A CASE FOR A PROVINCIAL MASSIVE HEMORRHAGE PROTOCOL (MHP)

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Outline

1. Is there room for saving lives?
2. Problems that arise from lack of a coordinated and standardized protocol across Ontario
3. Do MHPs work?
4. Experience from other jurisdictions that have implemented regional MHPs
5. The goals for today & long-term plan for Ontario

Disclosures

- Funding from TEM International, CSL Behring, and Octapharma for a step-wedged cluster RCT comparing ROTEM vs. conventional lab testing for cardiac surgery bleeding (participating site)
- Funding from the Defense Research and Development Canada for a fibrinogen concentrate RCT in trauma
- Funding from Canadian Blood Services to validate platelet bags for MHP protocols
- Funding from Canadian Blood Services for an RCT of lasix vs. no lasix before RBC transfusions – TACO-BEL trial
- Funding from Octapharma for the FIBRES RCT
- Site PI for the ROC Tranexamic acid trial in TBI
- Consultant for Transfusion Medicine, Canadian Armed Forces

Case

- 25 year old female unbelted passenger in a single vehicle collision with TBI, liver laceration, and pelvic fracture
- Taken to the nearest emergency room where she is hypotensive and disoriented
  - Interventions: intubated, 5L of normal saline, 8 units of O-negative RBC
  - Hospital had no MHP to activate
  - No tranexamic acid, no components
  - No group and screen drawn
  - No coagulation blood work drawn
  - Airlifted to a trauma centre for definitive management
- On arrival in trauma bay, patient is profoundly hypotensive, temperature 33.5ºC, GCS 4, INR>10, PTT>150, Platelets 34, fibrinogen 0.3 g/L

If you watch your pennies, the pounds will take care of themselves.
- Benjamin Franklin

If you adhere to the protocol, the mortality benefit will take care of itself.

believe

Preventable deaths in trauma

- n=4804 traumas over 5 years admitted to a level I trauma centre in Toronto
- n=558 deaths (study population)
- n=86 died of hemorrhagic shock (1 in 56 traumas)
- Major potential yield = blunt trauma (n=41)
  - 14/41 had delays in recognition and treatment of bleeding source

1 in 343 traumas

Tien H, et al. J Trauma 2007; 62: 142-146

Table 2 Delays in Controlling Bleeding After Blunt Trauma

Site of Bleed	Patient	Age	ISS Score	Initial Base Deficit	Delay (hours)	Nature of the Delay
Chest	1	46	38	3	5.5	Missed aortic injury on CT; died in OR after rupture
Abdomen	2	29	28	4	10	Missed bleeding vessel (in spasm) on first laparotomy; died during second laparotomy
Pelvis	3	84	50	10	3.2	Delay from obtaining CT (had arterial extravasation); died waiting for angiography
Pelvis	4	59	30	8	3.5	Delay from obtaining CT (had arterial extravasation) and then negative lap; died in OR
Pelvis	5	49	41	6	8	Delay from obtaining CT (no arterial extravasation). Had angiographic embolization despite negative CT
Pelvis	6	63	66	5	4.5	Delay from obtaining CT (no arterial extravasation). Had angiographic embolization despite negative CT
Pelvis	7	79	35	11	3.5	Delay from having CT scan (no arterial extravasation) and then negative laparotomy; died in OR
Pelvis	8	88	54	4	1.5	Delay from going for laparotomy and ex fix. Died in OR, awaiting angiography
Pelvis	9	42	24	13	4.5	Delay from going for laparotomy and ex fix. Died in OR, awaiting angiography
Pelvis	10	70	41	7	6	Delay from going for laparotomy and ex fix. Died in OR, awaiting angiography
Pelvis	11	55	57	10	3.5	Delay from going for laparotomy and ex fix. Died in OR, awaiting angiography
Pelvis	12	46	50	23	2.5	Delay from going for laparotomy and ex fix. Died in OR, awaiting angiography
Pelvis	13	27	42	15	4.0	Delay from going for laparotomy and ex fix. Died in OR, awaiting angiography
Pelvis	14	21	41	16	5.5	Delay from going for laparotomy and ex fix. Had angiographic embolization, then died ICU

>10

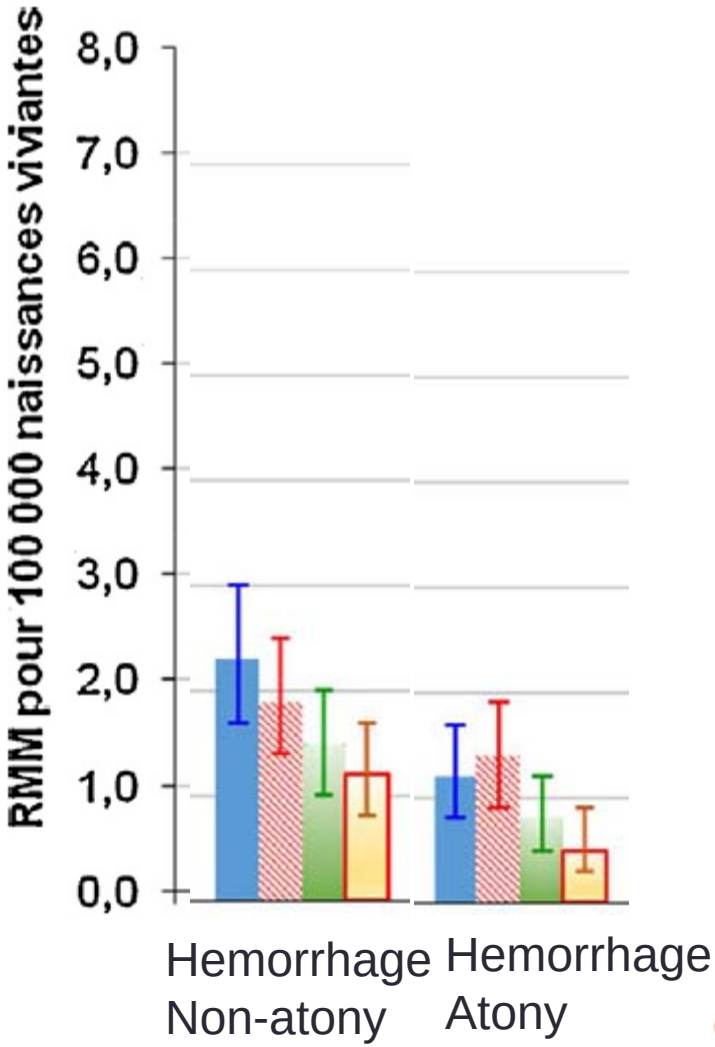
Tien H, et al. J Trauma 2007; 62: 142-146

Preventable maternal deaths

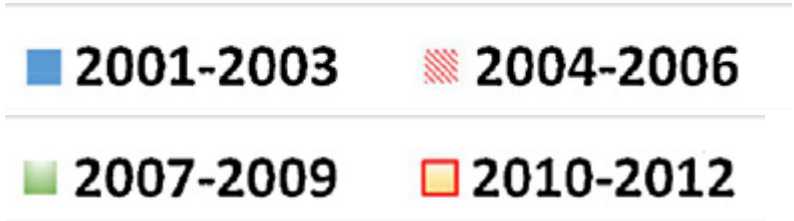
- 2005 review from North Carolina of pregnancy-related deaths found that 93% of deaths from hemorrhage were preventable
- 2002–2003 review from California reported that 69% of deaths from obstetric hemorrhage were found to have had a “good or strong chance” to alter the outcome
- 54 maternal deaths from hemorrhage between 2002-2010 (excluding Quebec)
- Maternal early warning triggers (MEWTs) widely implemented as a result

Berg CJ, et al. Obstet Gynecol 2005;106:1228–1234
California Department of Public 2011
http:// www.cdph.ca.gov/data/statistics/Documents/MO-CA-PAMR- MaternalDeathReview-2002-03.pdf
https://sogc.org/wp-content/uploads/2014/05/REVISEDMortality-EN-Final-PDF.pdf

Maternal Deaths from Hemorrhage

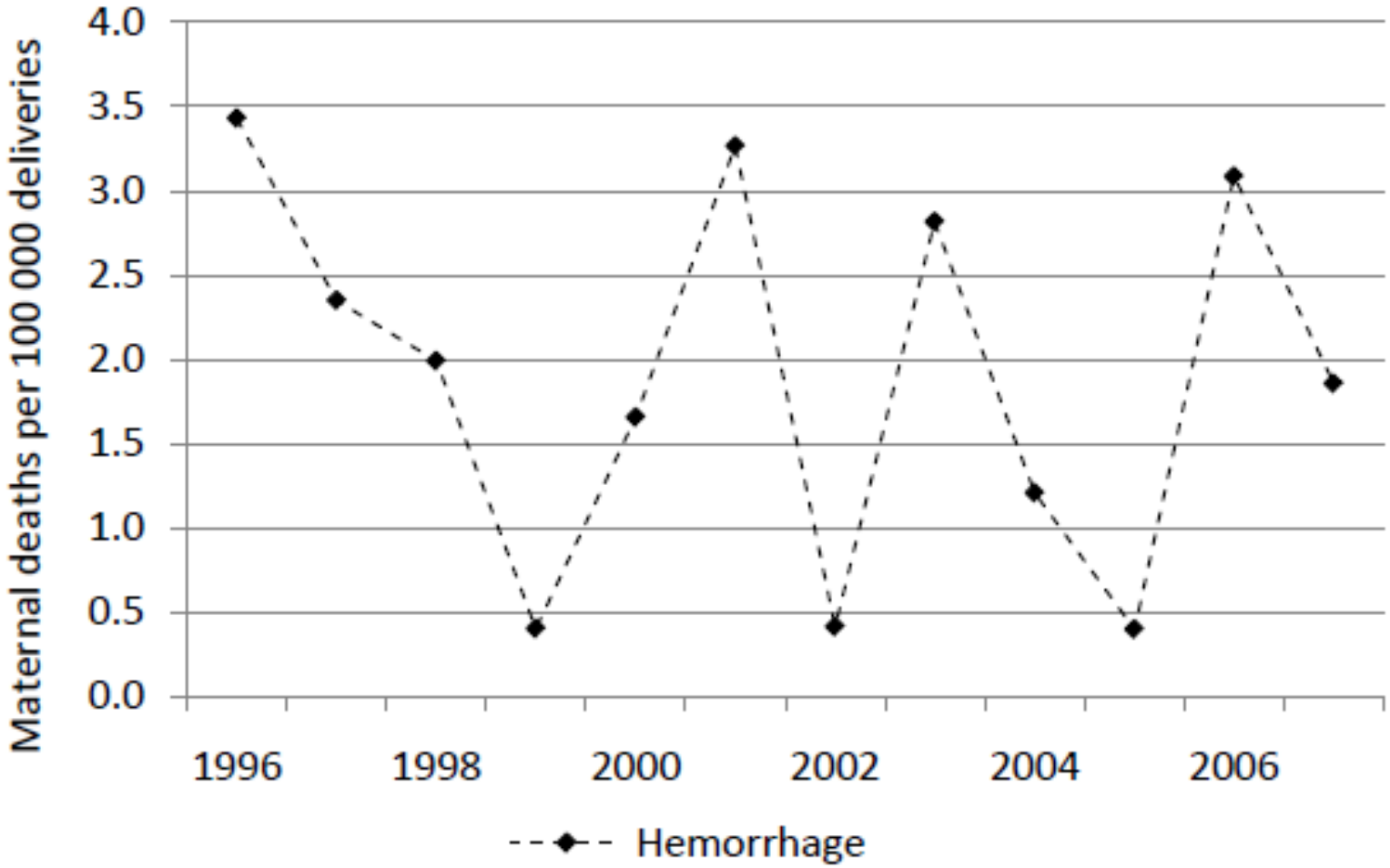


100% of deaths from hemorrhage
Attributed to suboptimal care



Gynécologie Obstétrique Fertilité & Sénologie 45S (2017) S8–S21

390,000 births per year = 3-9 preventable deaths per year (half in Ontario)



J Obstet Gynaecol Can 2011;33(10):1020-1030

1%: The end of single intervention trials?

CRASH-2

	Tranexamic acid (n=10 060)	Placebo (n=10 067)	RR (95% CI)	p value (two-sided)
Any cause of death	1463 (14·5%) **150**	1613 (16·0%)	0·91 (0·85–0·97)	0·0035
Bleeding	489 (4·9%)	574 (5·7%)	0·85 (0·76–0·96)	0·0077
Vascular occlusion*	33 (0·3%)	48 (0·5%)	0·69 (0·44–1·07)	0·096
Multiorgan failure	209 (2·1%)	233 (2·3%)	0·90 (0·75–1·08)	0·25
Head injury	603 (6·0%)	621 (6·2%)	0·97 (0·87–1·08)	0·60
Other causes	129 (1·3%)	137 (1·4%)	0·94 (0·74–1·20)	0·63

WOMAN

	Tranexamic acid group (n=10 036)	Placebo group (n=9985)	RR (95% CI)	p value (two-sided)
Bleeding	155 (1·5%) **36**	191 (1·9 %)	0·81 (0·65–1·00)	0·045
Pulmonary embolism	10 (0·1%)	11 (0·1)	0·90 (0·38–2·13)	0·82
Organ failure	25 (0·3%)	18 (0·2%)	1·38 (0·75–2·53)	0·29
Sepsis	15 (0·2%)	8 (0·1%)	1·87 (0·79–4·40)	0·15
Eclampsia	2 (0·02%)	8 (0·1%)	0·25 (0·05–1·17)	0·057
Other	20 (0·2%)	20 (0·2%)	0·99 (0·54–1·85)	0·99
Any cause of death	227 (2·3%)	256 (2·6%)	0·88 (0·74–1·05)	0·16

THE T^7 FOR MASSIVE HEMORRHAGE

- The goal of the MHP is to put in place a protocol to ensure massively hemorrhaging patients receive state-of-the-art care to achieve the best possible outcomes (based on the best available science at the time of creation)
- Uniform, high quality, standardized care
- Not just an order for 1:1:1

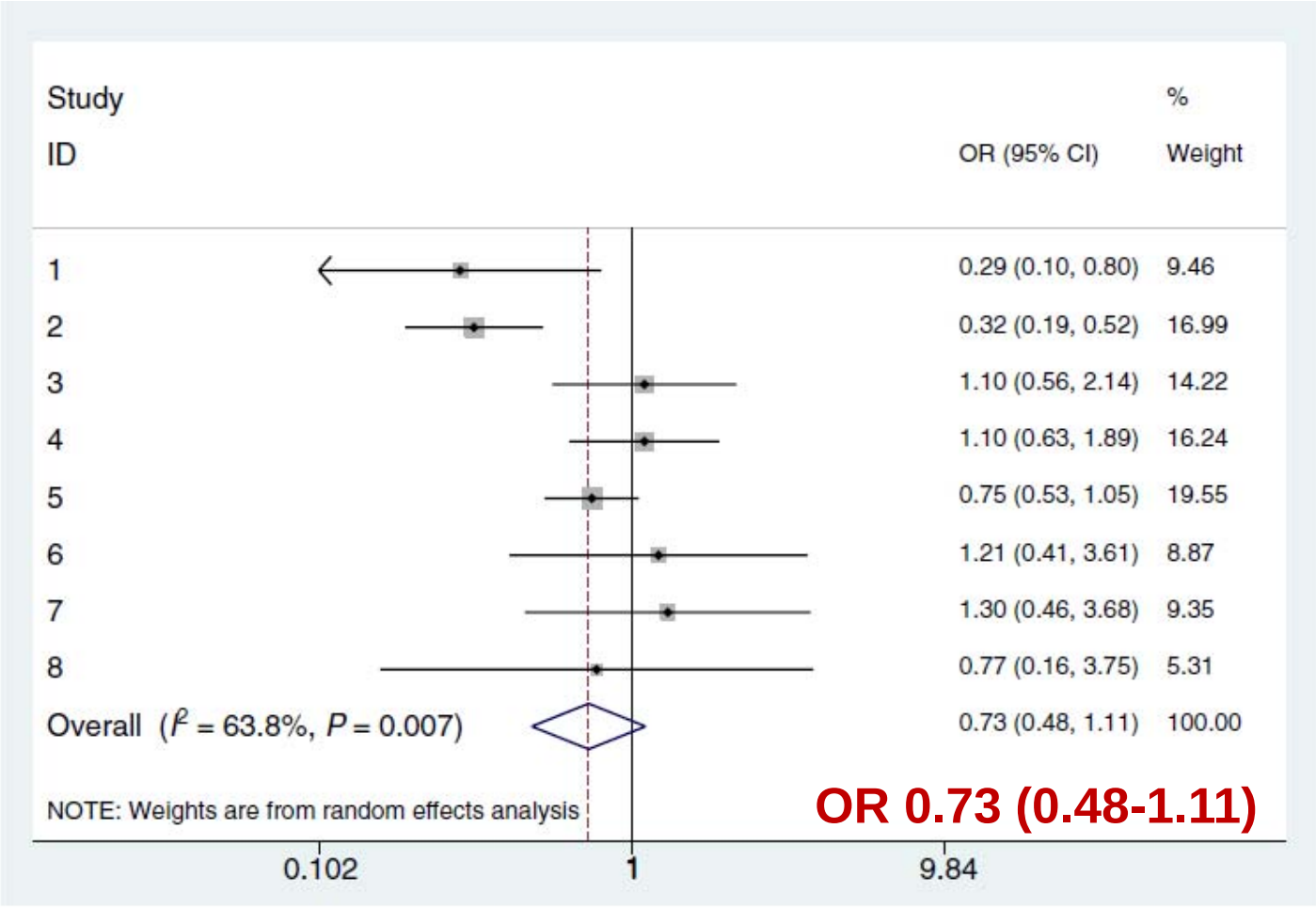
T^7 STOP THE BLEEDING!

	T	
1	Triggering	**Minimize underactivation**
2	Team	**Mobilize sufficient personnel for MHP adherence**
3	Testing	**Group & Screen complete, rest q1h minimum**
4	TXA	**Fast and high degree of compliance**
5	Temperature	**Monitored and kept over 36ºC**
6	Transfusion	**Minimize over and under transfusion**
7	Termination	**Eliminate blood wastage**

Where are we without a Provincial MHP?

	T	
1	Triggering	**35% no MHP, 10 different names**
2	Team	**Limited number of responders, 34% no porter**
3	Testing	**64% do not use lab testing to guide, 34% don't do fibrinogen**
4	TXA	**30% do not include TXA**
5	Temperature	**35% don't require temp monitoring**
6	Transfusion	**41% don't guide Rx reversal; 39% no predefined ratio**
7	Termination	**27% no RBC transport container used**

Systematic review, 8 adult trials (n=1586), compared to historical controls, no change in ratios, no change in outcomes, compliance not reported



ANZ J Surg 83 (2013) 918–923

Same selection criteria, different studies selected (n=1149 patients)

Study or Subgroup	MTP/DCR Events	MTP/DCR Total	No MTP/DCR Events	No MTP/DCR Total	Weight	Odds Ratio M-H, Random, 95% CI
Campion 2013 (38)	27	99	42	117	18.2%	0.67 [0.37, 1.20]
Cotton 2009 (14)	54	125	88	141	21.2%	0.46 [0.28, 0.75]
Duchesne 2010 (39)	19	72	56	124	16.7%	0.44 [0.23, 0.82]
O'Keeffe 2008 (13)	69	132	23	46	15.7%	1.10 [0.56, 2.14]
Riskin 2009 (40)	7	37	18	40	8.9%	0.29 [0.10, 0.80]
Shaz 2010 (41)	63	132	42	84	19.3%	0.91 [0.53, 1.58]
Total (95% CI)		**597**		**552**	**100.0%**	**0.61 [0.43, 0.87]**
Total events	239		269			

Heterogeneity: $Tau^2 = 0.09$; $Chi^2 = 9.58$, df = 5 (P = 0.09); $I^2 = 48\%$

Test for overall effect: Z = 2.72 (P = 0.006)

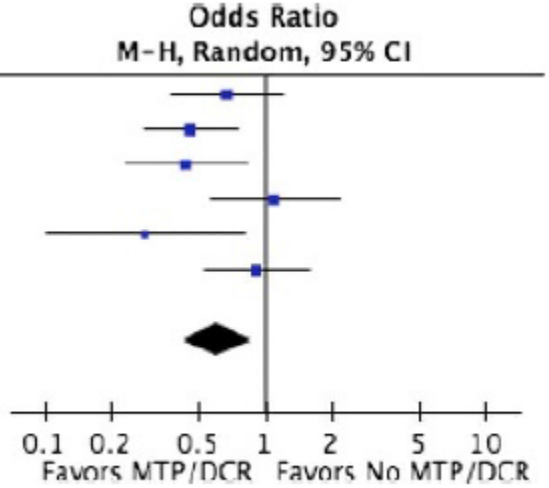


Figure 2. Forest plot for MT/DCR protocol vs no MT/DCR protocol; outcome = mortality.

OR 0.62 (0.43-0.87)

Mortality 49% without MHP vs 40% with MHP

Cannon JW, et al. J Trauma Acute Care Surg 2017; 82: 605-617

PPH - Only lab outcomes improved

Lab parameter	Period 1	Period 3	p
Lowest pH	7.23 (7.14-7.34)	7.35 (7.30-7.40)	<0.001
pH<7.32	67%	7%	<0.001
Lowest temp	35.2 (35.0-35.4)	36.4 (36.0-36.6)	<0.001
Coagulopathy (abnormal & bleeding requiring components)	58%	13%	<0.001

- No difference in clinically significant outcomes, morbidity, and mortality (but likely numbers too small – total of 44,782 births in periods 1 and 3)

Skupski DW, Brady D, Lowenwirt IP, et al. Obstet Gynecol 2017; 130: 770-7.

National MHP: Singapore

- Implemented a standardized MHP in all publically funded major hospitals in Singapore in October 2011
- Multidisciplinary team for assistance with the MHP build
- Collected standardized data on 434 MHP activations
  - 39% trauma, 30% surgical, 25% GI bleeds, 6% PPH
- No data collected on compliance or outcomes
- Major finding: overactivation at hospitals without trauma (66% of activations at non-trauma needed only the 1st pack of 4 RBC; vs. only 27% of the trauma centres and 37% of the obstetric hospital)

Chay J, et al. Vox Sang 2016; 110: 36-50

National pre-hospital code red protocol (Scotland)

- Activation criteria bleeding, BP<90 mmHg, and unresponsive to fluid boluses
- Activation resulted in a call to the trauma room RN who ensured 4 units of O-negative RBCs in ER and to get blood bank to prepare 4 more O-negative red cells, 4 AB plasma, and 1 platelet
- Medics had access to O-negative red cells for use during transport
- Time from 999 call to code red was 70 minutes
- Activation to hospital arrival was 25 minutes
- 71% were administered pre-hospital tranexamic acid
- 89% transfused 1 unit+ or hemorrhagic death; 11% received 10+ RBC

Reed MJ, et al. Injury 2017; 48: 41-46

Compliance associated with better survival

TABLE 4. Outcomes and Blood Utilization by Compliance

	Compliant (n = 34)	Noncompliant (n = 91)	*p*
24-h survival (%)	88.2 ± 5.5	61.5 ± 5.1	0.004
30-d survival (%)	86.7 ± 5.6	45.0 ± 5.2	<0.001
TEP cycles used	2.07 ± 1.0	2.28 ± 1.1	0.605
24-h RBC units	13.7 ± 1.3	19.5 ± 1.2	0.012
24-h plasma units	9.3 ± 0.7	10.7 ± 0.8	0.301
24-h platelets	4.1 ± 0.7	3.6 ± 0.7	0.372

Values are presented as mean ± SD.

Cotton BA, et al. J Trauma 2009; 67; 1004-1012

Compliance associated with better outcomes

Table 5
Comparison of compliance by mortality.

Protocol criteria	Non-survivors $N=34$ (% compliance)	Survivors $N=38$ (% compliance)
Was MTP activation based on the pre-specified indications?	30 (88%)	29 (76%)
Timely communication with blood bank (<15 min from arrival)?	14 (41%)	22 (58%)
Were group and screen sent?	29 (85%)	38 (100%)
Was haemorrhage panel sent?	2 (6%)	1 (3%)
Was there MTP-based administration of blood products?	16 (47%)	22 (58%)
Hypothermia corrected?	15/23 (65%)	34 (90%)
Acidosis corrected?	23/23 (100%)	37 (97%)
rFV11a given according to MTP?	2/2 (100%)	1/2 (50%)
ABG, lytes, CBC, INR, FN measured?	1/23 (4%)	7 (18%)
Was wastage of blood products prevented?	31 (91%)	37 (97%)
Timely MTP de-activation?	14 (41%)	22 (58%)
K measured?	19/23 (83%)	32 (84%)
Ca measured?	12/23 (52%)	30 (79%)
Average compliance	62%	70%

Bawazeer M et al. Injury 2015; 46: 21-28.

Measurement of temperature
n=495, 61% had a temperature done in the ER

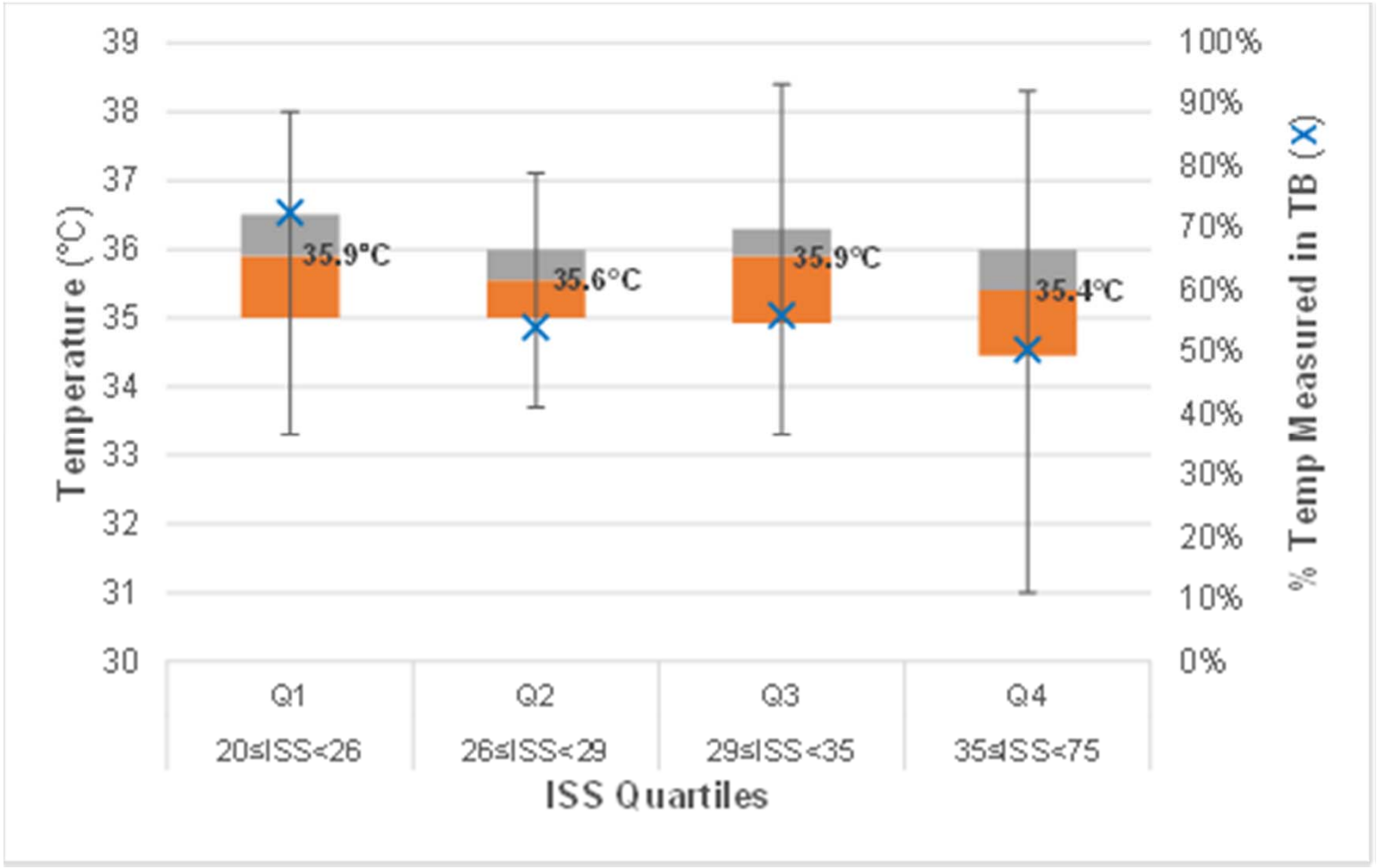
Table 3
Independent factors for in-hospital mortality in a multivariable analysis.

Variables	OR(95% CI)	P-value
No Temperature in TB	2.86 (1.64–4.99)	<0.001
No Temperature in the OPR	4.66 (2.50–8.69)	<0.001
Age >59 years	3.53 (1.95–6.39)	<0.001
ISS Score >=20	1.05 (1.03–1.08)	<0.001
INR > 1.3	4.03 (2.29–7.08)	<0.001

FAILURE TO MEASURE THE TEMPERATURE OCCURRED ACROSS THE WHOLE INJURY SEVERITY SCORE SPECTRUM

Alam A, et al. Injury Int J Care Injured 2018; 49: 117-123

It doesn't appear that the severity of the injury (chaos) is driving this

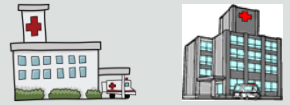
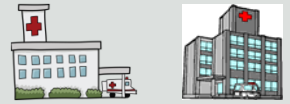


Personal communication, Asim Alam

Goals for today, tomorrow & 2018

- Today:
  - Presentations to review the literature behind most aspects of massive hemorrhage protocols (all types of hemorrhage)
  - Open and collegial discussion regarding the optimal transfusion support of bleeding patients
  - Be willing to give and take as we agree to harmonize
  - Primary focus on adults as very few of us have any experience with <14 year olds
- Tomorrow:
  - Smaller group will be continuing with a modified Delphi exercise to come to consensus on the key parts of the Provincial MHP
  - Plan: approximately 43 practice recommendations and 7 QI metrics
  - Stakeholder open review process
- 2018:
  - Build a multipart Provincial toolkit for MHP with policies, procedures, checklists, forms, training material, simulation exercises, quality metrics, on-line data entry portal for outcome reporting

One size will never fit all

	T	
1	Triggering	
2	Team	Smaller = more education, team building, simple
3	Testing	Standard tests, consider simple POCT
4	Tranexamic acid	
5	Temperature	
6	Transfusion	“European” strategy, clear transfer of care
7	Termination	

Review

1. Is there room for saving lives?
   - **Yes maybe 1%**
2. Problems that arise from lack of coordinated and standardized protocol across Ontario
   - **Multiple problems across all the 7Ts**
3. Do MHPs work?
   - **I “believe” so**
4. Experience from other jurisdictions that have implemented regional MHPs
   - **Not much out there**
5. The goals for today & long-term plan for Ontario
   - **Speak up – now is our chance to build the most comprehensive MHP on the planet**