issue is extremely pertinent to the neonatal population, as these patients have a decreased ability to metabolize citrate.

Frequent electrolyte evaluation, and the replacement and use of the freshest packed red blood cells (PRBCs) in the Blood Bank.

Pediatric MTP Barriers

- It is still currently unclear what constitutes massive transfusion in pediatrics and when an MTP should be called
- The optimal ratio for blood product administration in pediatric trauma patients in need of massive transfusion is unknown
- Initial vital signs may not be good predictors of early hemorrhage
- A specific level of blood loss or anemia that "triggers" RBC transfusion has not yet been defined in pediatric patients
- Inattentiveness to tracking blood-related complications

Whole Blood Use

Use of warm fresh whole blood used in combat settings for adult patients with traumatic injuries have shown to be independently associated with improved 30-day survival

Manno et al. conducted a small randomized controlled study of 161 children undergoing open heart surgery with cardiopulmonary bypass, meeting post-operative transfusion requirements with either 24-48 hour old whole blood stored at 4 degrees Celsius or reconstituted whole blood (RBC/FFP/PLT). It was found that there was significantly less post-operative blood loss in the group receiving fresh whole blood, and ascribed this to better functioning platelets.

Recently, refrigerated whole blood treated with pathogen reduction technology maintained in vitro hemostatic function for at least 10-14 days if stored appropriately

Based on these data, whole blood could potentially be used as an alternative to reconstituted whole blood in trauma settings for hemostatic resuscitation in centers that are able to handle and store it correctly (more investigation into the utility of whole blood in the emergency setting for pediatric resuscitation is warranted)

- Already possess ideal ratio of red blood cells, FFP, and platelets
- Separating whole blood into its constituent components results in the delivery of 3 times the volume of anticoagulant and additives compared to whole blood (if using ADSOL additive)
- Minimizes dilutional coagulopathy and essentially restores what was lost through hemorrhage

Anticoagulants and Additives: Whole Blood versus Component Therapy

	Total Volume	Anticoagulants and Additives
PRBC	360 ml	120 ml
FFP	240 ml	50 ml
Apheresed PLT	300 ml	35 ml
Whole blood	450 ml	63 ml

Note: Data from Spinella et al.[43]

Abbreviations: PRBC, packed red blood cells; FFP, fresh frozen plasma; PLT, platelets.

Comparing Whole Blood to Component Therapy

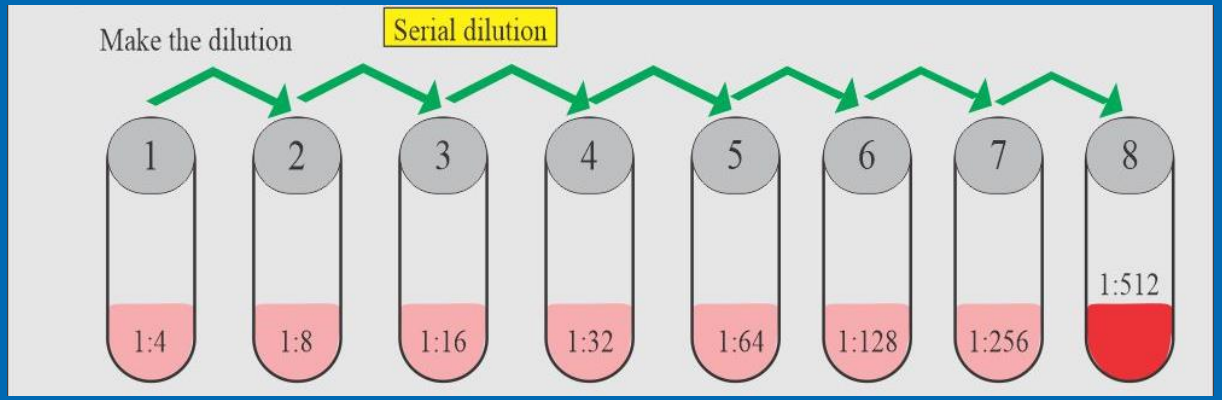
	Whole Blood	Component Therapy (1 PRBC, 1 FFP, 1 PLT)
Volume	570 ml	660 ml
Hematocrit	33–43%	29%
Platelets	130,000–350,000	88,000
Coagulation factors	86%	65%

Note: Data from Murdock et al.[44]

Abbreviations: PRBC, packed red blood cells; FFP, fresh frozen plasma; PLT, platelets.

Barriers and Risks

- Massive hemolysis arising from a type-O donor’s anti-A or anti-B antibodies attacking the recipient's RBCs. This has been mitigated by using low-titer group O whole blood.
- Small pool of low-titer O negative donors
- No standard for what constitutes "low titer"



Is LTOWB safe for Children?

Prospective observational study (2013 to 2020) assessing the survival impact of LTOWB in injured pediatric patients who required massive transfusion

Children ages 1-17 years who received a total of >40 mL/Kg LTOWB or conventional component therapy over 24 hours after admission: primary outcome was 28 day survival

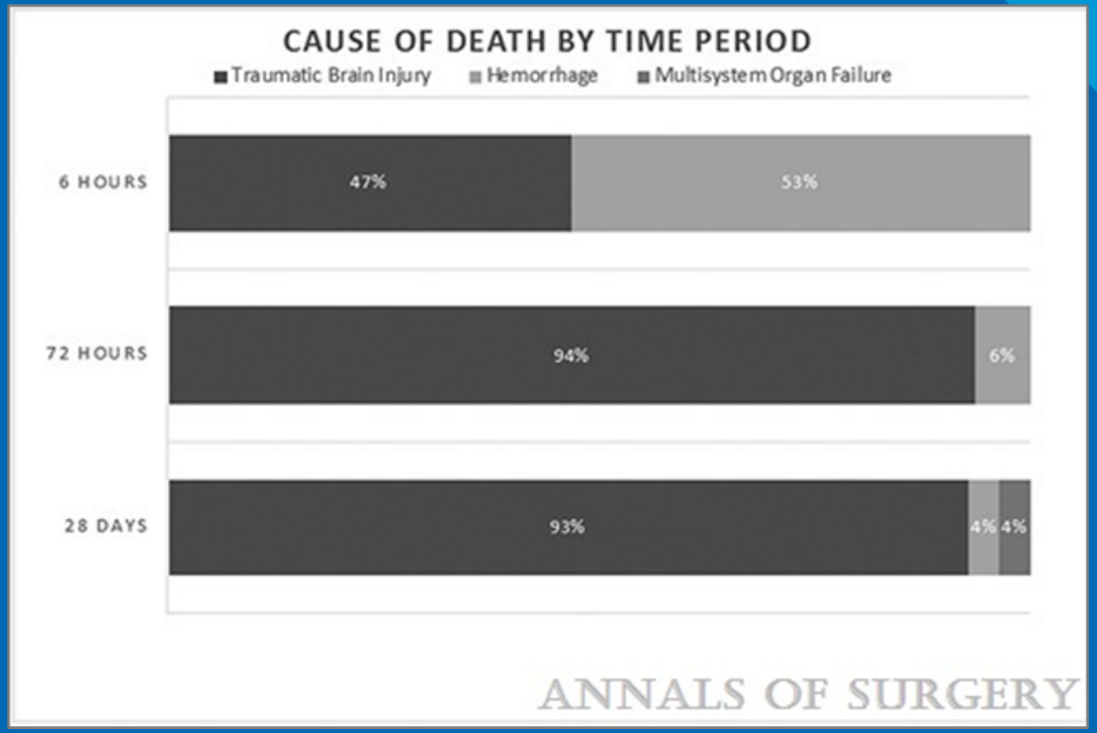
27/80 (33%) received LTOWB as part of hemostatic resuscitation: Demographic and physiologic parameters had some variation between the two groups, originally restricted to a maximum of 20 mL/kg be ≥ 3 years of age and ≥15 kg, later expanded to up to 40 mL/kg in ≥1 year of age

LTOWB (Anti-A and Anti-B titers <50) Rh negative units were stored in both ED and Blood Bank up to 14 days - patients in the LTOWB group received this as their initial resuscitation fluid then may have been transitioned to component therapy

Gaines at al. 2023

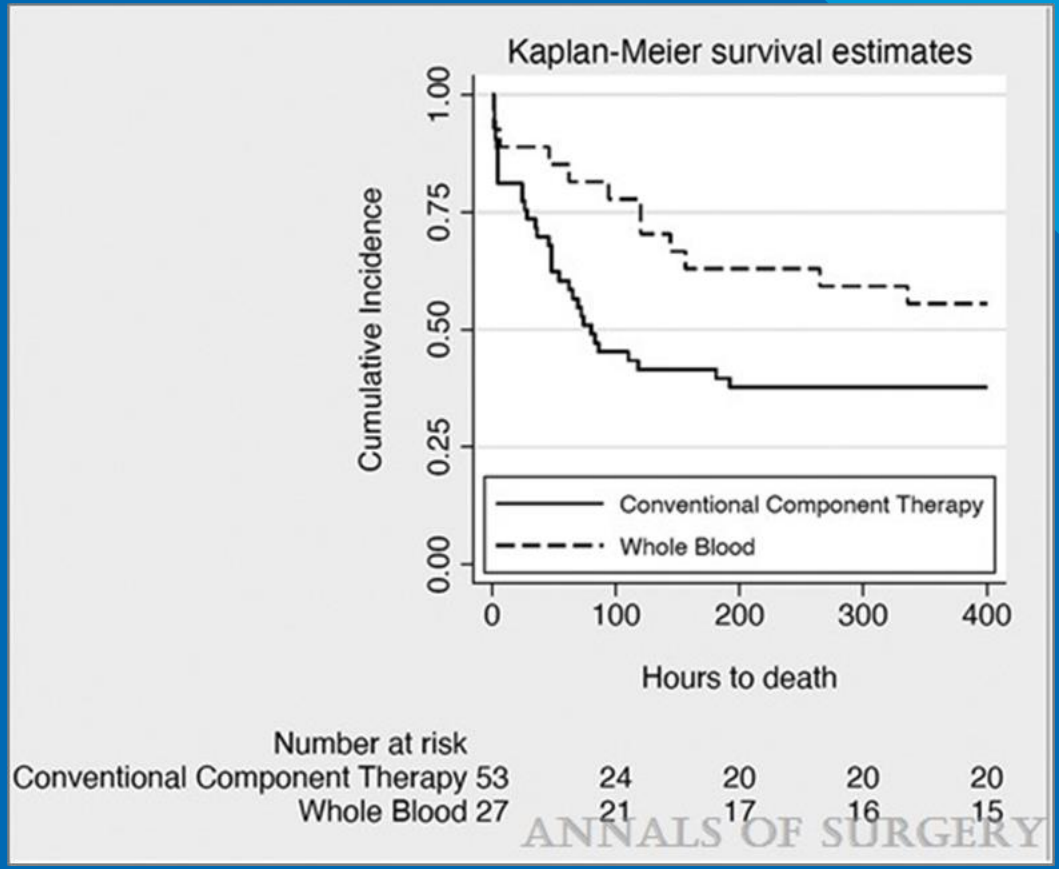
LTOWB vs Component Therapy

- 80 patients
- Median age 6 years (6-12)
- Median ISS of 30 (21-38)
- 6-hour mortality: 19%
- 72-hour mortality: 39%
- 28-day mortality: 56%
- No deaths between 6-24 hours



Pediatric LTOWB vs Component Therapy

- Median time to death was significantly shorter in the component therapy group (p=0.03)
- Mortality at 72 hours was significantly lower in LTOWB group (p=0.01)
- Overall mortality at 28 days was not statistically significant, however after COX regression model adjustment for age, ISS total blood product received admission base deficit and INR the AOR 0.41 (p= 0.02)
- Decreased ICU stay, overall hospital days, and days on ventilator compared to CT group



Implementation Barriers for Low Titer Whole Blood

CHCO has an internal blood collection center which provides 95-100% of all blood products.

Additional products are purchased from American Red Cross and Vitalant when needed.

How many units? Do we vary it based on weight?

Store in ED, Blood Bank, or both?

Implementing LTOWB is not as simple as purchasing...

Table 1 - Demographics and Characteristics of CT Group Versus LTOWB Group

	Component Therapy (n = 53)	Whole Blood (n = 27)	P
Total volume, mL/kg	61 (45–84)	50 (41–74)	0.06
Whole blood, mL/kg	-	20 (15–33)	-
Red blood cell volume, mL/kg	30 (20–60)	18 (12–25)	0.002
Plasma volume, mL/kg	30 (14–37)	15 (7–30)	0.02
Platelet volume, mL/kg	4 (0–10)	2 (0–5)	0.36
Cryoprecipitate (yes/no)	19 (37%)	9 (33%)	1.00
Plasma:red blood cell ratio	0.74 (0.32–1.33)	0.70 (0.42–1.18)	0.60
Platelet:red blood cell ratio	0.05 (0–0.25)	0.09 (0–0.21)	0.79

Emergency Transfusion With Whole Blood vs PRBC: A Study of 1400 Patients

- Retrospective single center compared costs of ER PRBC vs LTOWB after implementation
- LTOWB associated with increased use at 24 hrs ($p<.0001$) and at 7 days ($p<.0001$)
- LTOWB not associated with better survival
  - 82% survival at 24 hrs for pRBC group
  - 81% survival at 24 hrs for LTOWB group
  - $P=0.68$
  - No significant differences in MTP subgroup or non-lethal adverse events, no difference in mortality at 30 days
- Median acquisition cost for total blood products transfused from initial release through 7 days:
  - PRBC: $1110 ($631-22575; $222-30,985)
  - LTOWB: $1686 ($1068-3203; $534-40,855)
  - $p<.0001$

Ruby et al. Transfusion 2023

Transfusion-Related Cost Comparison of Trauma Patients Receiving Whole Blood vs Component Therapy

- Retrospective review of cost of LTOWB or CT from time of injury to 4 hours from arrival (848 patients 2016-2022)
- Found a 17% drop in overall cost of blood, with the largest impact being the reduction in FFP and PLT use
- MTP had a lower cost as CT
- Overall net difference in cost was statistically significant ($p<.0001$) at 4 hours, 24 hours, and overall in cost/patient and overall cost
- Costs for storage, processing, etc. were not evaluated

Ciaraglia et al. J Trauma Acute Care Surg 2023

Steps for Implementing Low Titer O Whole Blood at CHCO

Blood Donor Center

- Re-contract for new platelet sparing LR bags (more expensive)
- Validate new bags
- Update computer system (HemaConnect)
- Update all ISBT labels
- Train staff on new bags

Donor Recruitment

- Increased staff time and/or hiring of more staff
- Extend blood center hours
- Increased costs for promotions and incentives to draw in donors
- Develop process to encourage low titer donors to continue to donate

Transfusion Service

- Update computer system
- Revise standard operating procedures
- Train staff on new procedure
- Delay processing to wait for results of Anti-A and B titers
- Determine how to track which units should be processed

Inventory Management

- Impact to O units freshness availability
- May cause increased loss of plasma (wastage; must be frozen within 8 hours)
- Increased wastage of O units
- Manage new inventory item-number of units, location (units in ED?)
- If units are not used in 7 or 14 days make into red cells

Future Directions

- More use of TXA
- Accessible plasma in the ED
- TEG: How to interpret and use "real time" results
- Change of activation triggers
- Incorporate electrolyte replacement during MTP
- Supply low titer O whole blood

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