Acute Traumatic Coagulopathy
Implication to Massive Transfusion Protocol for Trauma And Intensive Care Management

Dr. Lai Kang Yiu
Intensive Care Unit
Queen Elizabeth Hospital


The Story Begins
Transfusion Protocol for Trauma
2003

Worldwide, 1 in 7 deaths is due to injury, and this is expected to rise to 1 in 5 in the next 15 years, despite advances in resuscitation, trauma surgery, and critical care.

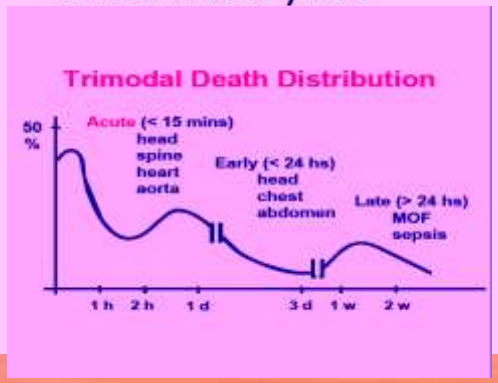
Injury Chart Book

Geneva: World Health Organization **2003**

Trauma

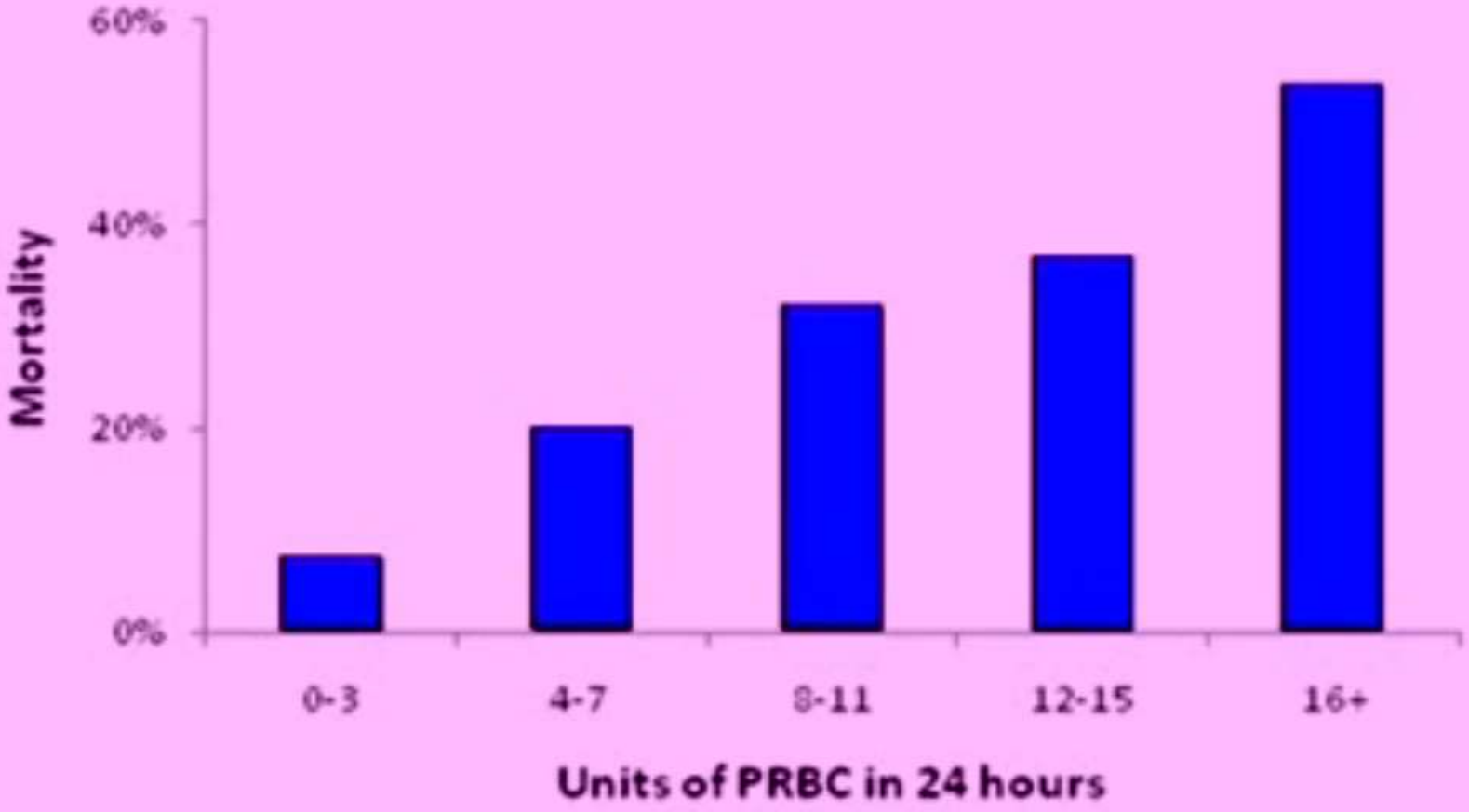
- Injury is the leading cause of death worldwide in those age 5-44 years
- 5 million people die from trauma world wide each year

Timing and mechanism of traumatic death.



Trimodal Death Distribution

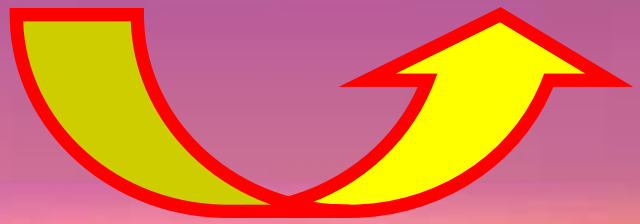
Haemorrhage is the major potentially treatable cause of death in the initial 24 hours



Massive blood transfusion (> 10U of PRBC w/i 24 hoursand not accounting for other blood component therapy), carries a mortality rate between 20-50%, with most patients dying within 6-12 hours of hospital arrival.

Independent Predictors of Trauma Mortality

- **Severity of Injury**
- **Shock with tissue hypoperfusion**
- **Acute Trauma Coagulopathy**



Massive Blood Loss

- **Replacement of patient's blood volume within 24 hours**
- **Transfusion of more than 10 units of red cells in 24 hours**
- **Replacement of more than 50% of the patient's blood volume in 3 hours**
- **Blood loss more than 150 mL/ minute in an adult**

- **Activation of the anticoagulant protein C pathway by elevated thrombomodulin**
- **Hyperfibrinolysis**

American College of Surgeons Classification of Acute Hemorrhage

Class	I	II	III	IV
Blood loss (ml)	<750	750-1,500	1,500-2,000	≥ 2,000
% Blood volume lost	<15%	15-30%	**30-40%**	**≥ 40%**
Pulse rate	<100	>100	**>120**	**≥ 140**
Blood pressure	Normal	Normal	**Decreased**	**Decreased**
Pulse pressure (mmHg)	Normal or increased	Decreased	Decreased	Decreased
Capillary refill	Normal	Delayed	Delayed	Delayed
Respiratory rate	14-20	20-30	30-40	>45
Urine output	>30	20-30	5-15	Negligible
Mental status	Slightly anxious	Mildly anxious	Anxious confused	Confused, lethargic
Recommended fluid replacement	0.9% saline, 3:1	0.9% saline, 3:1	0.9% saline + red cells	0.9% saline + red cells

Estimation of Blood Volume Deficit in Trauma

Unilateral hemothorax	3000ml
Hemoperitoneum with abdominal distension	2,000–5,000 ml
Full-thickness soft tissue defect 5 cm3	500ml
Pelvic fracture	1500-2000 ml
Femur fracture	800-1200 ml
Tibia fracture	350-650 ml
Smaller fracture sites	100-500 ml

ATLS Resuscitation Protocol
A standard since 1985

- Start **two large bore IVs**
- **Give 2 L of crystalloid if SBP < 100**
- Start RBC if SBP is still <100
- Start RBC if SBP normalizes and falls again
- Start RBC if bleeding is > 100 mL/min
- Continue RBC as long as above
- **Give fresh frozen plasma if INR > 1.5**
- **Give platelets if < 50 x 10^9/L**
- **Give cryoprecipitate if fibrinogen < 1g/L**

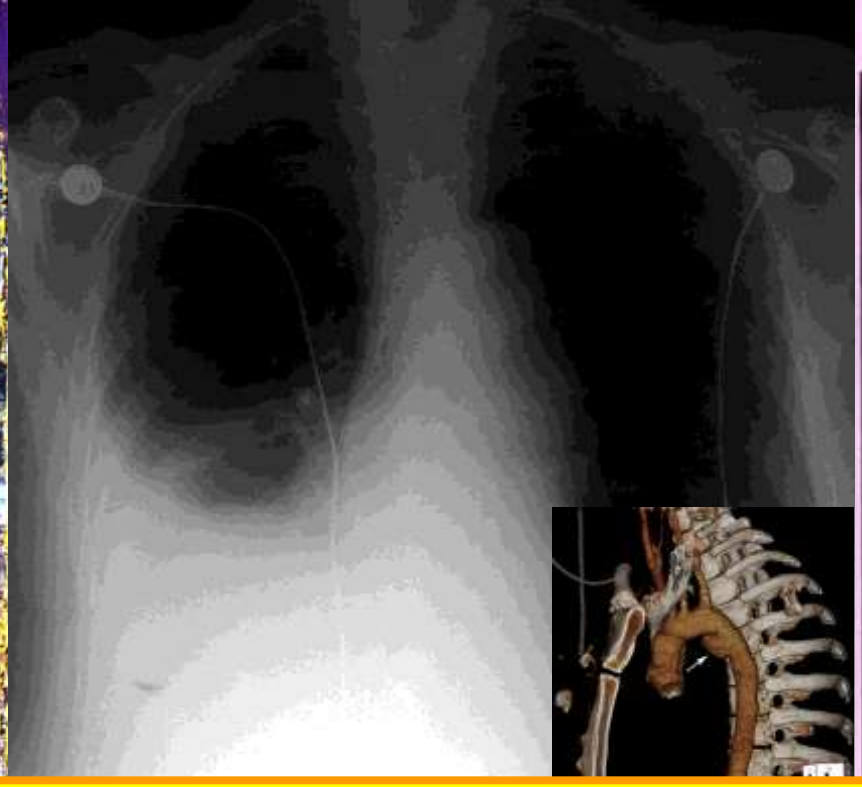
CATHETER	RATE OF FLOW
Peripheral:	(cc/min)
IV tubing	220
14 gauge	175-200
16 gauge	100-150
Central:	
Introducer	250
14 gauge	150
16 gauge	50-100

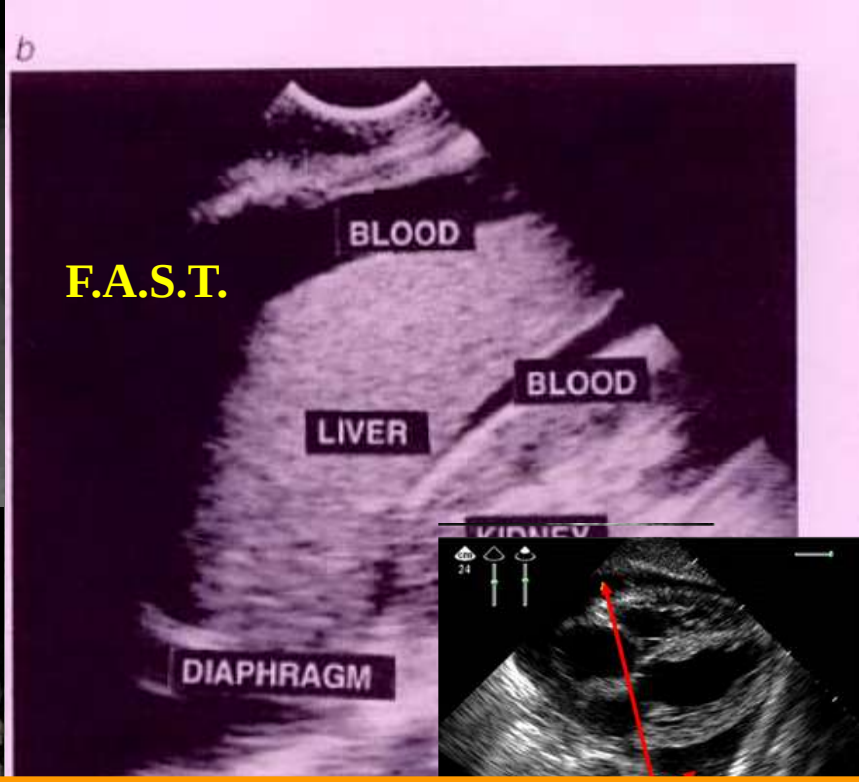
Based on 3:1 rule when using crystalloids

Responses to Initial Fluid Resuscitation*

	Rapid Response	Transient Response	No Response
Vital Signs	Return to normal	Transient improvement; recurrence of ↓BP and ↑HR	Remain abnormal
Estimated Blood Loss	Minimal (10% - 20%)	Moderate and ongoing (20% - 40%)	Severe (> 40%)
Need for More Crystalloid	Low	High	High
Need for Blood	Low	Moderate - high	Immediate
Blood Preparation	Type and crossmatch	Type-specific	Emergency blood release
Need for Operative Intervention	Possibly	Likely	Highly likely
Surgical Consultation	Yes	Yes	Yes

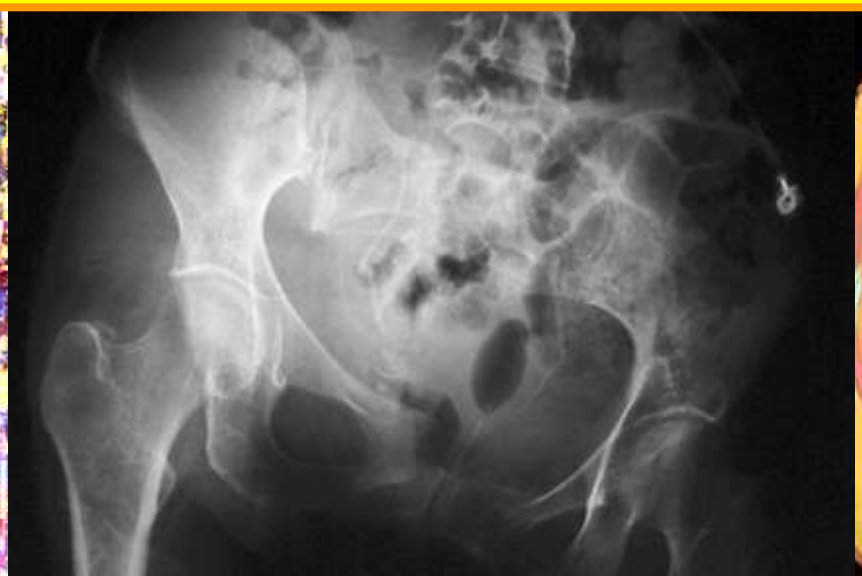
*2000 mL Ringer's lactate in adults, 20 mL/kg Ringer's lactate in children, over 10 to 15 minutes.

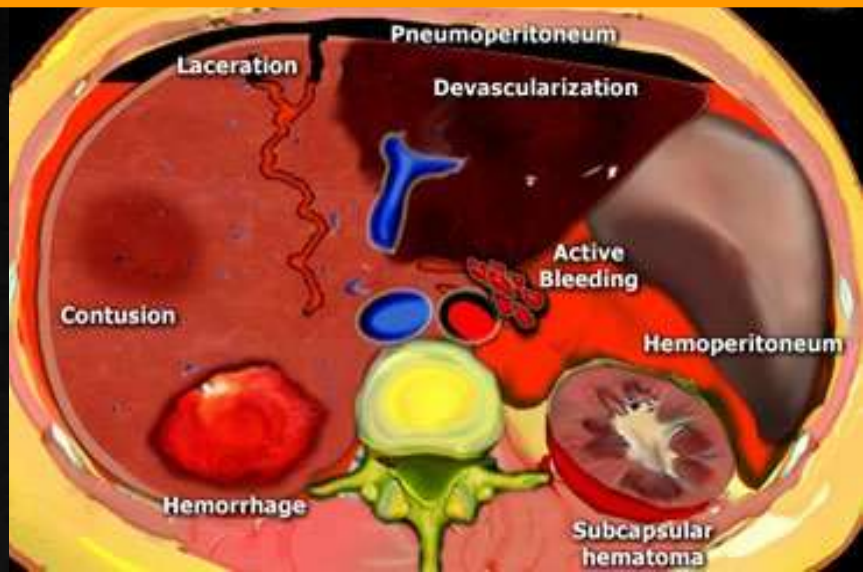


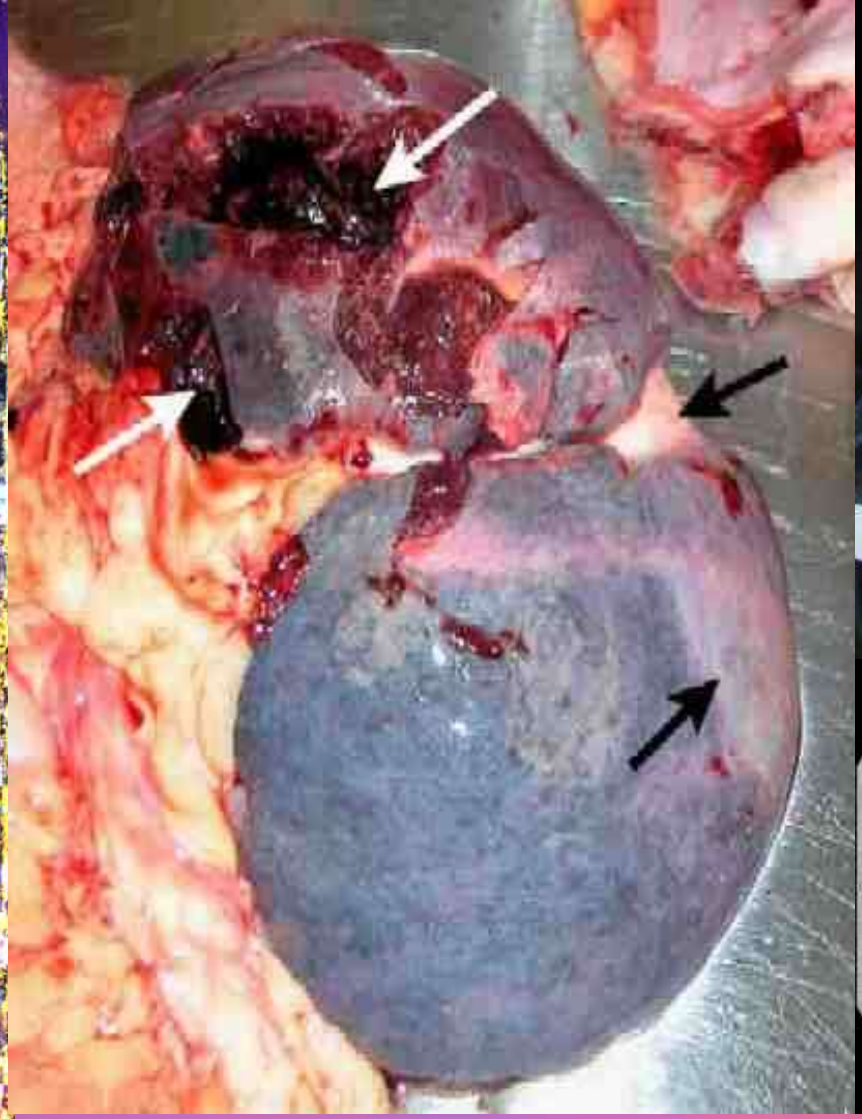


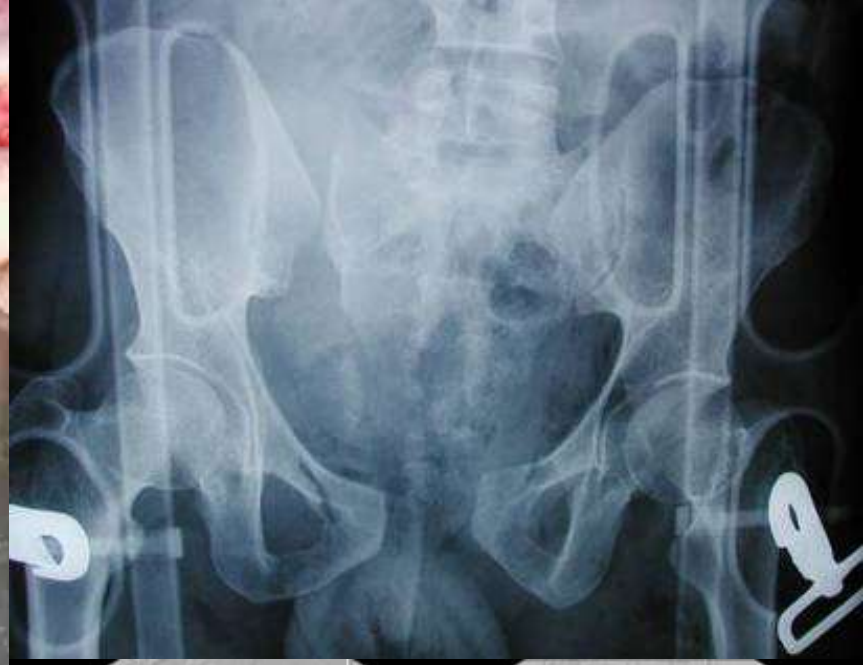
F.A.S.T.

Control External Bleeding + Diagnostic Adjunct to locate source of internal bleeding



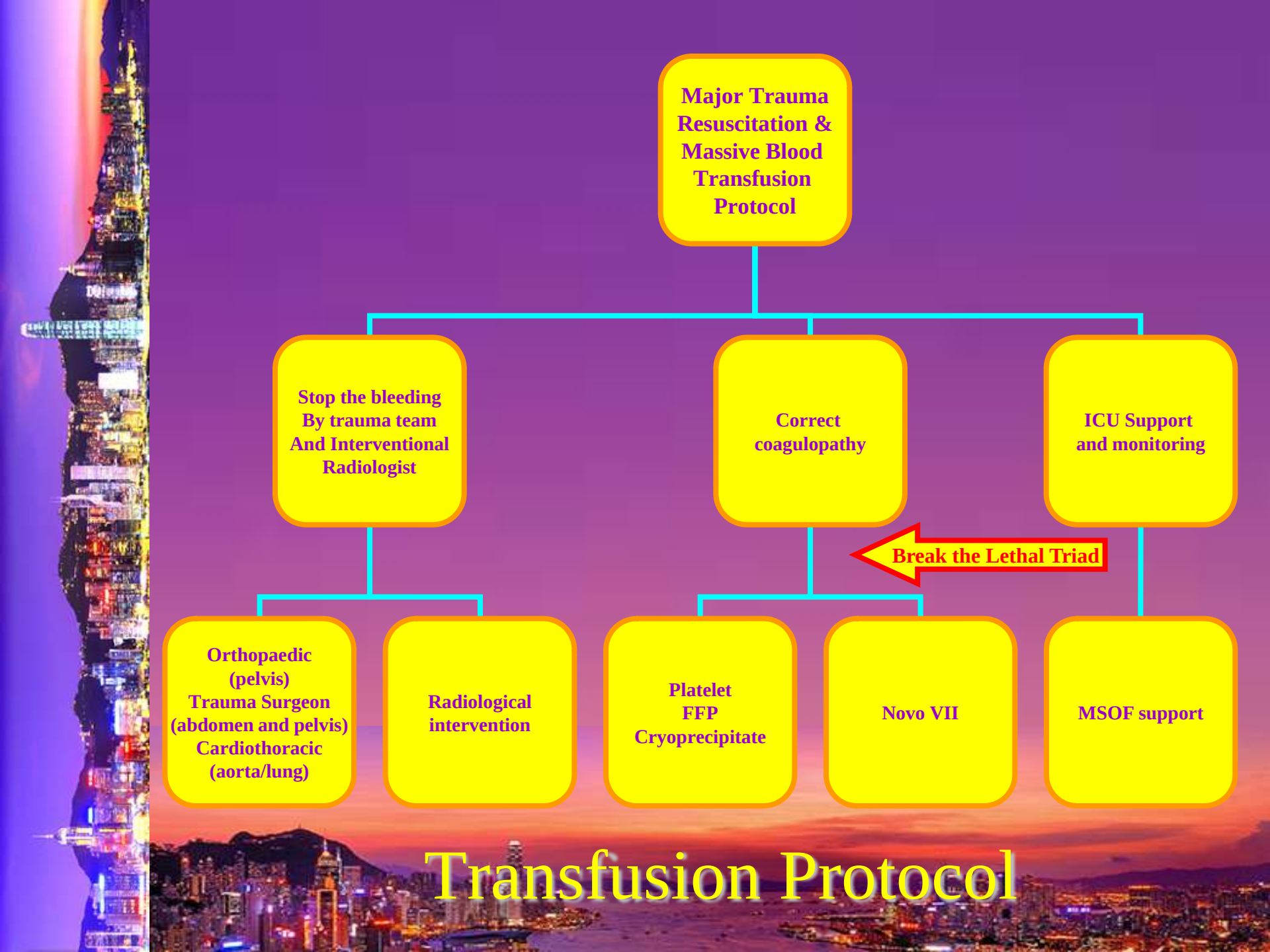






Emergency Laparotomy

External fixation
Pelvic Selective Embolization

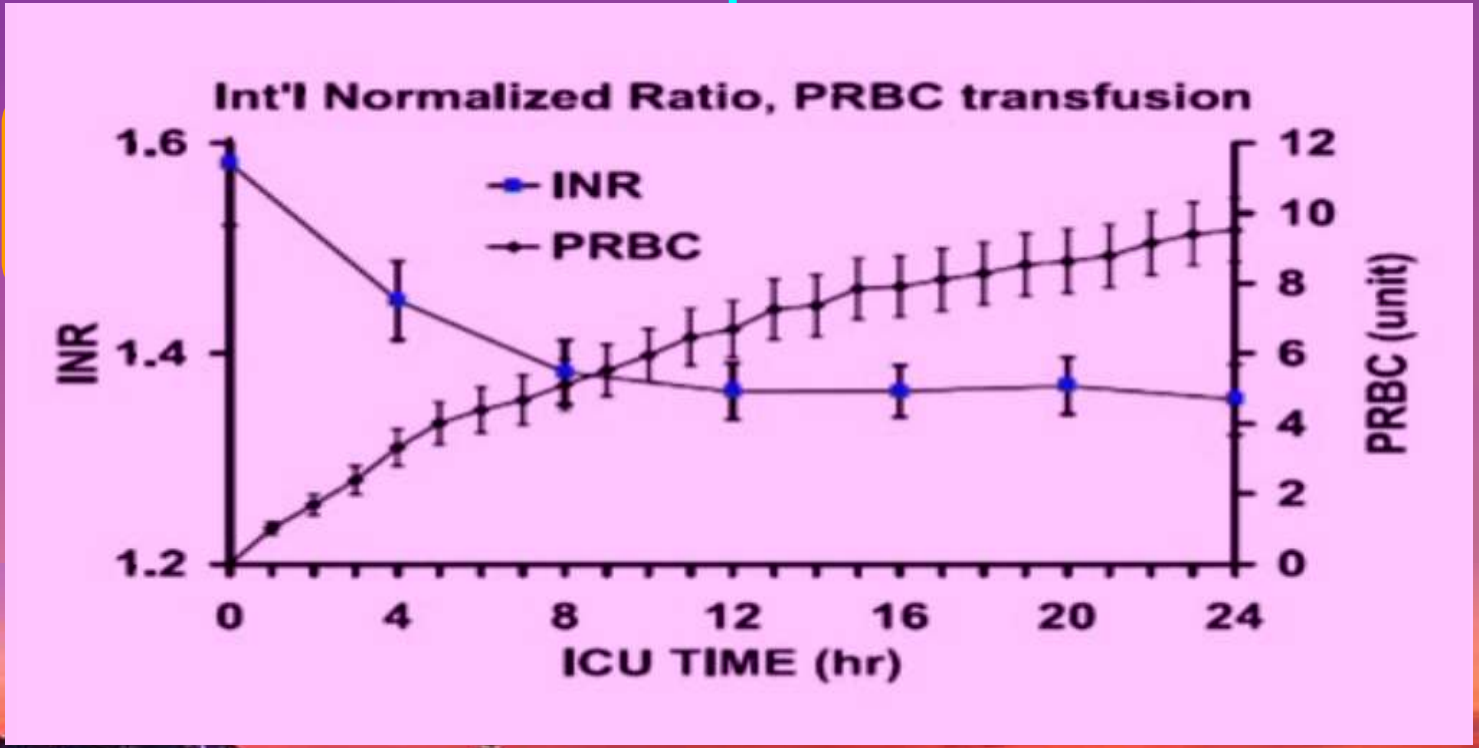

Major Trauma Resuscitation & Massive Blood Transfusion Protocol
Stop the bleeding By trauma team And Interventional Radiologist
Correct coagulopathy
ICU Support and monitoring
Break the Lethal Triad
Orthopaedic (pelvis) Trauma Surgeon (abdomen and pelvis) Cardiothoracic (aorta/lung)
Radiological intervention
Platelet FFP Cryoprecipitate
Novo VII
MSOF support
Transfusion Protocol

Clinical Strategies to Reduce Complications of Transfusion Therapy

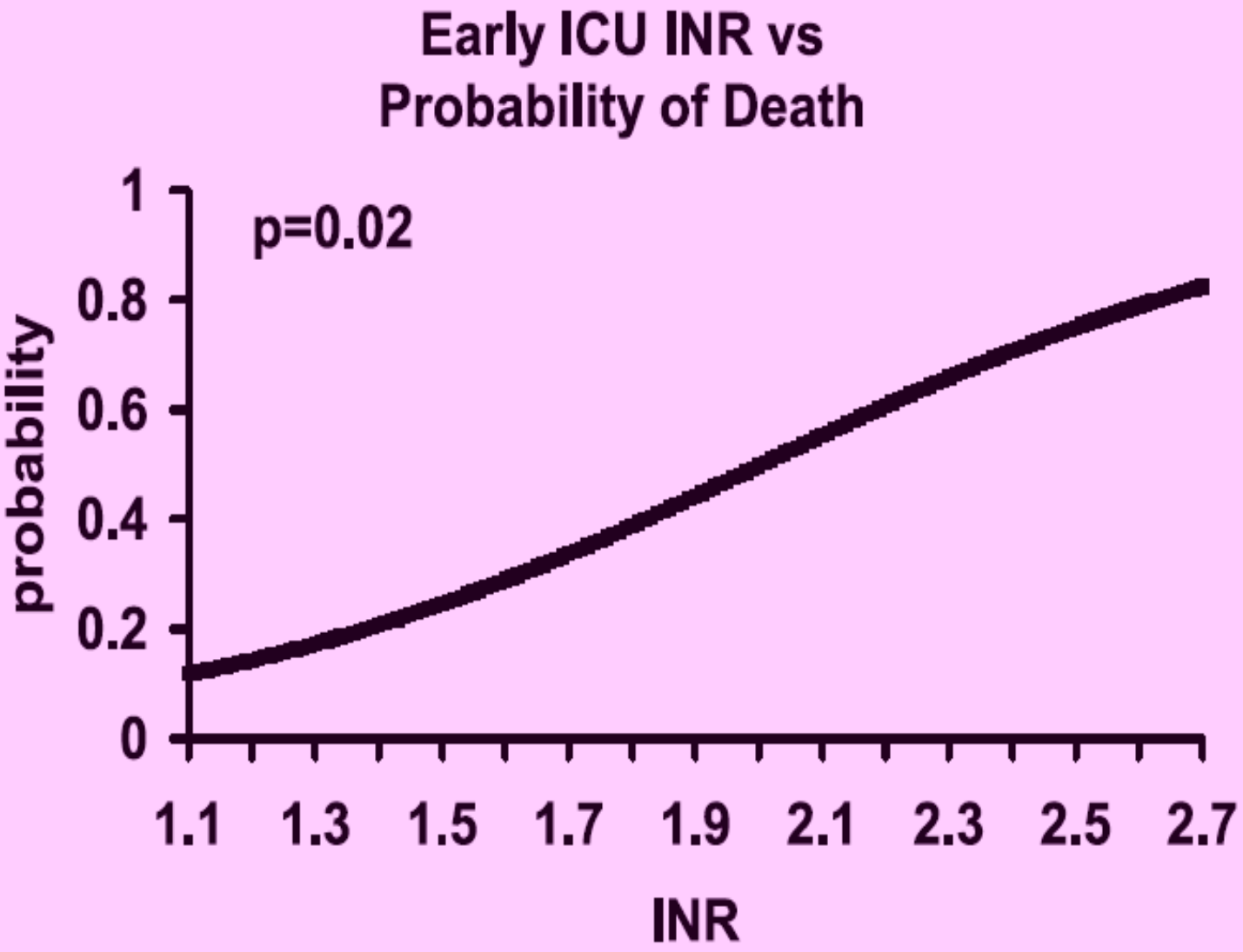
Complication	Clinical Strategies to Reduce Complication
Impaired oxygen release from Hb	Warm all blood. Avoid alkalosis. Maintain normothermia (core temperature 36-37°C)
Dilutional coagulopathy	Fresh frozen plasma for PT>1.5 x normal and clinically excessive bleeding. Platelets for thrombocytopenia <75,000/μl and clinically excessive bleeding.
Hypothermia	Warm all IV fluids and blood. Warm room >28°C. Convective warming. Humidify all inspired gases.
Decreased ionized calcium	Treat with calcium chloride, 20 mg/kg, insetting of massive transfusion and hypotension
Hyperkalemia	Monitor ECG and treat with calcium chloride, 20 mg/kg, if hemodynamically significant. Otherwise, monitor and treat with glucose and insulin and/or bicarbonate.
Hemolytic transfusion reaction	Check and recheck every donor unit. Once occurred, stop transfusion and maintain systemic perfusion and renal blood flow. Alkalinize urine. Watch for DIC. Send suspected unit to blood bank for crossmatch.
Infection	Lower transfusion trigger. Red cell salvage. Avoid indiscriminate platelet transfusions. Oxygen-carrying red blood cell substitutes.
Transfusion-induced immunosuppression	Lower transfusion trigger. Red cell salvage, oxygen-carrying red blood cell substitutes. Third-generation leukocyte filters.

A&E Department INR 1.8

ICU Admission INR 1.6



Fresh frozen plasma should be given earlier to patients requiring massive transfusion
GONZALEZ Ernest A. The Journal of trauma, injury, infection, and critical care 2007, vol. 62, no1, pp. 112-119



Fresh frozen plasma should be given earlier to patients requiring massive transfusion

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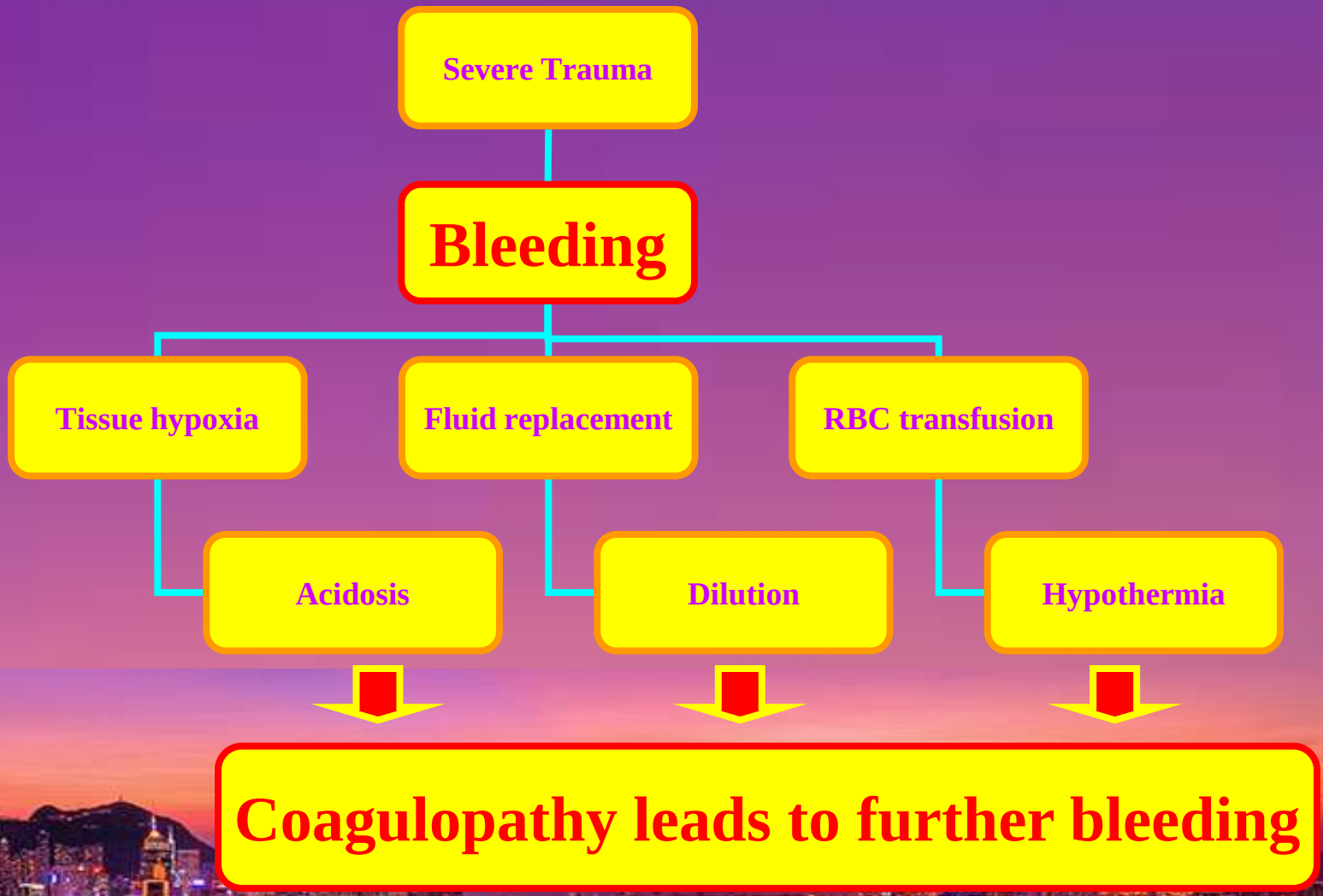
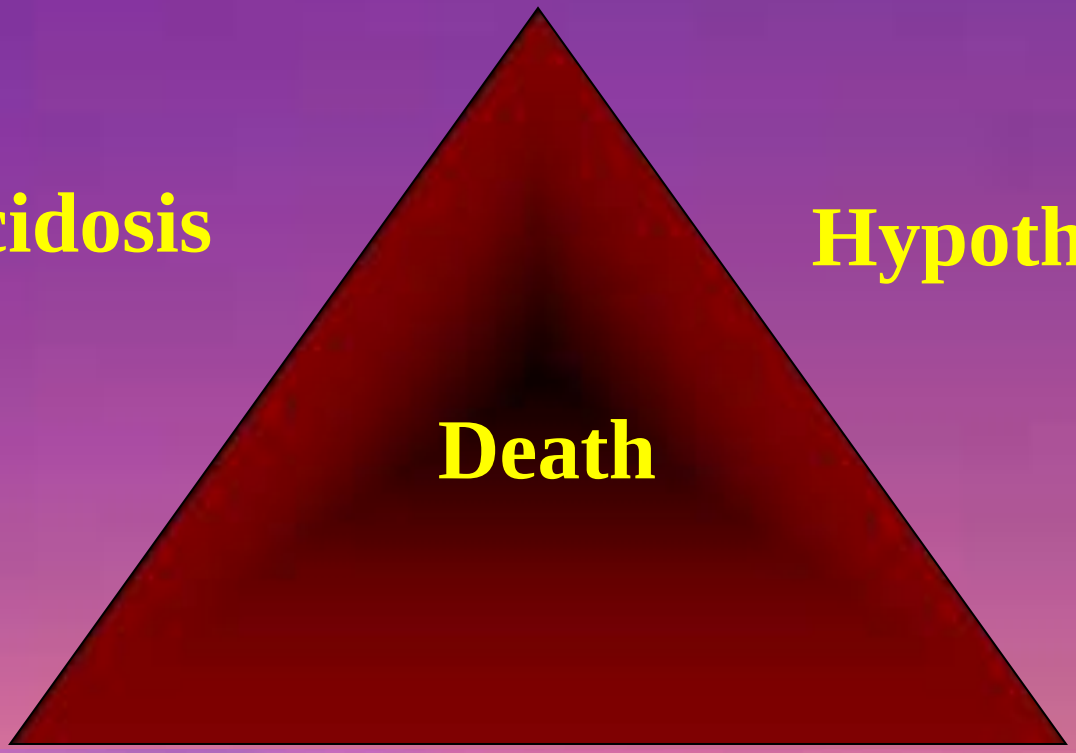
The Lethal Triad of Massive Blood Transfusion During Trauma



The Lethal Triad



If this “lethal triad“ is present ..... surgical control of bleeding is unlikely to be successful!

Acidosis

Base deficit (BD) ≥ 6 identifies patients that

- require early transfusion,
- increased ICU days and
- risk for ARDS and MOF

- BD of ≥ 6 is strongly associated with the need for MT and mortality in both civilian and military trauma.
- Patients have an elevated BD **before** their blood pressure drops to classic "hypotension" levels.
- Acidosis contributes more to coagulopathy more than hypothermia (**not reversible**)
  - Xa-Va complex activity reduced:

pH:	
7.2	50%
7.o	70%
6.8	90%

Temperature

- A temperature < 96˚F or 35˚C is associated with an increase in mortality.
- Trauma patients that are hypothermic are not perfusing their tissue
- The coagulation cascade is an enzymatic pathway that degrades with temperature and ceases at 92 F (33.3C)
  - Reduces activity of clotting factors by 50% at 34 C
  - Platelet activation almost eliminated at 30 C

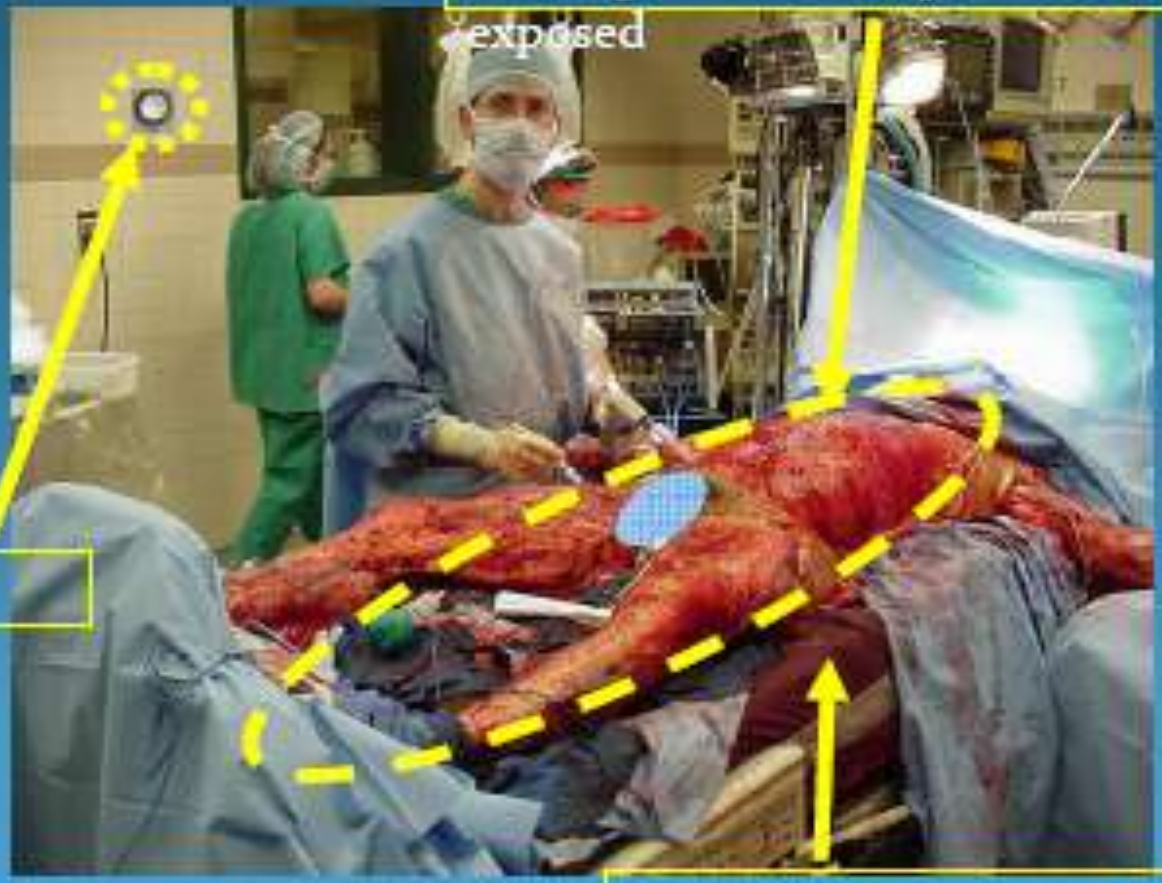
Rate of Heat Transfer

Gentilello LM. In: Maull KI, et al, eds. *Advances in Trauma and Critical Care*. Vol 9. St Louis, MO: Mosby; 1994:39-79.

Rewarming Technique	Heat Transfer (kcal/hr)
Airway rewarming	8-12
Overhead radiant warmer	17
Heating blankets	20
Convective warmers	15-26
Body cavity lavage	36
Continuous arteriovenous rewarming	92-139
Cardiopulmonary bypass	710

$$Q=mc(T2 - T1)$$

Problems...

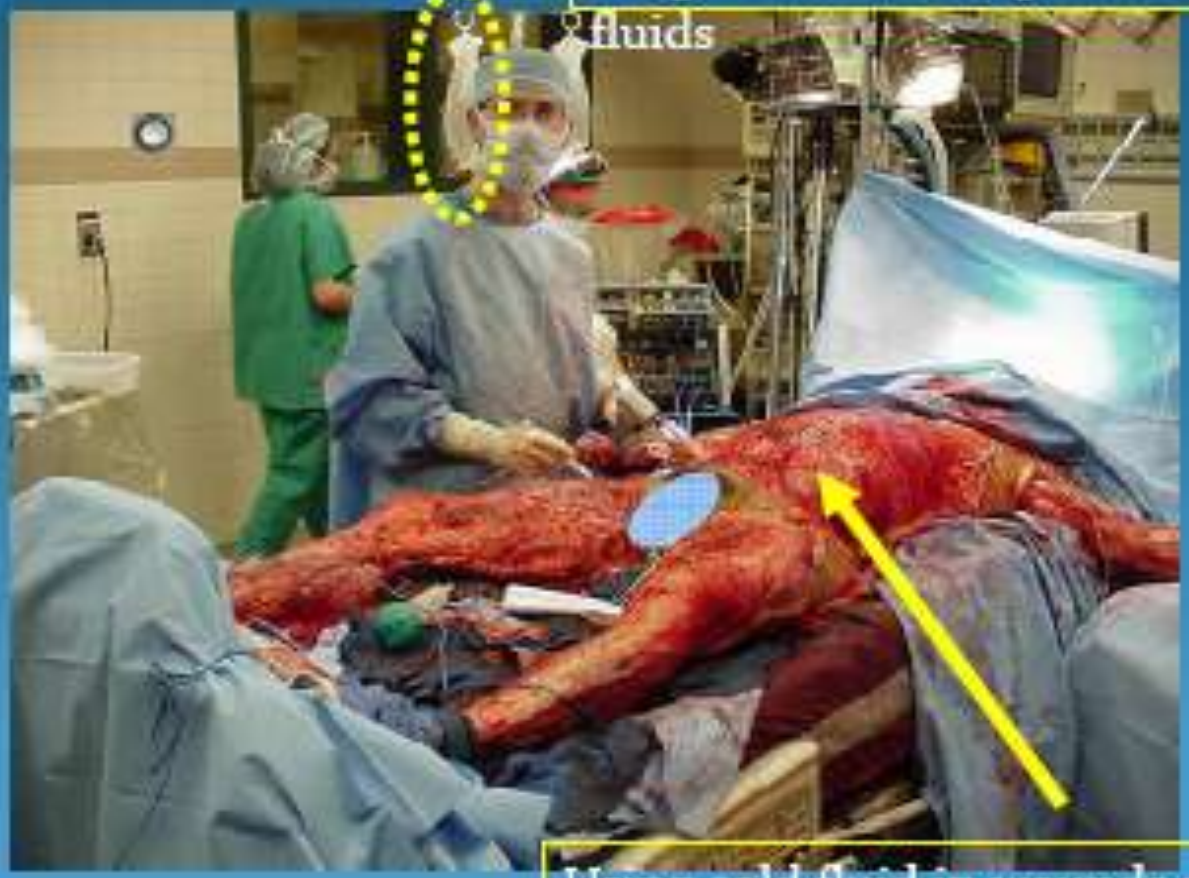


Sherry Porter Biddy Chang Sunnybrook Health Sciences Centre

Prevention Is Better Than Cure

Sunnybrook

Problems...



Sherry Porter Biddy Chang Sunnybrook Health Sciences Centre

Prevention Is Better Than Cure

Sunnybrook

Better...

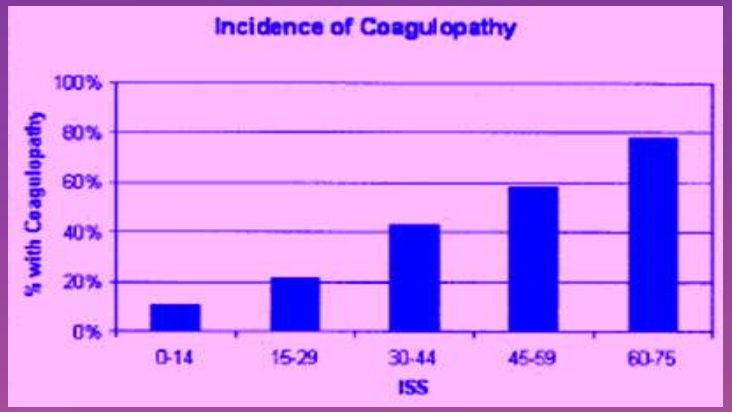
- Adjust thermostat to warm up the room
- Limit patient exposure and passive heat loss
  - cover as much as possible (from the start)
  - reduce area exposed as operation permits
  - place on dry sheets (wet sheets causes heat loss)

Sherry Porter Biddy Chang Sunnybrook Health Sciences Centre

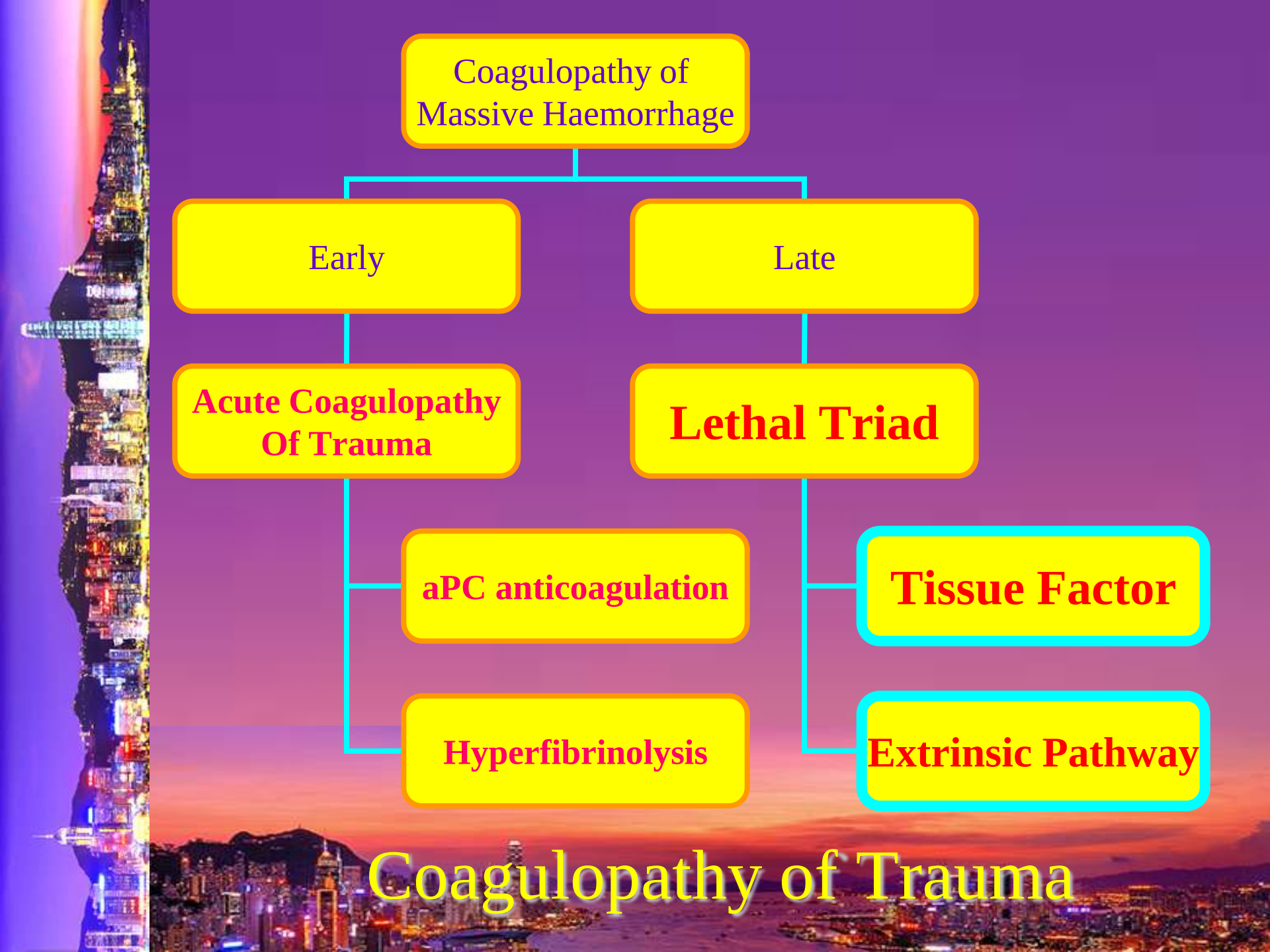
Prevention Is Better Than Cure

Coagulopathy and Trauma

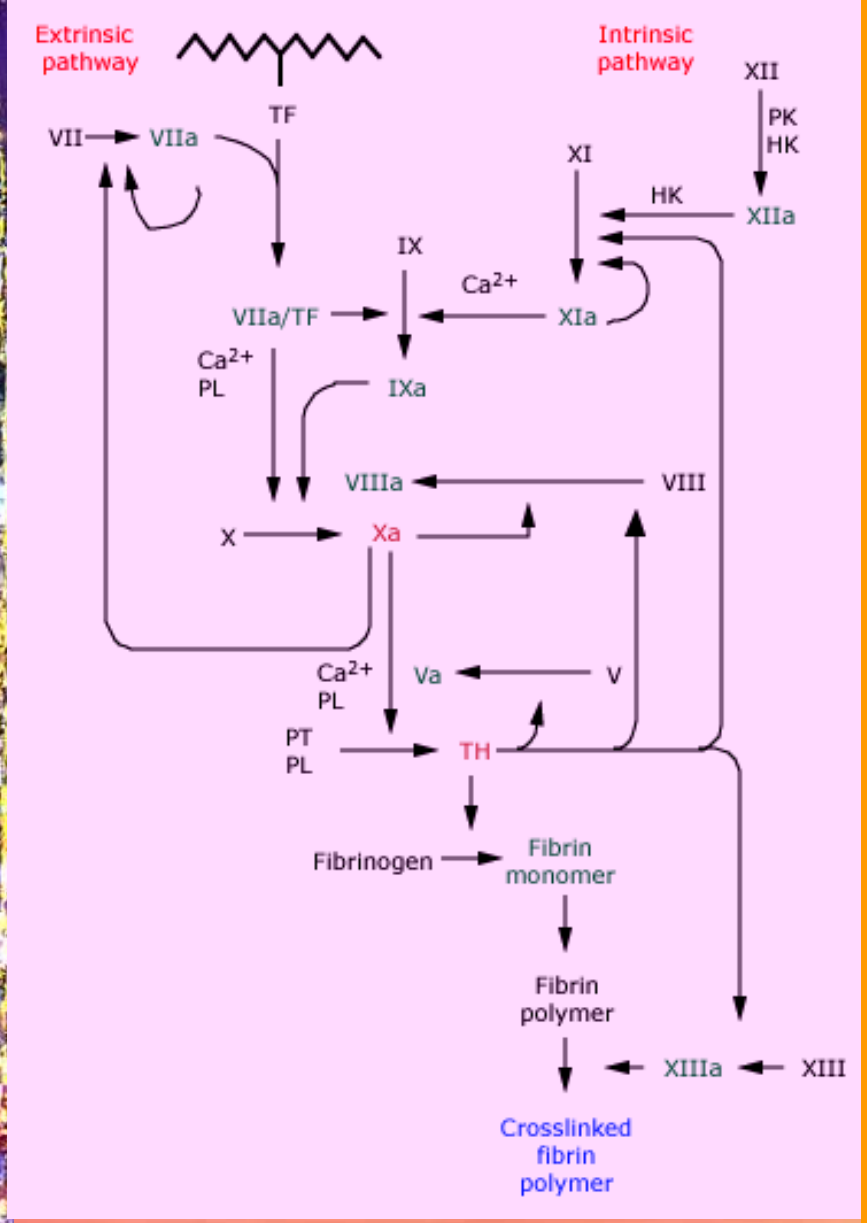
- Derangements in coagulation occur rapidly after trauma
- By the time of arrival at the ED, 28% (2,994 of 10,790) of trauma patients had a detectable coagulopathy that was associated with poor outcome



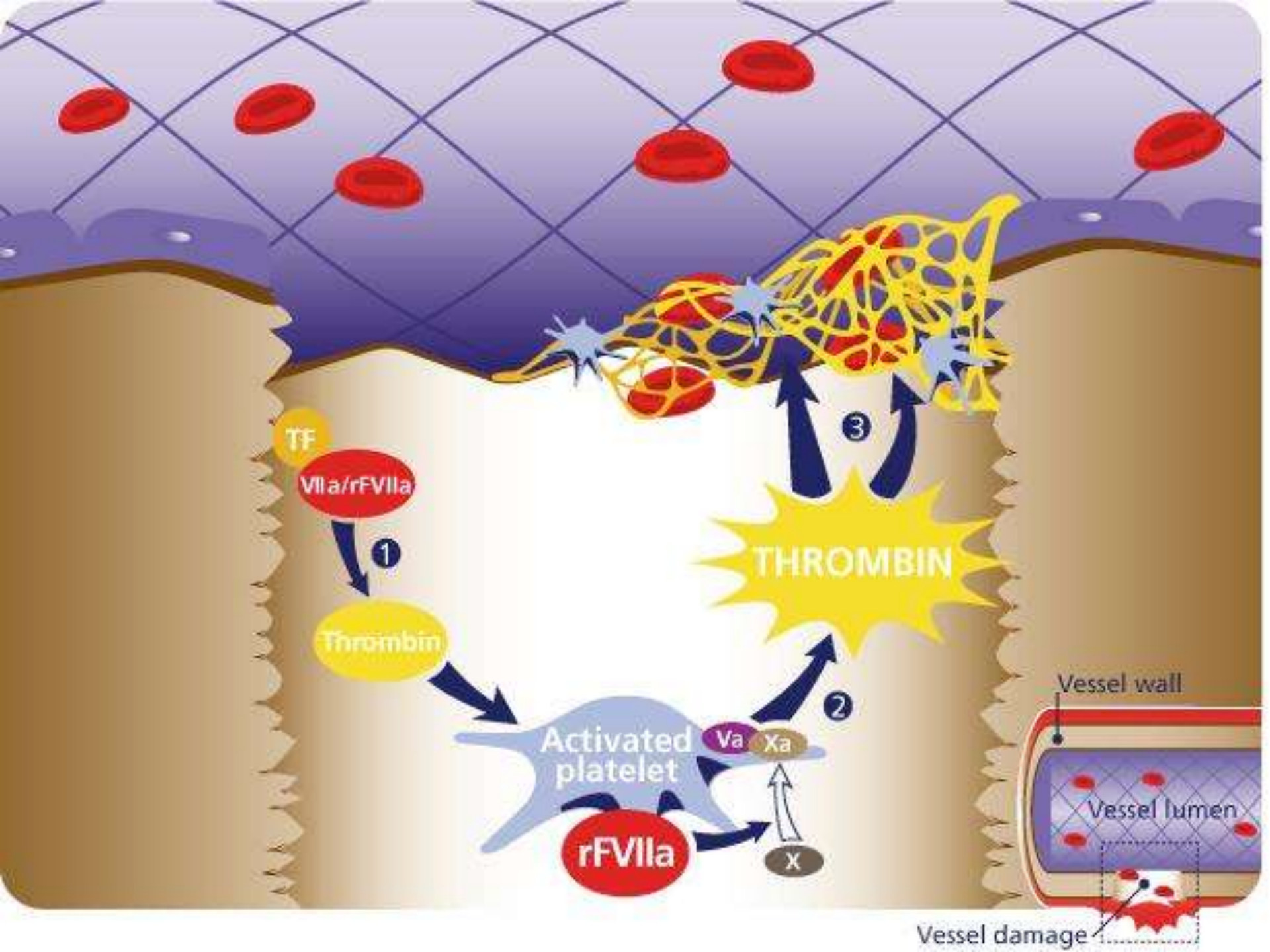
Acute Trauma Coagulopathy is the Natural Body Defence Against DIC !



Coagulopathy of Trauma



The generation or exposure of TF at the wound site, and its interaction with factor VII, is the **PRIMARY** physiologic event in initiating clotting. The components of the intrinsic pathway (ie, factors VIII, IX, XI) are responsible for **AMPLIFICATION** of this process only after a small initial amount of thrombin has been generated through the extrinsic pathway.


TF
VIIa/rFVIIa
1
Thrombin
THROMBIN
3
2
Activated platelet
Va
Xa
rFVIIa
X
Vessel wall
Vessel lumen
Vessel damage

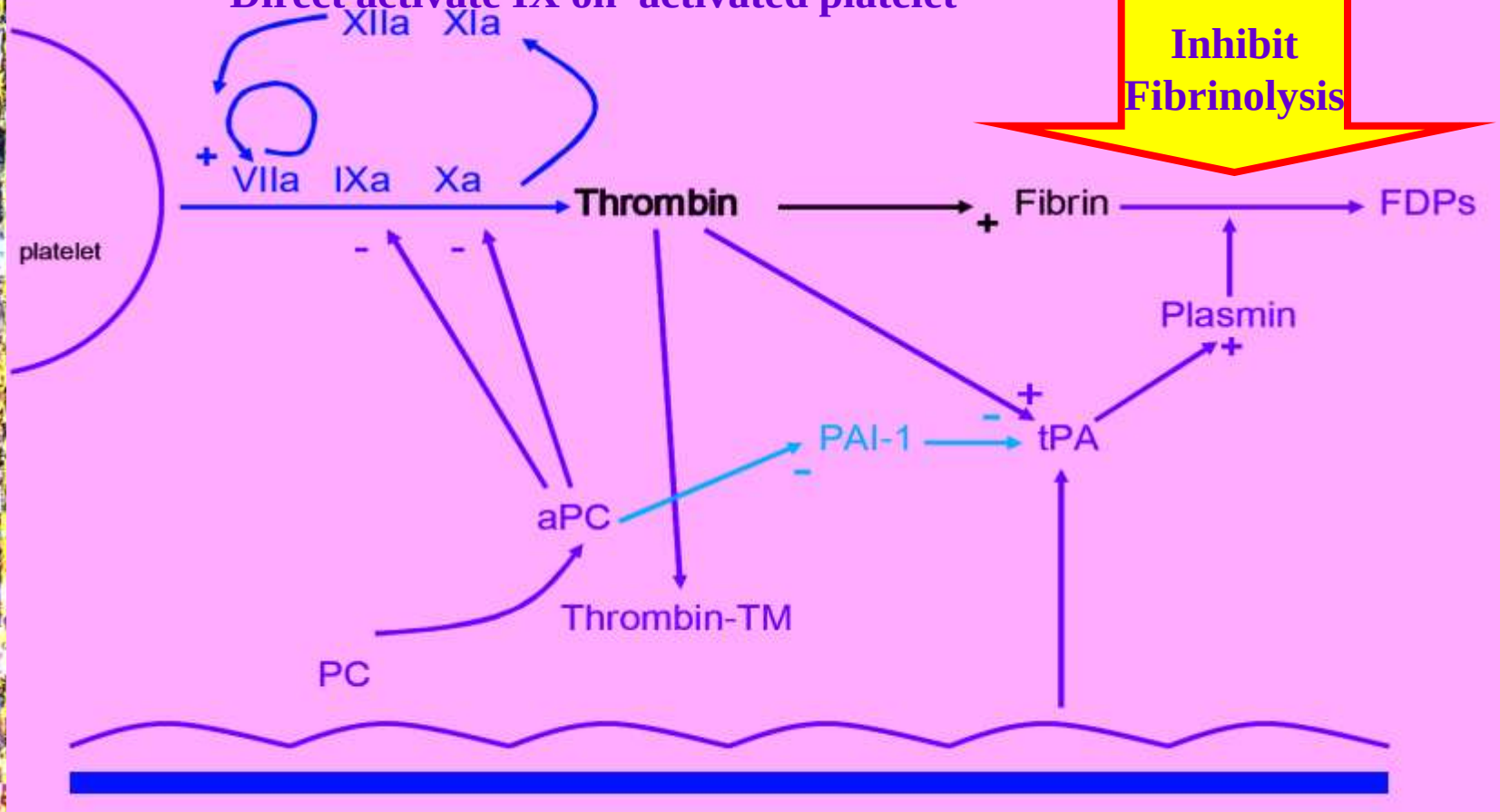
Direct thrombin generation even in the absence of FVIII and FIX

Increase Xa

Direct activate IX on activated platelet

FVIIa

Inhibit Fibrinolysis



Potential Role of FVIIa in Acute Traumatic Coagulopathy

In 2007,the European Task Force for Advanced Bleeding Care in Trauma

(Spahn et al., Crit Care 2007; 11:R17)

- We suggest that the use of rFVIIa be considered if major bleeding in blunt trauma persists despite standard attempts to control bleeding an best practice use of blood components.
- We suggest an initial dose of 200 microgramm/kg followed by two 100 microgramm/kg doses administered at 1 and 3 hours following the first dose. (Grade 2C)

Israel Defense Forces NovoSeven Treatment Guideline for Trauma

J. Thromb Haemost 2005; 3: 640-8

- **Massive bleeding:**
  - **Loss of entire blood volume in 24h (10U PRBC in 70kg)**
  - **Loss of 50% blood in 3h**
  - **Blood loss rate 150mL/min**
  - **Blood loss rate 1.5mL/kg for over 20 min**
- **Failure to arrest hemorrhage despite:**
  - **FFP: 10-15mL/kg (4-6U for 70kg)**
  - **Cryo: 1-2U/10kg (10-15U for 70kg)**
  - **Platelets: 1-2U/10kg (10-15U for 70kg)**
  - **Correction of acidosis: pH□ 7.2**
  - **Warming of hypothermic patients (recommended, not mandatory for rFVIIa)**

Israel Defense Forces NovoSeven Treatment Guideline for Trauma

J. Thromb Haemost 2005; 3: 640-8

- **Preconditions**
  - **Fibrinogen 50 mg/dL (100 mg/dL preferred)**
  - **Platelet 50000*109/L (100000 *109/L preferred)**
  - **pH 7.2**
- **Treatment**
  - **Initial 100~140 (120) □ g/kg IV bolus, 15 to 20 min. Repeat 100 □ g/kg IV**
  - **Total dose > 200 □ g/kg, check and correct preconditions.**
  - **If correction not feasible, give FFP 10-15mL/kg or 4-6 U/70kg**
  - **Cryo 1-2 U/10kg or 10-15 U/70kg**
  - **Platelet 1-2 U/10kg or 10-15 U/70kg**
  - **Correct pH and calcium**
  - **Third dose 100 □ g/kg IV**

Safety: Shock Trauma Center

Thomas, GOR et al. J Trauma 62, 2007

- 9% thromboembolic complications
  - Mesenteric ischemia
  - Cerebral ischemia
  - Myocardial ischemia
  - Other arterial / venous thrombosis
- 3% highly associated with FVIIa
- **1% serious and highly associated**

TACO: Volumes of FP transfusion for changes in coagulation results

Holland and Brooks, Am J Clin Pathol 2006; 126:133-139

	Target INR							
	1.3		1.5		1.7		3.0	
Initial INR	Volume (L)	Dose (mL/kg)	Volume (L)	Dose (mL/kg)	Volume (L)	Dose (mL/kg)	Volume (L)	Dose (mL/kg)
6.0	4.5	64	3.5	50	2.5	36	1.5	21
5.0	4.3	61	3.0	43	2.3	32	1.0	14
4.0	4.0	57	2.5	36	2.0	29	0.5	7
3.0	3.5	50	2.0	29	1.5	21	-	-
2.0	2.5	36	1.5	21	0.5	7	-	-

? The Role of Prothrombin Complex Concentrate

Fibrinogen Content in Various Blood Products (mg)

1 10U bag cryoprecipitate	2,500mg in 150 mL
1U fresh whole blood	1,000 mg
1 six-pack platelets	480mg in 300 mL (80mg per unit x 6U)
1U FFP	400mg in 200-250 mL
1U apheresis platelets	300mg in 200-250 mL
1U pRBCs	< 100 mg

Haemodilution markedly prolonged prothrombin time and reduced peak thrombin generation.

Prothrombin complex concentrate(25 IU/kg) but not FFP (15 ml/Kg), fully reversed those effects.

Conclusions: PCC was effective in correcting dilutional coagulopathy and controlling bleeding in an *in vivo* large-animal trauma model. In light of its suitability for more rapid administration than FFP, PCC merits further investigation as a therapy for dilutional coagulopathy in trauma and surgery.

Prothrombin complex concentrate *vs* fresh frozen plasma for reversal of dilutional coagulopathy in a porcine trauma model

G. Dickneite ,* and I. Pragst

BJA Advance Access published online on January 24, 2009

Administration of fibrinogen (200 mg/ kg) and PCC (35 IU/Kg) was able to reduce mortality and bleeding in a porcine liver laceration model to induce uncontrolled haemorrhage although APTT remain unchanged.

Blood loss after liver injury was significantly less in the treatment group as compared with placebo: 240 ml (50–830) *vs* 1800 ml (1500–2500) ($P<0.0001$). All treated animals survived, whereas 80% of the placebo group died ($P<0.0001$).

Efficacy of fibrinogen and prothrombin complex concentrate used to reverse dilutional coagulopathy—a porcine model

D. Fries1 et al BJA Advance Access originally published online on August 1, 2006

Prothrombin Complex Concentrate (PCC)

- **PCC: Clotting factors (II, VII, IX, and X) that can be used to reverse coagulopathy**
- **PCC: Effects are fast and long acting**
- **PCC: Use in trauma patients appears safe and beneficial in critically injured population**
- **Associated with thrombogenicity**

Kalina M, et al. *Am Surg*. 2008;74:858-861; Köhler M. *Thromb Res*. 1999;95(4 suppl):S13-S17; Riess HB, et al. *Thromb Res*. 2007;121:9-16.

No Consensus on Use of PCC

- **Risk of PCC**
  - **Thrombotic complication**
  - **It contains heparin 200 IU/500 Unit vial**
  - **No FVII in HA CSL's brand**
- **The European guideline on the Management of bleeding following major trauma: a European guideline 2007 recommend the use of PCC according to the manufacturer's instructions only for the emergency reversal of vitamin K-dependent oral anticoagulants.**

Probability of Life-Threatening Coagulopathy Increases with Shock, Hypothermia and Acidosis

Clinical Status	Conditional Probability of developing Coagulopathy
No risk factor	1%
ISS > 25	10%
ISS > 25 + SBP < 70 mmHg	39%
ISS > 25 + pH < 7,1	58%
ISS > 25 + temperature < 34°C	49%
ISS > 25 + SBP < 70 mmHg + temperature < 34°C	85%
ISS > 25 + SBP < 70 mmHg + temperature < 34°C + pH < 7,1	98%

ISS = Injury Severity Score

SBP = Systolic Blood Pressure

Cosgriff et al., J Trauma 1997; 42: 857-861

If this "lethal triad" is present ..... surgical control of bleeding is unlikely to be successful!

Damage Control Resuscitation

Revised Trauma Score

Respiratory Rate	10-29	4
	> 29	3
	6-9	2
	1-5	1
	0	0
Systolic BP	>89	4
	76-89	3
	50-75	2
	1-49	1
	0	0
GCS Conversion	13-15	4
	9-12	3
	6-8	2
	4-5	1
	<4	0

May not be able to identify patient at risk of massive transfusion.

- **New Diagnostic Criteria**
  - Acidosis- Base Deficit > - 6
  - Coagulopathy – INR > 1.5
  - Hypotension – Systolic BP < 90 mmHg
  - Hemoglobin - < 11 g/dL
  - Temperature - < 96. 5 F (35.8C)
- Pattern recognition
  - Weak or absent radial pulse
  - Abnormal mental status
  - Severe Traumatic Injury

DCR

Within 5 minutes

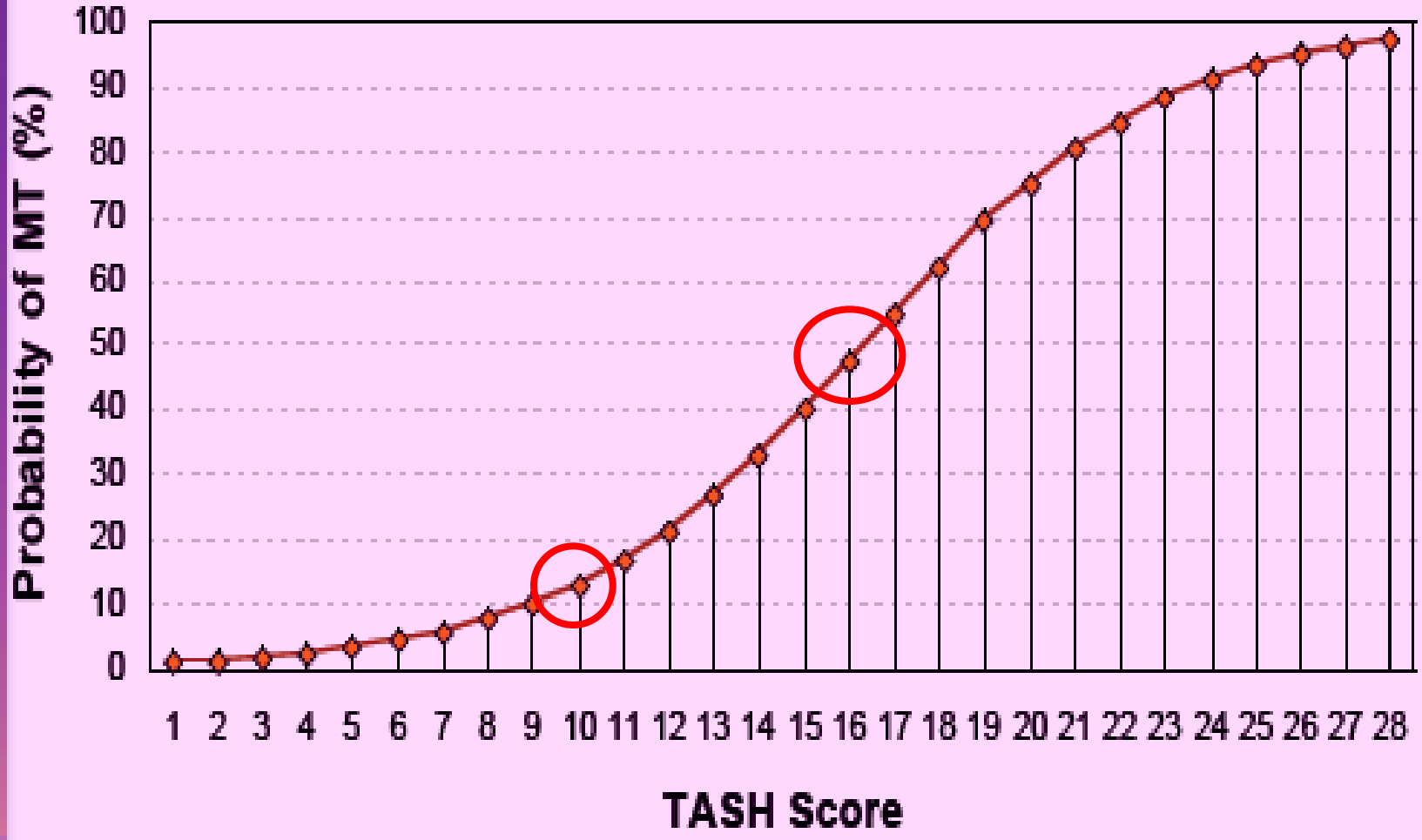
- **Identify patients in trouble**
- **Identify patients with increased mortality**
- **Identify patients with increased probability of massive transfusion**

TASH: Final Score

Variable	Value	Score
Hb	< 7	8
	< 9	6
	< 10	4
	< 11	3
	< 12	2
Base Excess	< -10	4
	< -6	3
	< -2	1
SBP	< 100	4
	< 120	1
HR	> 120	2
Free fluid on abdom. ultrasound		3
Femur or open/disloc. Fracture		3
Pelvic Fracture with blood loss		6
Male patient		1

Trauma Associated Severe Hemorrhage (TASH)-Score: probability of mass transfusion as surrogate for life threatening hemorrhage after multiple trauma.Yücel N, J Trauma. 2006 Jun;60(6):1228-36; discussion 1236-7.

- The TASH score is a simple method for quickly predicting need of mass transfusion
- It can be calculated within the first 10 minutes after admission



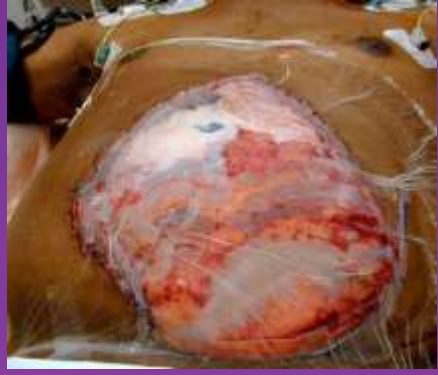
Probability PMT for Mass derived from TASH

ABC (Assessment of Blood Composition) Score for Risk of Massive Transfusion

Parameter	Finding	Points
Penetrating trauma	absent	0
	present	1
systolic blood pressure	> 90 mm Hg	0
	<= 90 mm Hg	1
heart rate	< 120 beats per minute	0
	>= 120 beats per minute	1
FAST	negative	0
	positive	1

- For a cutoff of >= 1, the sensitivity was 95% and specificity 56%.
- For a cutoff of >= 2, the sensitivity was 75% and specificity 86%.

Major Shift In Trauma Care



Major Trauma

Definitive Care → Damage Control Laparotomy

Resuscitation Protocol (Since 1985) → Damage Control Resuscitation
("Haemostatic" resuscitation)

"Damage Control Resuscitation represents the most important advance in trauma care for hospitalized civilian and military casualties from this war."
Cordts, Brosch and Holcomb, *J Trauma*, 2008

Damage Control Resuscitation

Cotton BA, et al. *J Trauma*. 2008;64:1177-1183

- **Damage control hematology: the impact of a trauma exsanguination protocol on survival and blood product utilization**
- **(Cotton et al. *Journal of Trauma*, 2008)**
- **Three components**
  - **Hematologic**
  - **Limited crystalloid**
  - **Permissive hypotension**

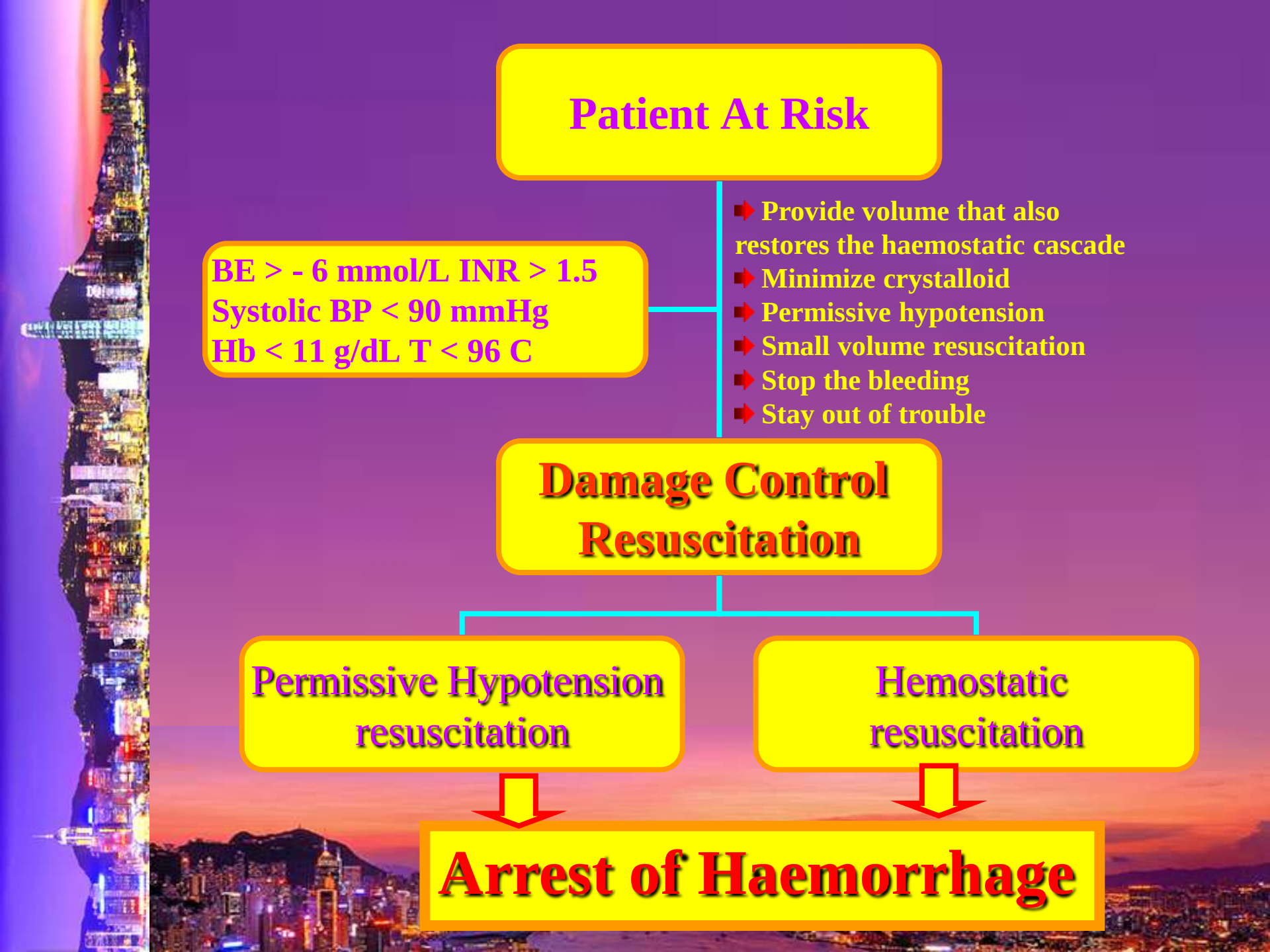
Damage Control Resuscitation

Cotton BA, et al. *J Trauma*. 2008;64:1177-1183

- **74% reduction in the odds of mortality**
- **Increase in unexpected survivors**
- **Decrease in unexpected deaths**
- **Less intraoperative crystalloid; fewer postoperative blood products**

Damage Control Surgery

- Performed in the setting of massive transfusion, refractory shock, hypothermia, & coagulopathy
- Stop hemorrhage
- Control contamination
- Temporary abdominal closure
- Return patient to ICU for correction of shock, coagulopathy, & hypothermia
- Re-exploration for definitive repair when stable (12-48 hrs)


Patient At Risk
BE > - 6 mmol/L INR > 1.5
Systolic BP < 90 mmHg
Hb < 11 g/dL T < 96 C
Provide volume that also restores the haemostatic cascade
Minimize crystalloid
Permissive hypotension
Small volume resuscitation
Stop the bleeding
Stay out of trouble
Damage Control Resuscitation
Permissive Hypotension resuscitation
Hemostatic resuscitation
Arrest of Haemorrhage

Permissive Hypotension Rediscovered

"If the pressure is raised before the surgeon is ready to check any bleeding that may take place, blood that is sorely needed may be lost."

The Preventative Treatment of Wound Shock

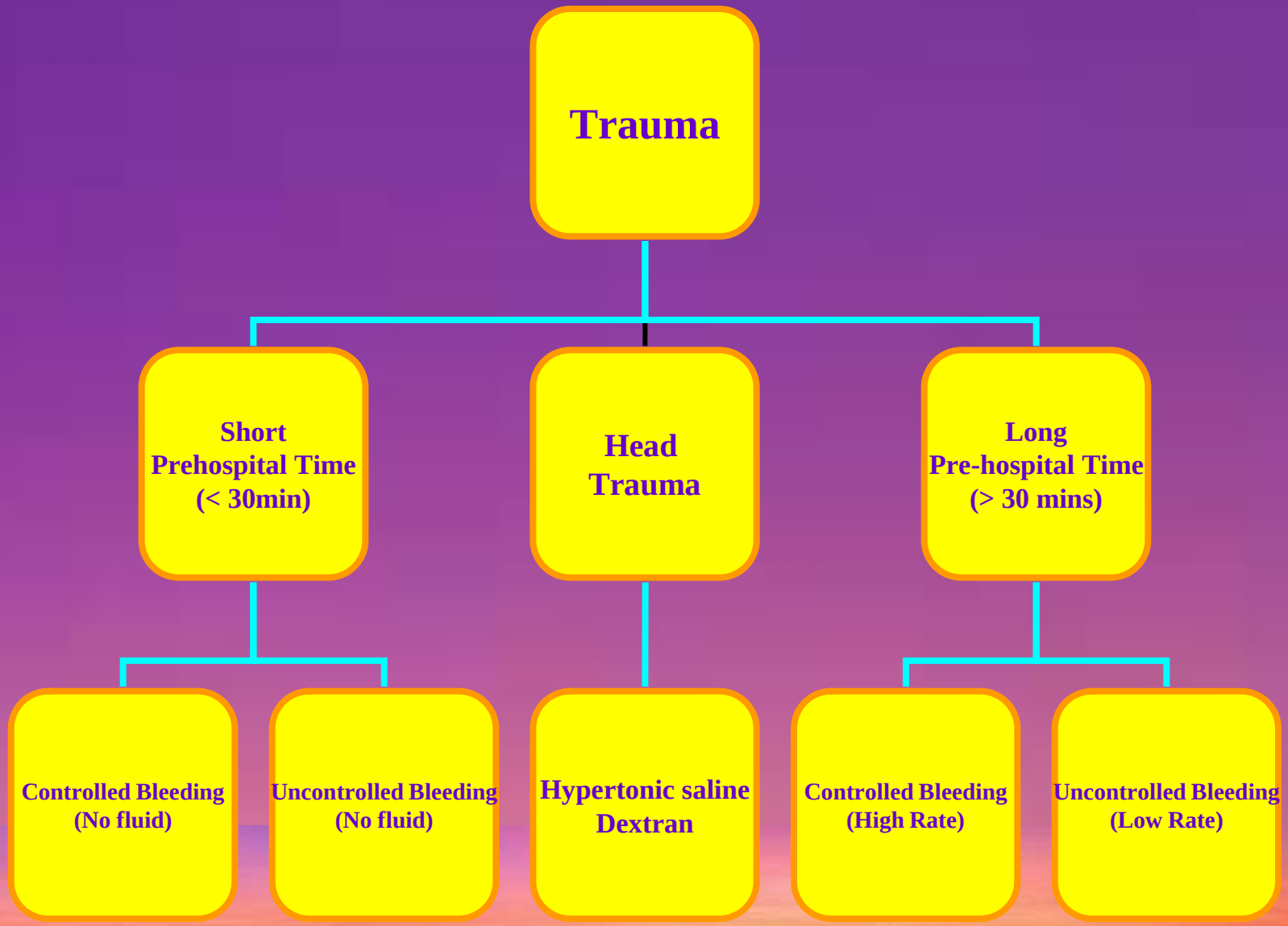
Cannon W, Fraser J, Cowell E JAMA 1918:618-621

Permissive Hypotension

- ATLS and others:
  - 15-20 years of ‘high volume’ fluid resuscitation
  - Chasing the tachycardia
  - Crystalloid versus colloid
  - NO TRUE EVIDENCE OF IMPROVED SURVIVAL
- Current UK consensus guidelines
  - **Permissive hypotension**: avoid ‘popping the clot’
    - Radial or femoral pulse
    - **Systolic 70-80mmHg**
  - **‘Small volume’ resuscitation**
    - **Hypertonic + colloid**

Permissive hypotension: theory

- Decrease in vasoconstriction
- Earlier dislocation of the thrombus
- Increased blood loss
- Dilution coagulopathy
- Decrease oxygen transport capacity
- Metabolic acidosis
- Hypothermia



Permissive hypotension: Clinical

Ineffectiveness of On-Site Intravenous Lines: Is prehospital time the culprit?

Sampalis JS et al. J Trauma 1997 Oct;43(4):608-617

- 217 patients on-site intravenous fluid replacement (IV group) with patients for whom this intervention was not performed (no-IV group).
- The mortality rates for the IV and no-IV groups were 23 and 6% ($p < 0.001$)
- **Use of on-site intravenous fluid replacement was associated with a significant increase in the risk of mortality** (adjusted odds ratio = 2.3; $p = 0.04$)

Immediate versus delayed fluid resuscitation for hypotensive patients with penetrating torso injuries

Bickell WH et al Engl J Med 1994 Oct 27; 331:1105-9

- Prospective, randomized pre-hospital trial
- 598 patients with penetrating torso trauma and systolic BP < 90 mmHg
- Initial BP averaged 72 mmHg in 'limited' resusc, 78mmHg in 'standard'
- Standard resuscitation vs Limited resuscitation (until surgical intervention)
- 2480 mls vs 375 mls IV fluids
- Limited resuscitation : 30% mortality and 23% complication rate
- Standard Resuscitation : 38% mortality (p=0.04) and 30% complication rate

Hypotensive resuscitation during active hemorrhage: Impact on in-hospital mortality

Dutton RP et al J Trauma 2002 June;52(6):1141-1146

- Patients in hemorrhagic shock randomized to target BP of 70mmHg or 100mmHg
- Fluid administered to this endpoint until hemorrhage control
- 114 mm Hg vs. 100 mm Hg, $p < 0.001$
- **No difference in mortality**

Haemostatic Resuscitation

- Damage control philosophy can be extended to hemostatic resuscitation
  - restoring normal coagulation
  - minimizing crystalloid
  - Traditional resuscitation strategies dilute the already deficient coagulation factors and increase multiple organ failure
- The aggressive haemostatic resuscitation should be combined with equally aggressive control of bleeding

Hemostatic Resuscitation

- Early Dx in ED
- 1:1 ratio (PRBC to FFP)
- ED use of rFVIIa
- Call for Fresh Whole Blood from the ED
- Frequent cryoprecipitate and platelets
- Repeated doses of rFVIIa in OR and ICU as required
- Minimal crystalloid

Fresh Frozen Plasma

- Fresh frozen plasma should be used as a primary resuscitative fluid.
- This product should be present upon arrival of the casualty in the ED
- This approach not only addresses the metabolic abnormality of shock, but initiates reversal of the coagulopathy present.

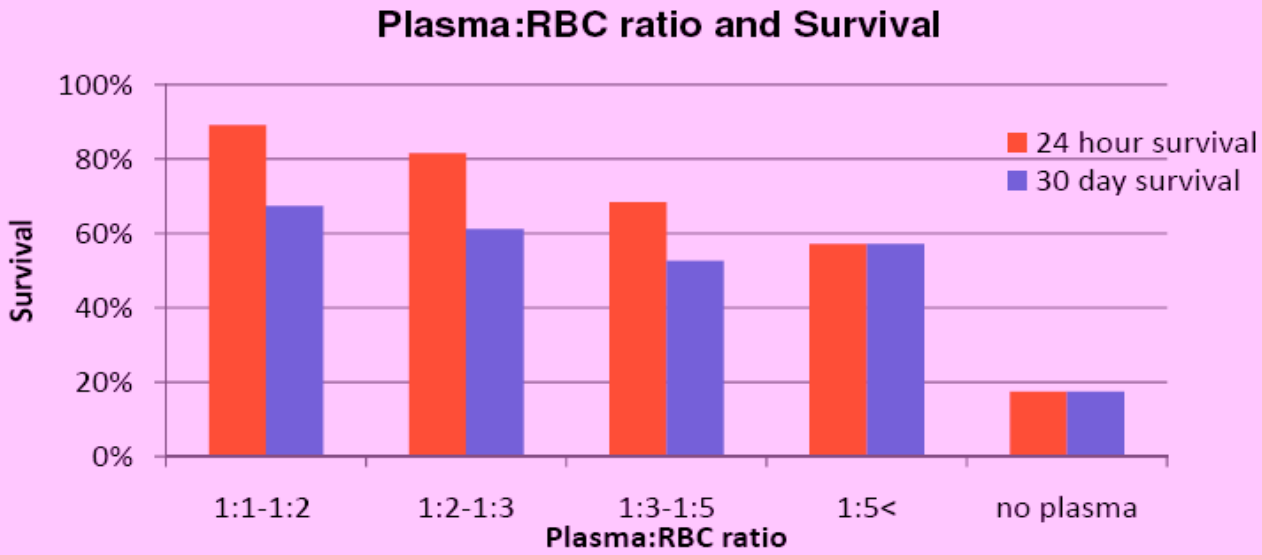
Fresh Whole Blood

- Fresh whole blood (FWB) must be called for early after ED arrival, takes 60 minutes
  - Injury Pattern recognition
- Fresh whole blood is the optimal resuscitation fluid for severely injured casualties.
- Fresh whole blood is the best fluid for hypotensive resuscitation for hemorrhagic shock.

Increased number of plasma products in relationship to red blood cell products transfused improves mortality in trauma patients.

Shaz B, Young A, Harris R, Nicholas J, Hillyer C, Dente C

Transfusion 2008;48;25A-26A

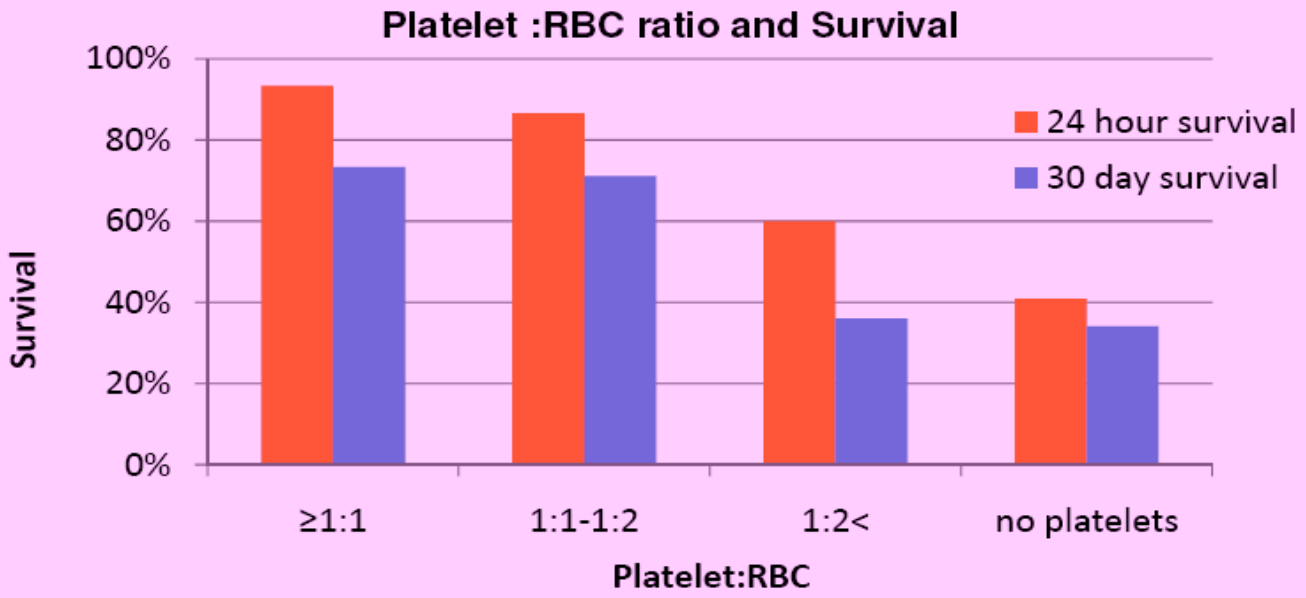


Plasma:RBC	1:1-1:2	1:2-1:3	1:3-1:5	1:5<	no plasma
n	46	49	19	14	23
ISS (ave)	31	28	26	26	23
Penetrating	39%	39%	53%	36%	52%
MTP	65%	41%	26%	57%	26%

Increased number of plasma products in relationship to red blood cell products transfused improves mortality in trauma patients.

Shaz B, Young A, Harris R, Nicholas J, Hillyer C, Dente C

Transfusion 2008;48;25A-26A

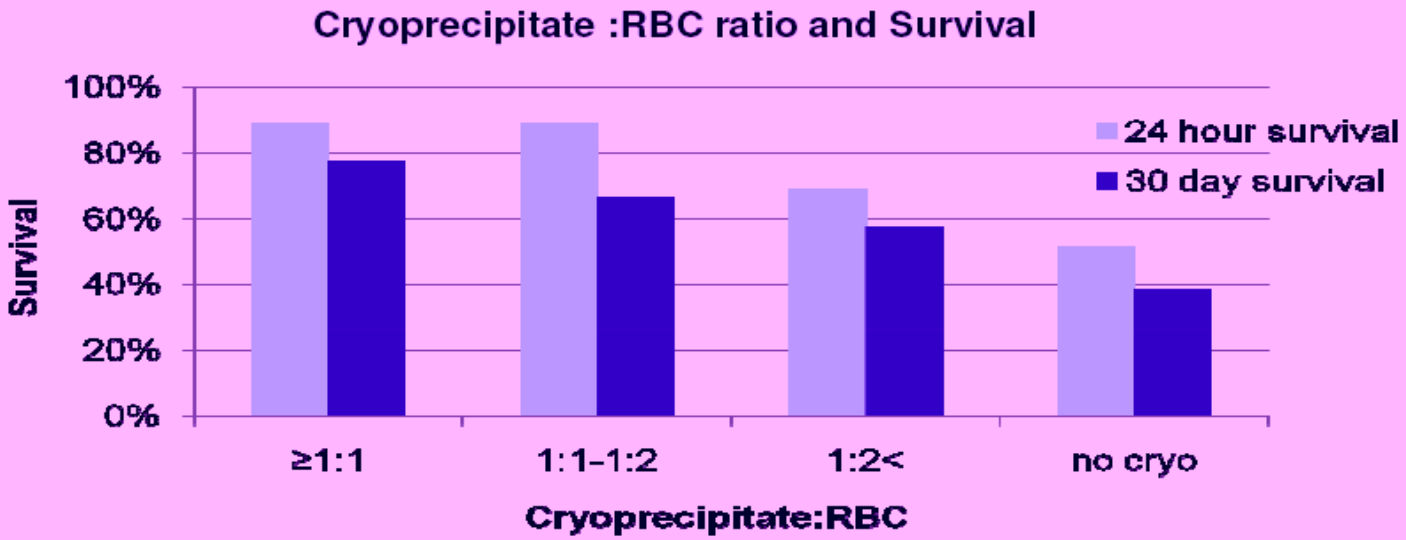


Platelet:RBC	≥1:1	1:1-1:2	1:2<	no platelets
n	52	52	25	44
ISS (ave)	34	26	27	29
Penetrating	30%	44%	52%	41%

Increased number of plasma products in relationship to red blood cell products transfused improves mortality in trauma patients.

Shaz B, Young A, Harris R, Nicholas J, Hillyer C, Dente C

Transfusion 2008;48;25A-26A



Cryo:RBC	≥1:1	1:1-1:2	1:2<	no cryo
n	18	45	26	62
ISS (ave)	29	30	28	28
Penetrating	39%	36%	46%	45%

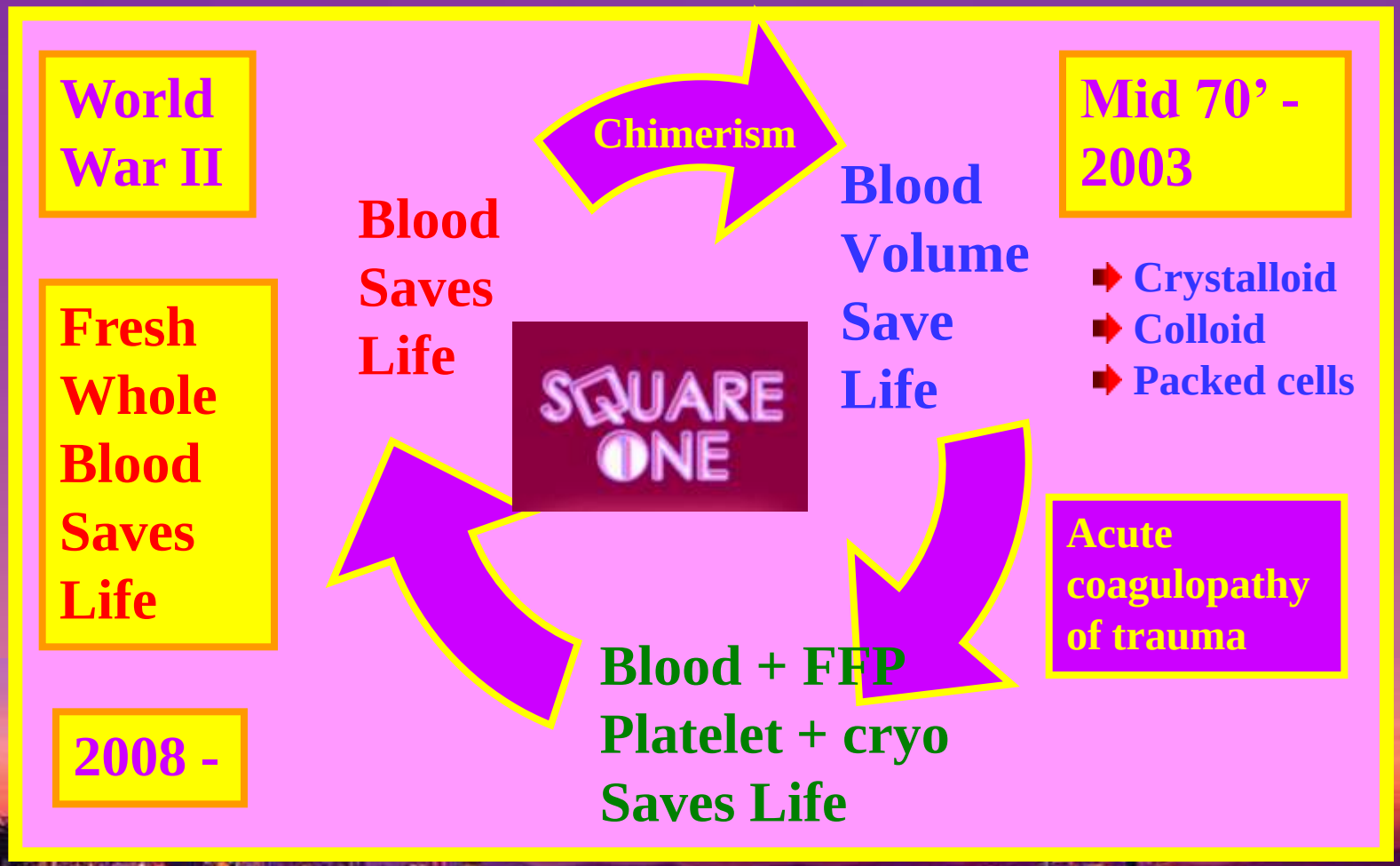

New Approach To Major Trauma Requring Massive Transfusion
ATLS Gudieline
Blood Bank
OT/ICU
A&E Department Triage criteria
Fluid resuscitation Guideline
Surgical Approach
Prevention and Rx Of Lethal Triad Oran support
Early Indentification Of At Risk Population
Haemostatic Resuscitation
Damage Control Laparotomy
Systolic BP < 90 mmHg
BE > - 6 mmol/L
INR > 1.5
T < 96 ˚F (35.6 ˚C)
Hb < 11 g/dL
Hypotensive Resuscitation
Stop the Bleeding And contamination
Are We Ready For The Change ?

Fluid resuscitation – a history

Era	Focus	Resuscitation	Outcome
World War I	Wound toxins	None	Early death
World War II, Korean war	Intravascular repletion	Colloids, blood	↑ Early survival ARF → death
Vietnam war	Intravascular and extracellular fluid repletion	Crystalloids, banked blood	↑ Early survival ↓ ARF ARDS → death
1970s–80s	ICUs, organ failure, metabolic support	PA catheters, endpoints of resuscitation	↓ ARF ARDS ? MOF ↑ MOF deaths
Mid-1980s to present	Trauma centres, trauma systems	Rapid triage, damage control, shock and trauma ICUs	↑ Early survival ↑ ARDS/MOF ↓ ARDS/MOF deaths

ARF=acute renal failure. ARDS=adult respiratory distress syndrome. MOF=multiple organ failure.

Development of Resuscitation Protocol For Major Haemorrhagic Shock



Transfusion Packages: A Pro-Active Approach

for massive / life-threatening bleedings

5 RBCs + 5 FFPs + PCs, resulting in a haematocrit - 30%, factor concentration > 30% and a platelet count -80 x 10^9/L

administered consecutively until heamostasis is secured

Johansson et al., Transfusion 2007; 47:593-598

Component Therapy vs Fresh Whole Blood

PRBC	Platelet	FFP
Hct 55%	5.5x1010	80%
335 mL	50 mL	275 mL

So Component Therapy Gives You

1U PRBC + 1U PLT + 1U FFP + 10 pk Cryo =

660 COLD mL
Hct 29%
Plt 87K
Coag activity 65%
750 mg fibrinogen

Dilution Is Inevitable When Giving Blood Components

Whole blood 500 mL

(Hct 38%–50%; Plts 150 K–400 K; Plasma coagulation activity100%)

↓

150 mL anticoagulant added; centrifuged

↙ ↓ ↘

1 Unit PRBC
(335 mL, Hct 55%)

1 Unit Plasma
(275 mL, coagulation activity 80%)

1 Unit Platelets
(50 mL, 5.5 x 10^{10} plts

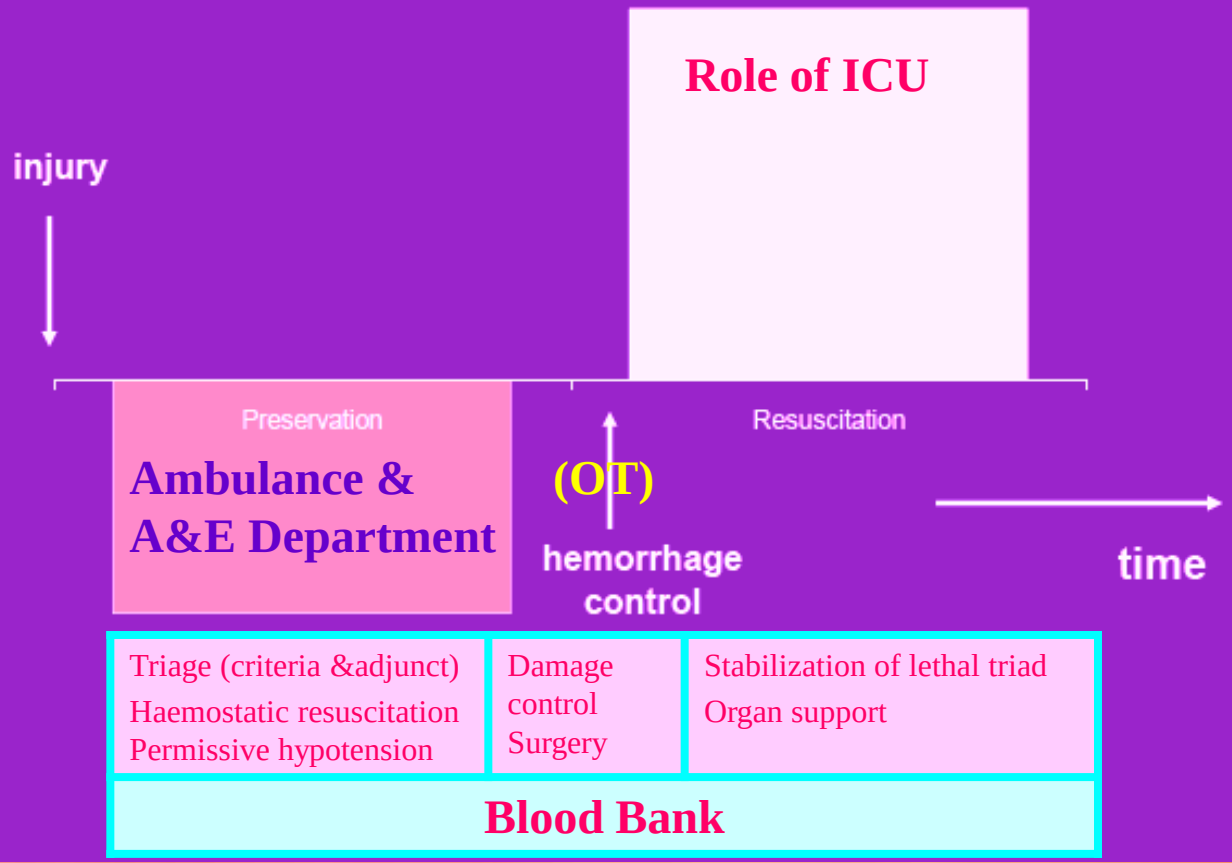
↘ ↓ ↙

Patient Receives 650 mL fluid:
Hct 29%, Plts 88 K, 65% coagulation activity

Best option – your own blood!

- Minimise loss as much as possible
  - Circulation preservation
  - Urgent transfer to theatre
- More effectively carries oxygen
  - Fresh vs stored blood
- No Allograft transfusion problems
  - Antigens
  - White cells
  - Transfusion complications

Trauma resuscitation



Management of Trauma Patient Requring Massive Transfusion

Conclusion (I)

- Data are starting to support changes in transfusion approaches and policy:
  - Trauma is a leading case of death worldwide and 30-40% of trauma patients die secondary to bleeding and coagulopathy
  - Early trauma induced coagulopathy occurs in ~25% of trauma patients and predicts four fold increased in mortality
  - Implementation of a MTP with aggressive use of plasma/cryoprecipitate/platelets may reduce mortality and may reduce blood product usage.
  - Increased amount of coagulation products relative to RBC products transfused improves mortality
  - Until results from prospective trials, current data support a **target ratio of plasma:red blood cell:platelet transfusions of 1:1:1. during massive blood loss**

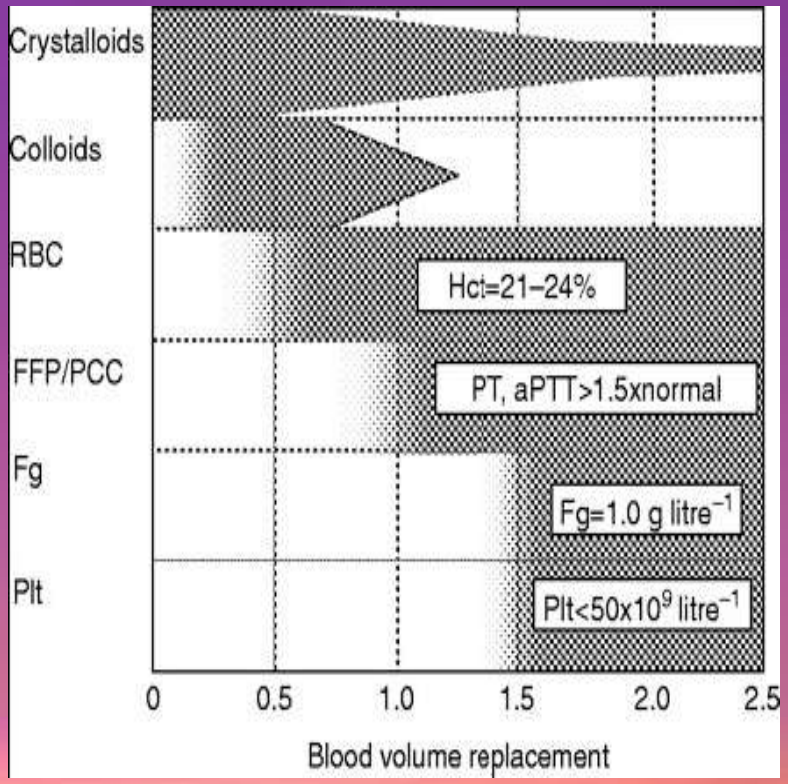
Conclusions (II)
Goal for Resuscitation - Early

- Expedite control of hemorrhage with damage control surgery
- Maintain blood pressure 80-100 mmHg systolic!
- Limit crystalloid infusion and consider vasopressors early!
- Give blood products early and often: pRBC: FFP:Platelet at 1:1:1 ratio
- Frequent laboratory studies!

Conclusions (III)

Key Goals for the Management of critical bleeding in the Trauma Patient : 8 Steps to Support Coagulation

1. Achieve normothermia
2. Achieve normal pH
3. Achieve normal Ca2++
4. Treat with FFP, if PT or aPTT abnormal
5. Treat with platelets, if < 80 x 109
6. Treat with Fibrinogen, if < 1g/l
7. Treat with Antifibrinolytics,if hyperfibrinolysis
8. Treat with rFVIIa, if all else fails Plt > 50x109, Fg > 1g/l, Hct >24, pH > 7,2



Modified from Spahn D, Roissaint R, Br J Anaesth 2005; 95(2): 130-139


The Story Begins
Acute Coagulopathy of Trauma
2003

One quarter of major trauma patients has acute coagulopathy on arrival to A&E Department

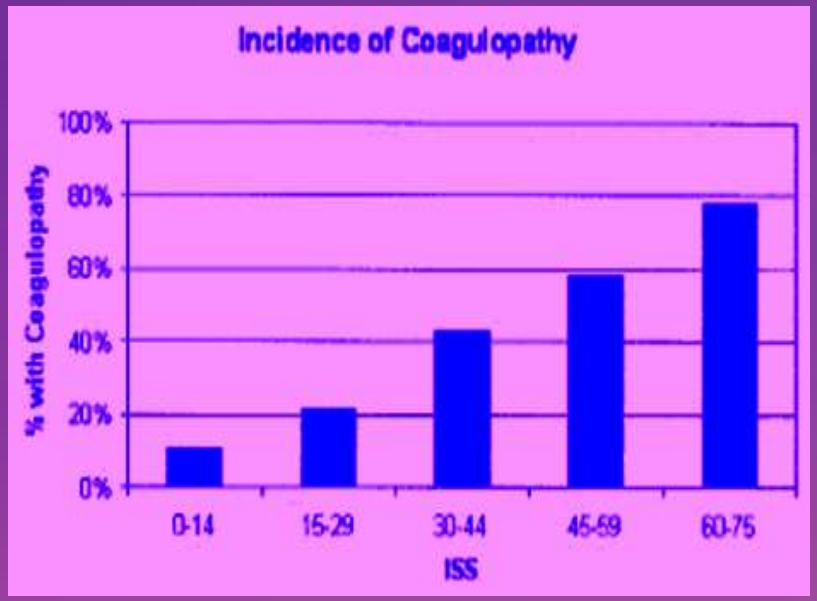
Patients arriving with a coagulopathy were **4 times more likely to die** than those with normal coagulation. This effect was independent of injury severity.

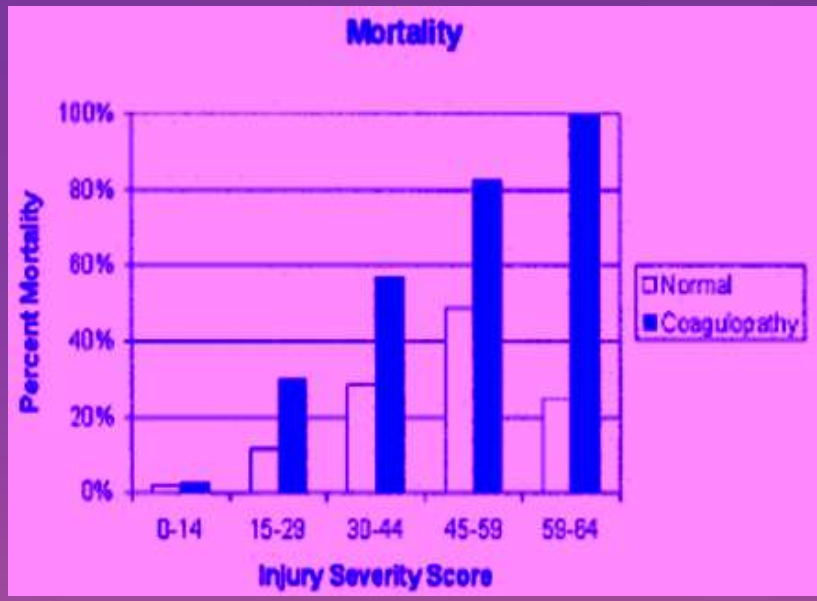
Acute coagulopathy of trauma: hypoperfusion induces systemic anticoagulation and hyperfibrinolysis.

Brohi K, Cohen MJ, Ganter MT, Schultz MJ, Levi M, Mackersie RC, Pittet JF 1: J Trauma. 2008 May;64(5):1211-7

Summary of studies of acute coagulopathy of trauma

	Definition of coagulopathy	Number of patients	Percentage with coagulopathy	ISS	Mortality normal	Mortality coagulopathy
Brohi, 2003 [6]	PT >18 s or PTT >60 s	1088	24%	20[a]	11%	46%
MacLeod, 2003 [7]	PT >14 s or PTT >35 s	10 790	28%	9[a]	6%	19%
Maegele, 2007 [8•]	Quick test <70%	8724	34%	24[b]	8%	28%
Brohi, 2007 [9••]	PT >18 s or PTT >60 s[c]	208	10%	17[a]	8%	62%
Rugeri, 2007 [10•]	INR > 1.6 or PTT >60 s	88	28%	22[b]	n/a	n/a

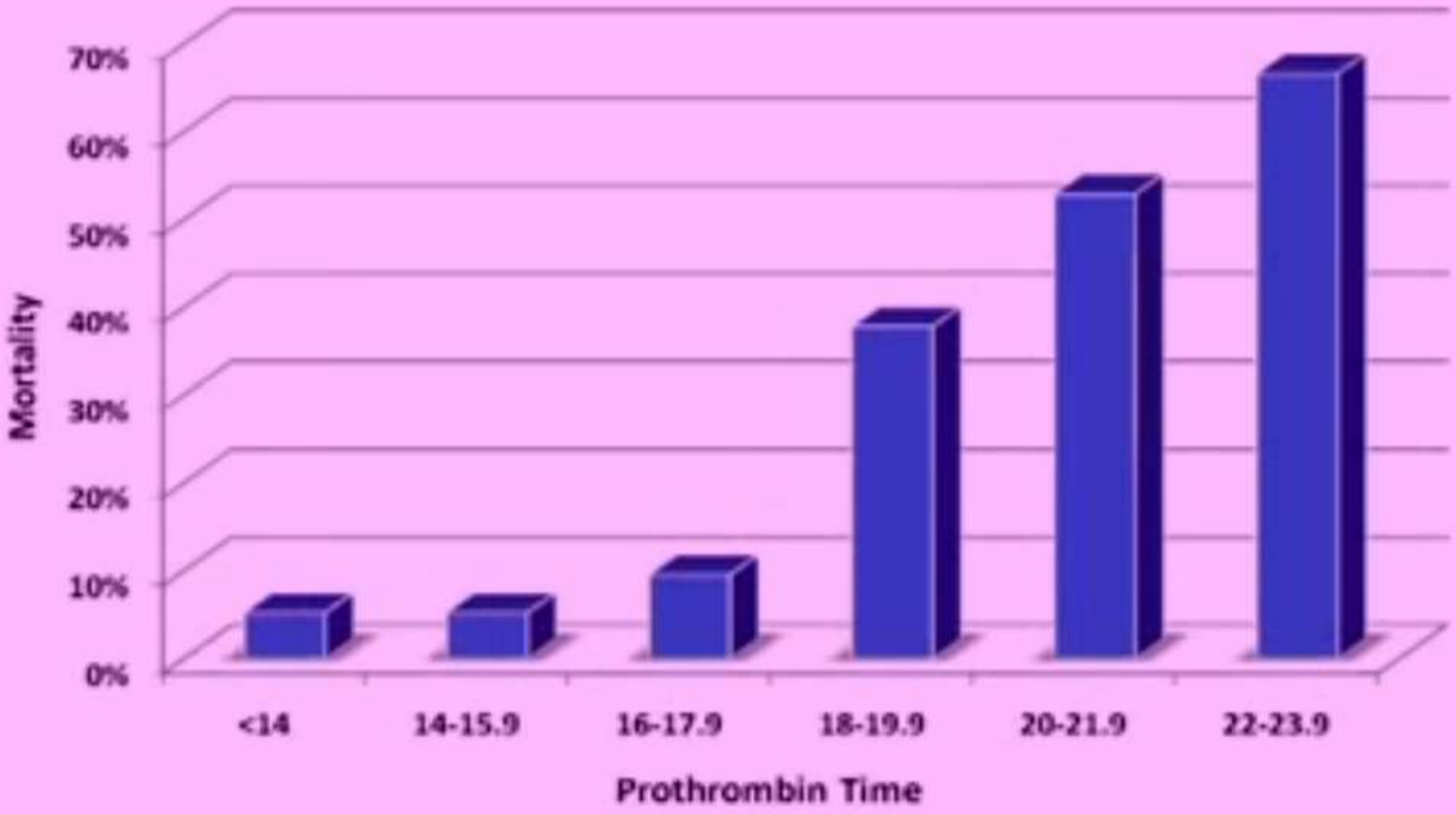




- Derangements in coagulation occur rapidly after trauma and are related to the injury severity score (ISS)
- By the time of arrival at the ED, 1/4 of trauma patients had a coagulopathy associated with a poor outcome

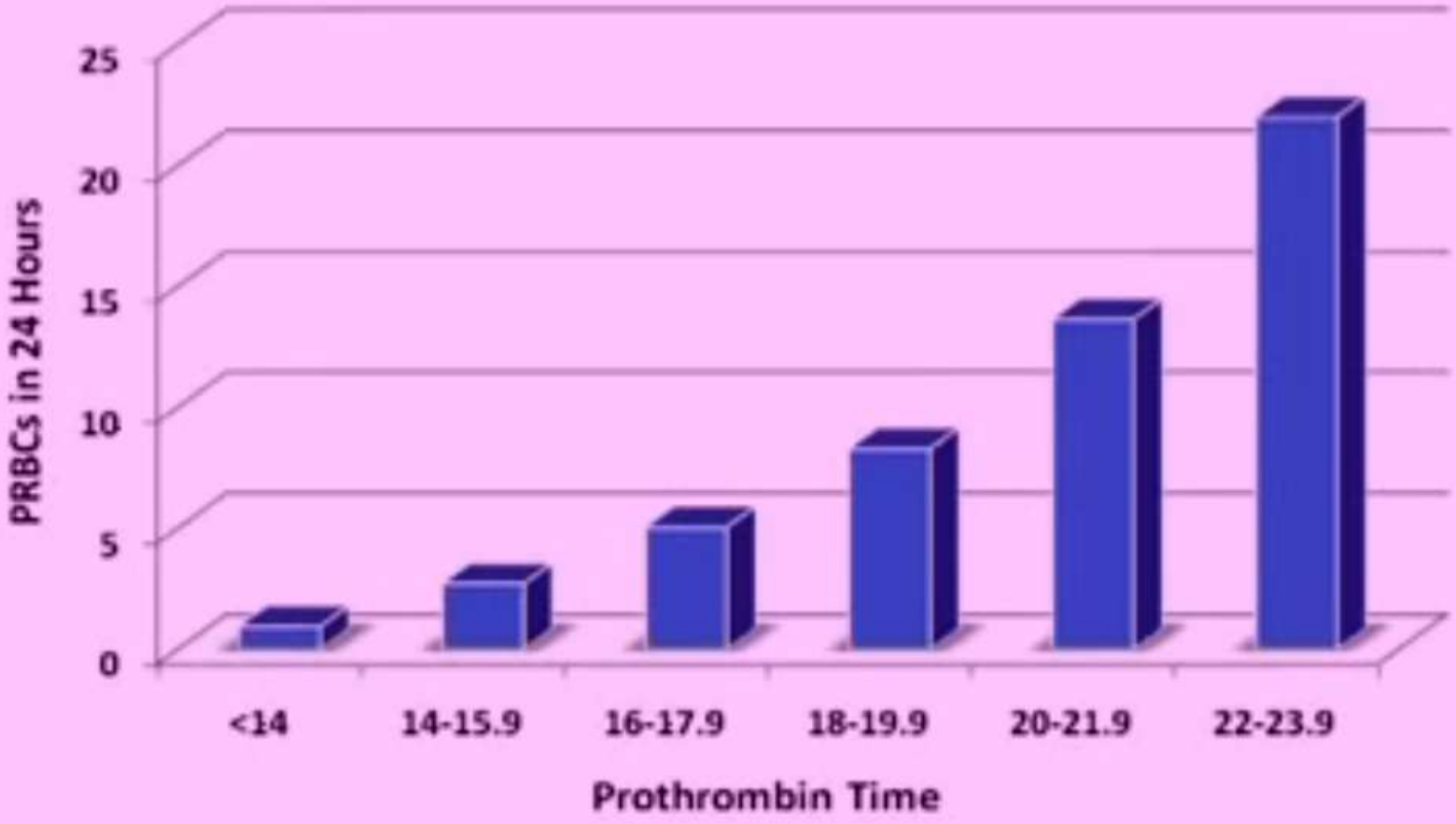
Acute Traumatic Coagulopathy

Brohi, Karim BSc, FRCS, FRCA; Singh, Jasmin MB, BS, BSc; Heron, Mischa MRCP, FFAEM; Coats, Timothy MD, FRCS, FFAEM The Journal of Trauma: Injury, Infection, and Critical Care: June 2003 - Volume 54 - Issue 6 - pp 1127-1130



Retrospective analysis of 5000 Patients

European Collaborative Study



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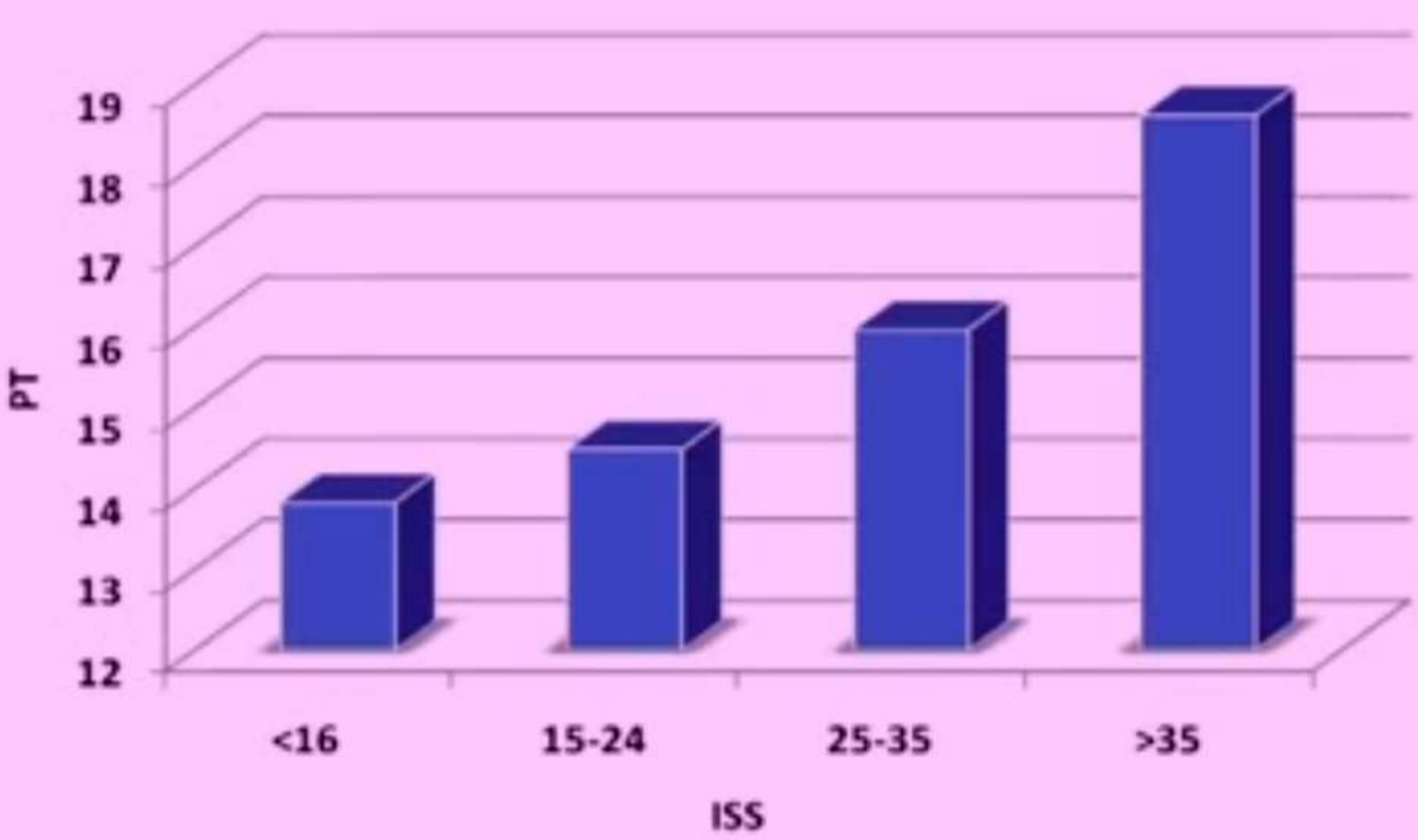

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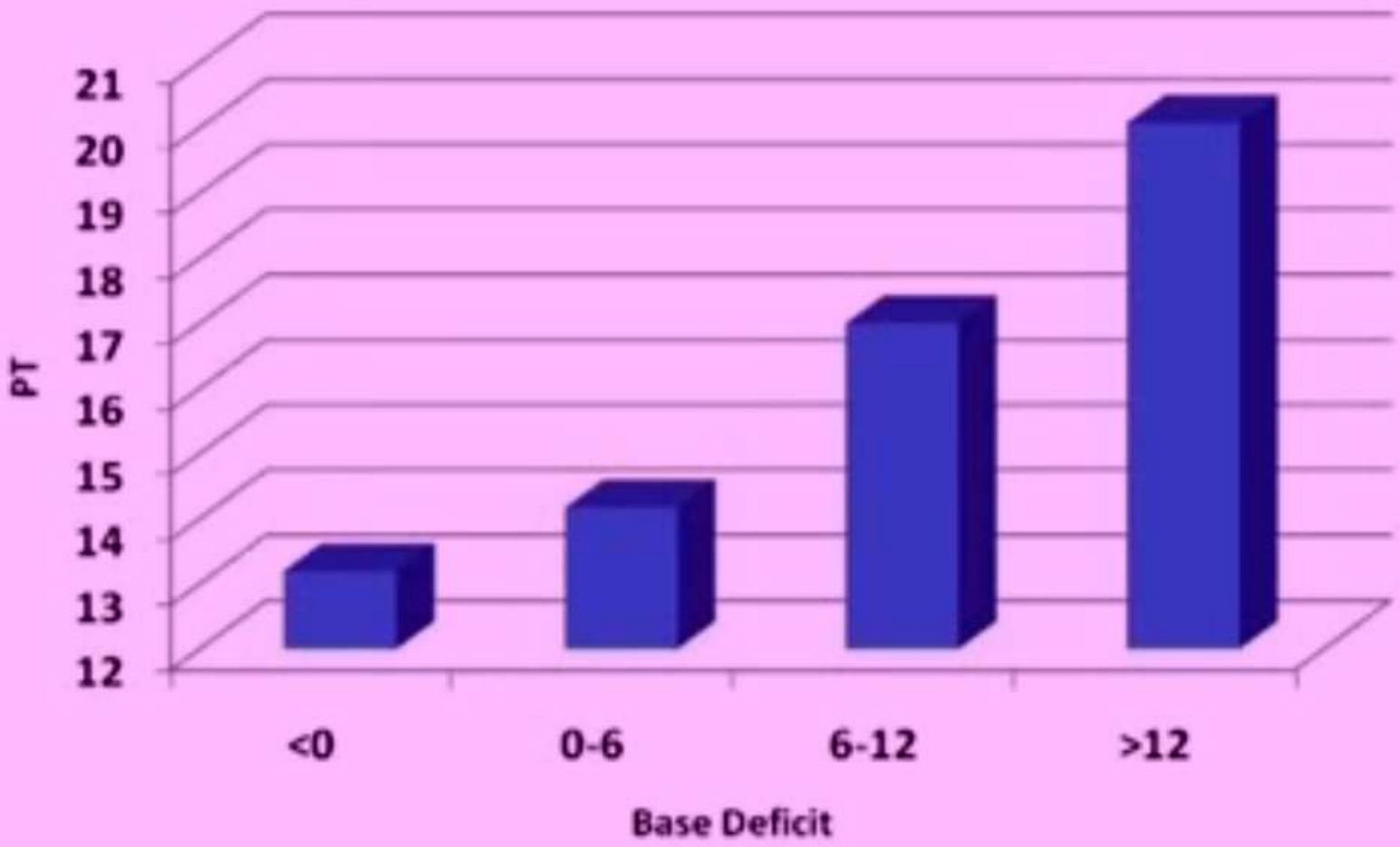

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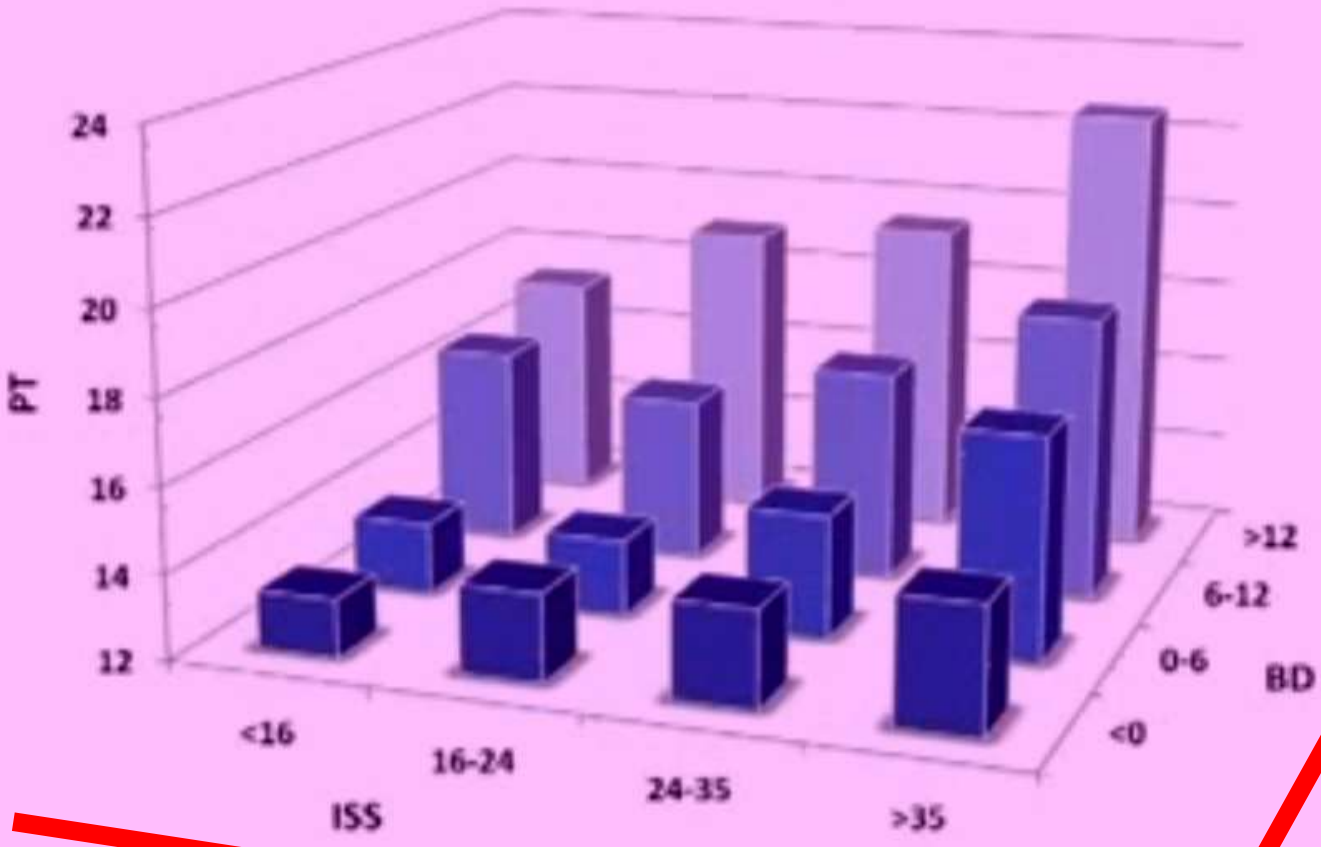
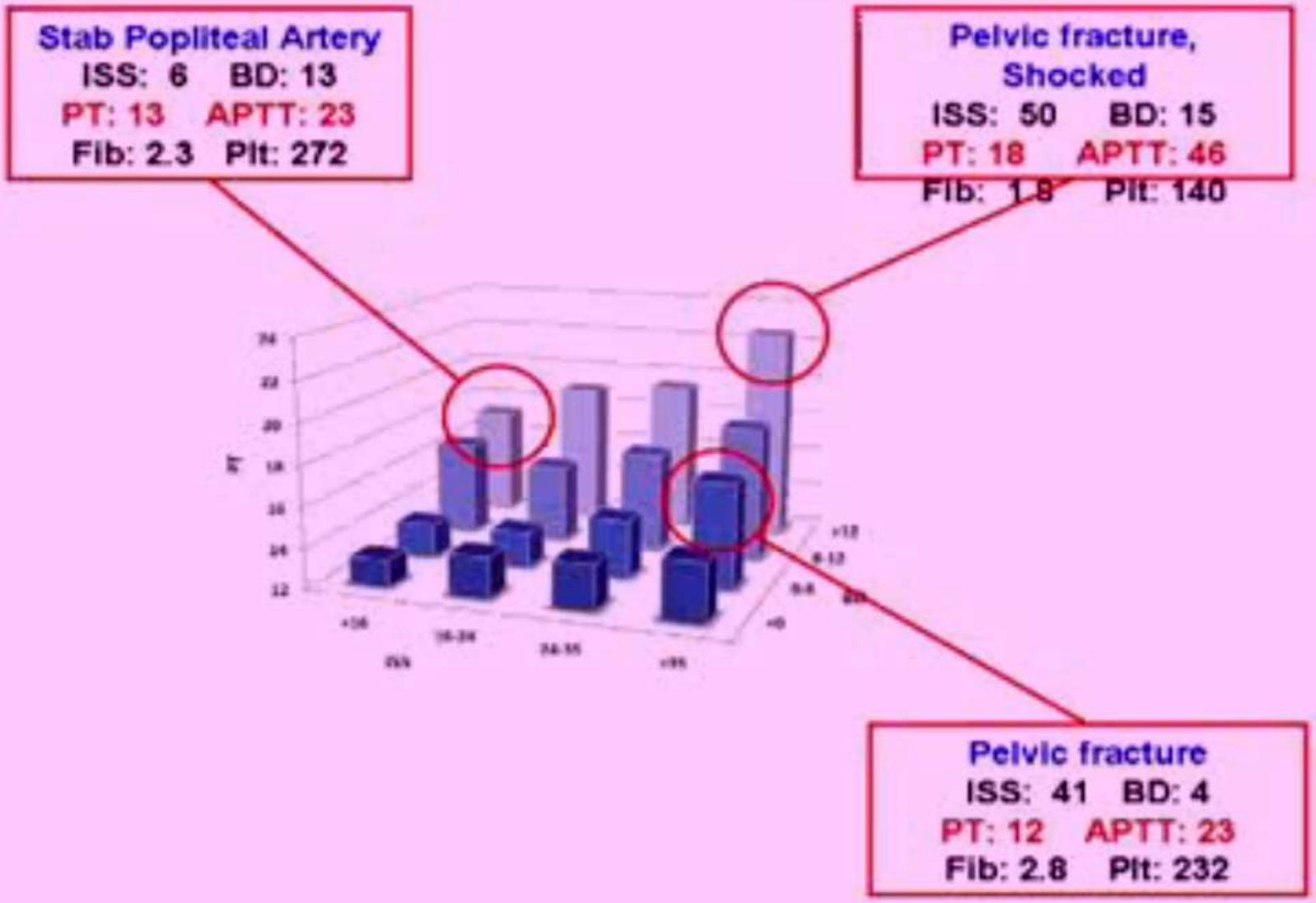


Injury

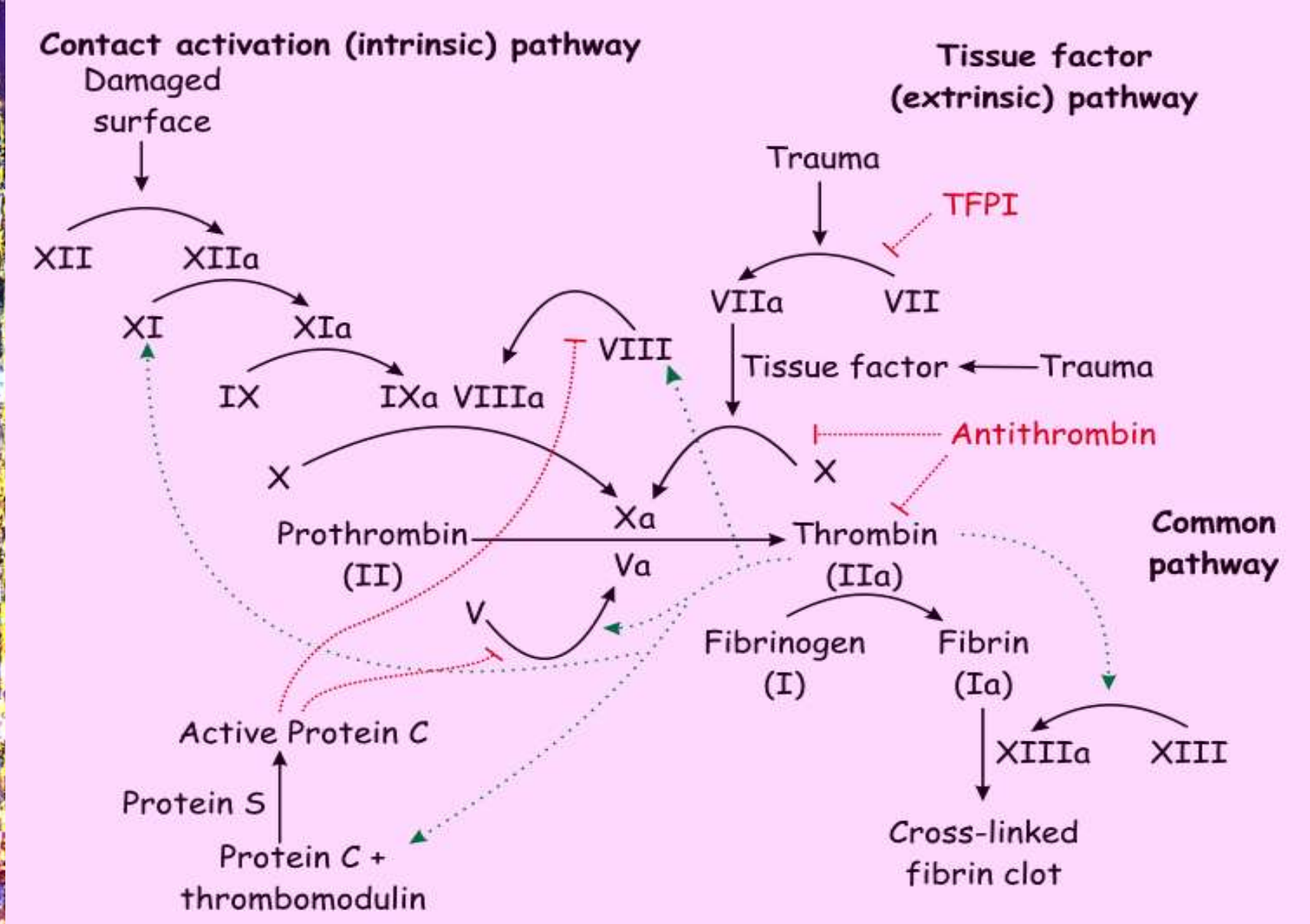
Shock

Retrospective analysis of 5000 Patients

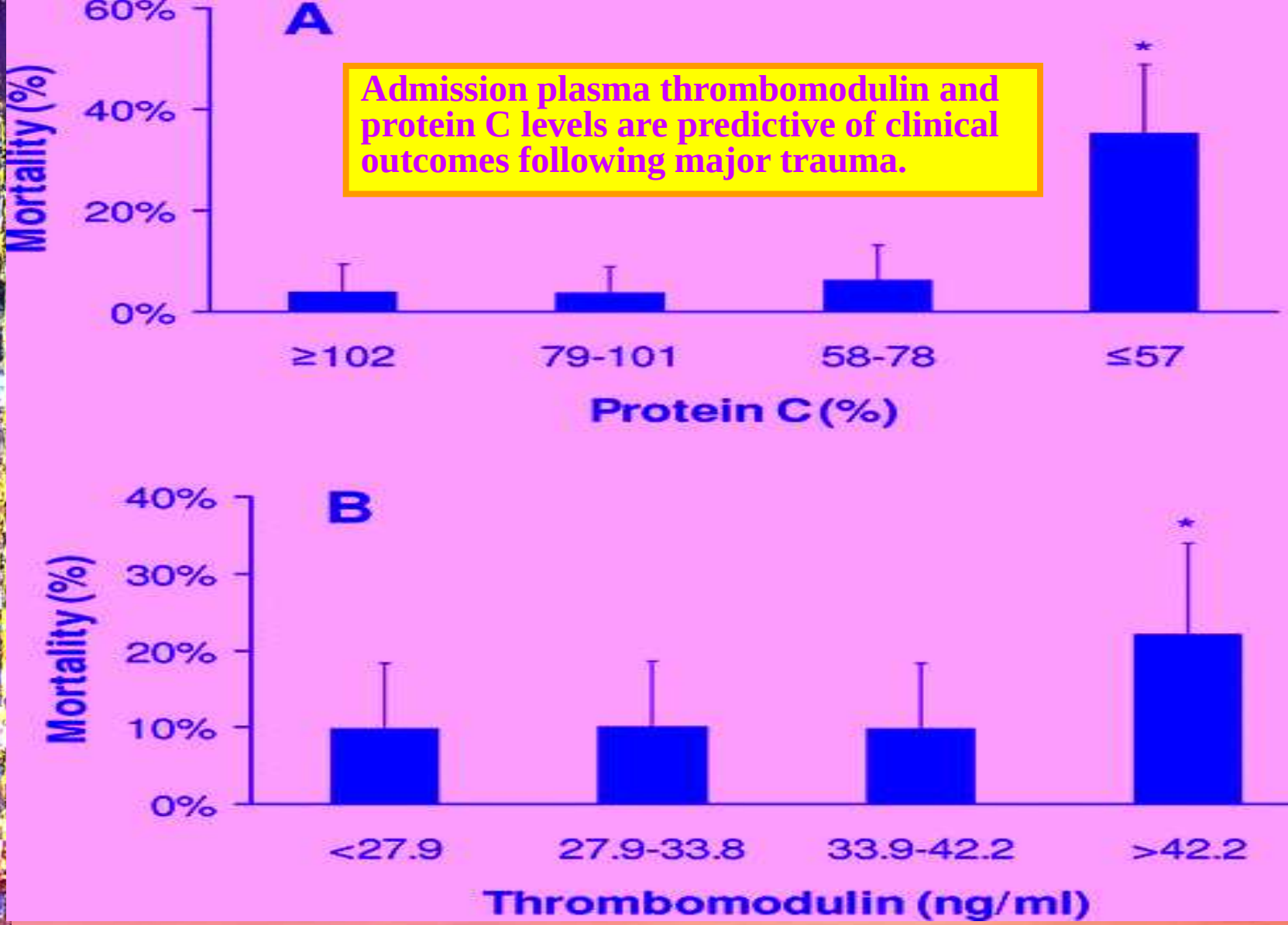
European Collaborative Study



Retrospective analysis of 5000 Patients European Collaborative Study



Coagulation Cascade



Admission plasma thrombomodulin and protein C levels are predictive of clinical outcomes following major trauma.

Acute Traumatic Coagulopathy: Initiated by Hypoperfusion Modulated Through the Protein C Pathway?

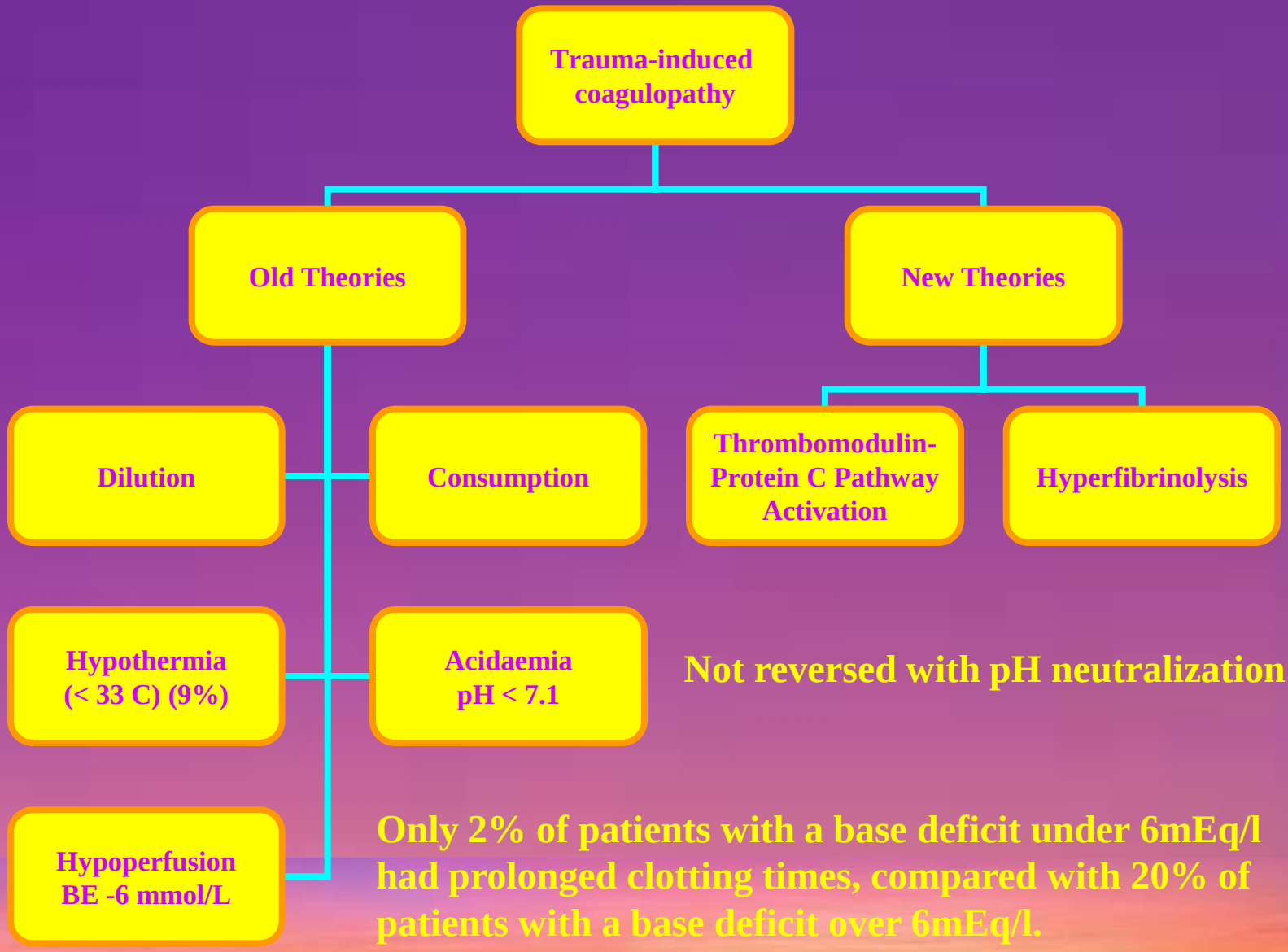
Karim Brohi, FRCS, FRCA;* Mitchell J. Cohen, MD,* Michael T. Ganter, MD,† Michael A. Matthay, MD,‡ Robert C. Mackersie, MD,* and Jean-François Pittet, MD†‡ Ann Surg. 2007 May; 245(5): 812–818.

The Relationship of Low Protein C and High Thrombomodulin Levels to Clinical Outcomes

N.B. OR = Odd Ratio	Low protein C (OR 95% CI)	High Thrombomodulin (OR 95% CI)
Mortality	6.2 (2.7-14.1) (P <0.01)	2.5 (1.2-5.4) (P<0.02)
Ventilator free days at D28	2.2 (1.5-3.3) (P <0.01)	1.6 (1.0-2.6) (P 0.07)
Acute renal injury	3.6 (1.7-6.7) (P <0.01)	3.2 (1.5-6.7) (P 0.02)
Acute lung injury	1.4 (0.9-4.6) (P 0.34)	2.1 (0.9-4.6) (P 0.09)

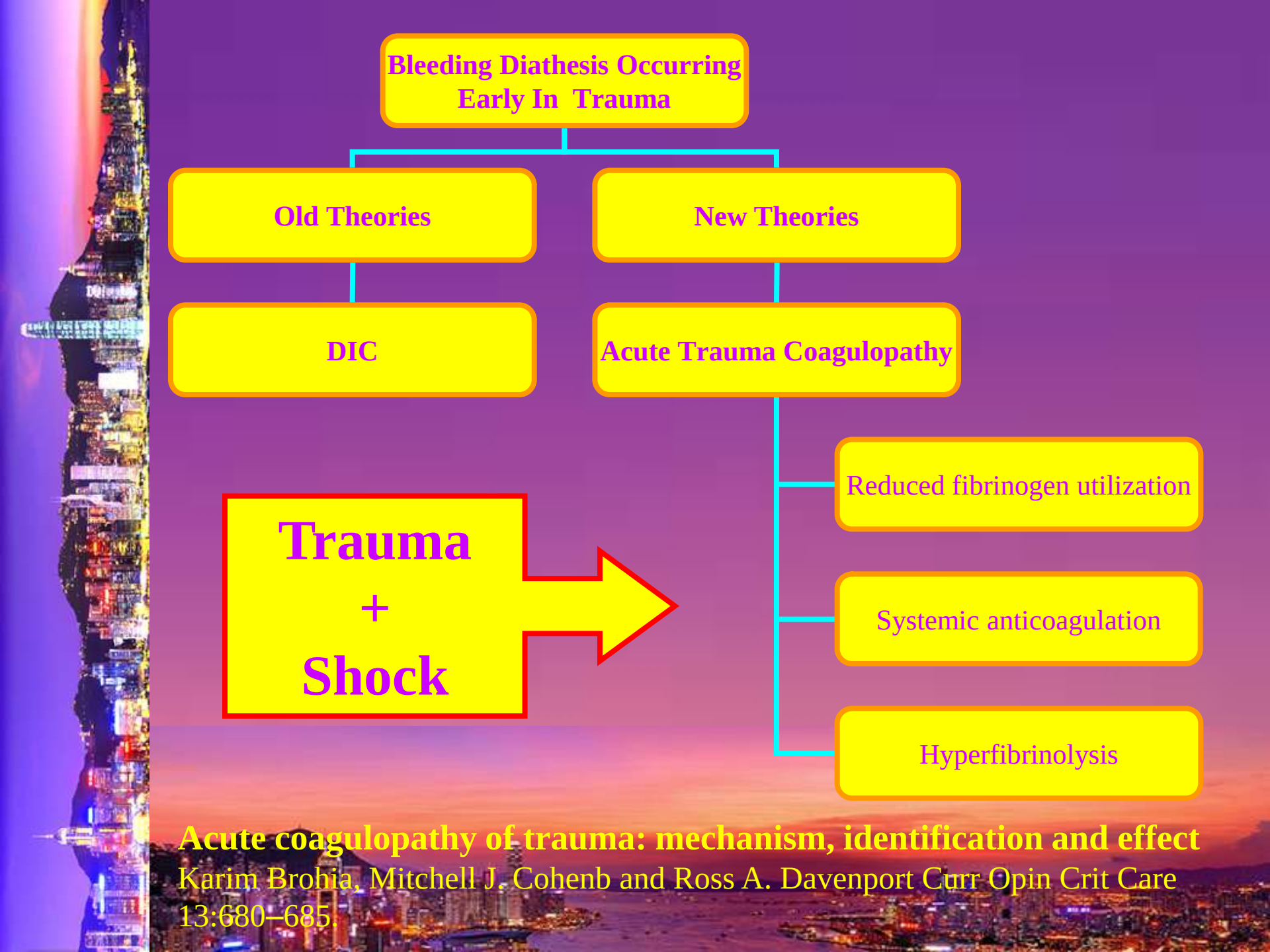
High thrombomodulin and low protein C levels were significantly associated with increased mortality, blood transfusion requirements, acute renal injury, and reduced ventilator-free days.

Acute Traumatic Coagulopathy: Initiated by Hypoperfusion Modulated Through the Protein C Pathway?
Karim Brohi, FRCS, FRCA,* Mitchell J. Cohen, MD,* Michael T. Ganter, MD,† Michael A. Matthay, MD,‡ Robert C. Mackersie, MD,* and Jean-François Pittet, MD†‡ Ann Surg. 2007 May; 245(5): 812–818.



Acute coagulopathy of trauma: mechanism, identification and effect

Karim Brohia, Mitchell J. Cohenb and Ross A. Davenport Curr Opin Crit Care 13:680–685



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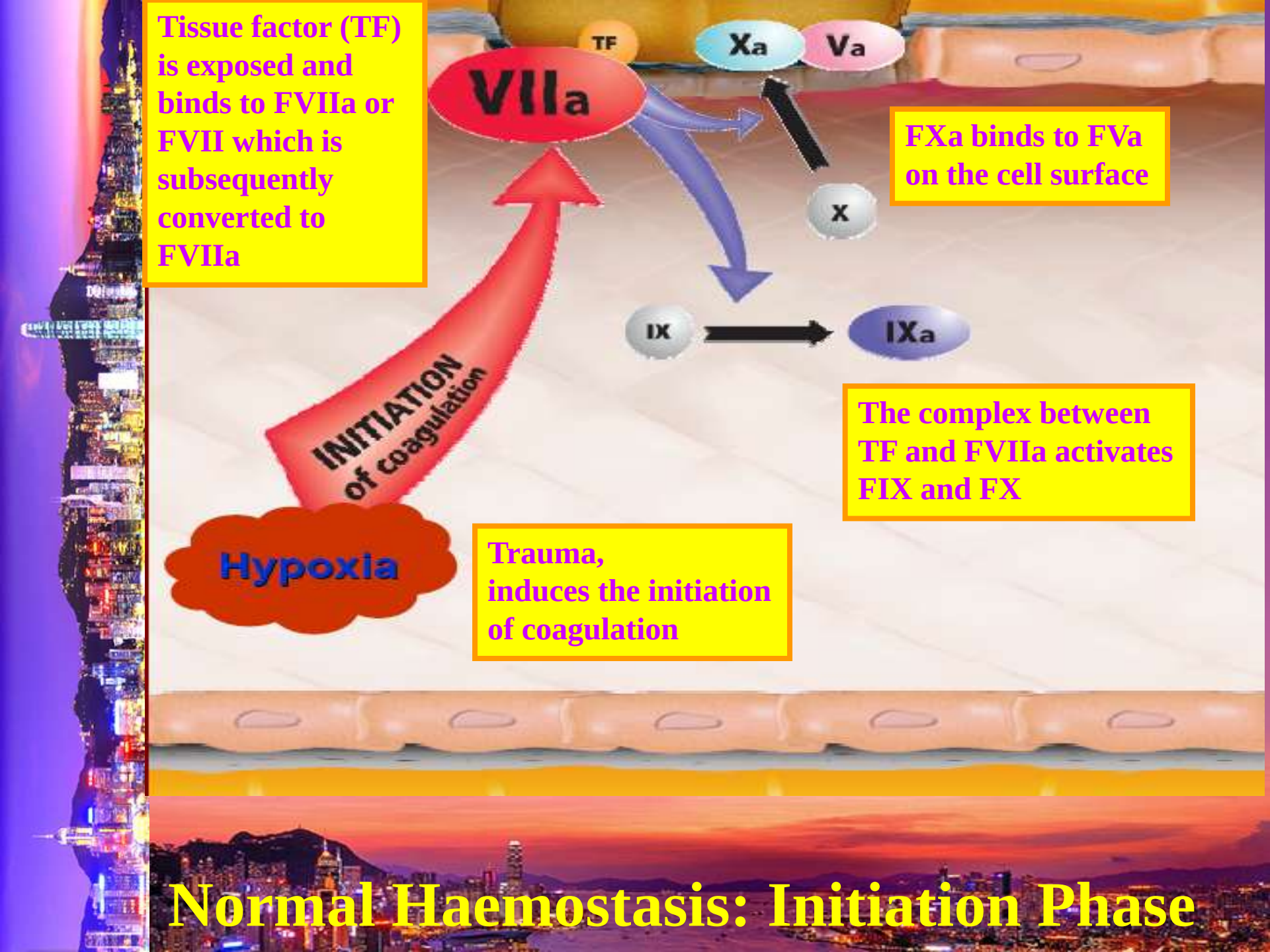
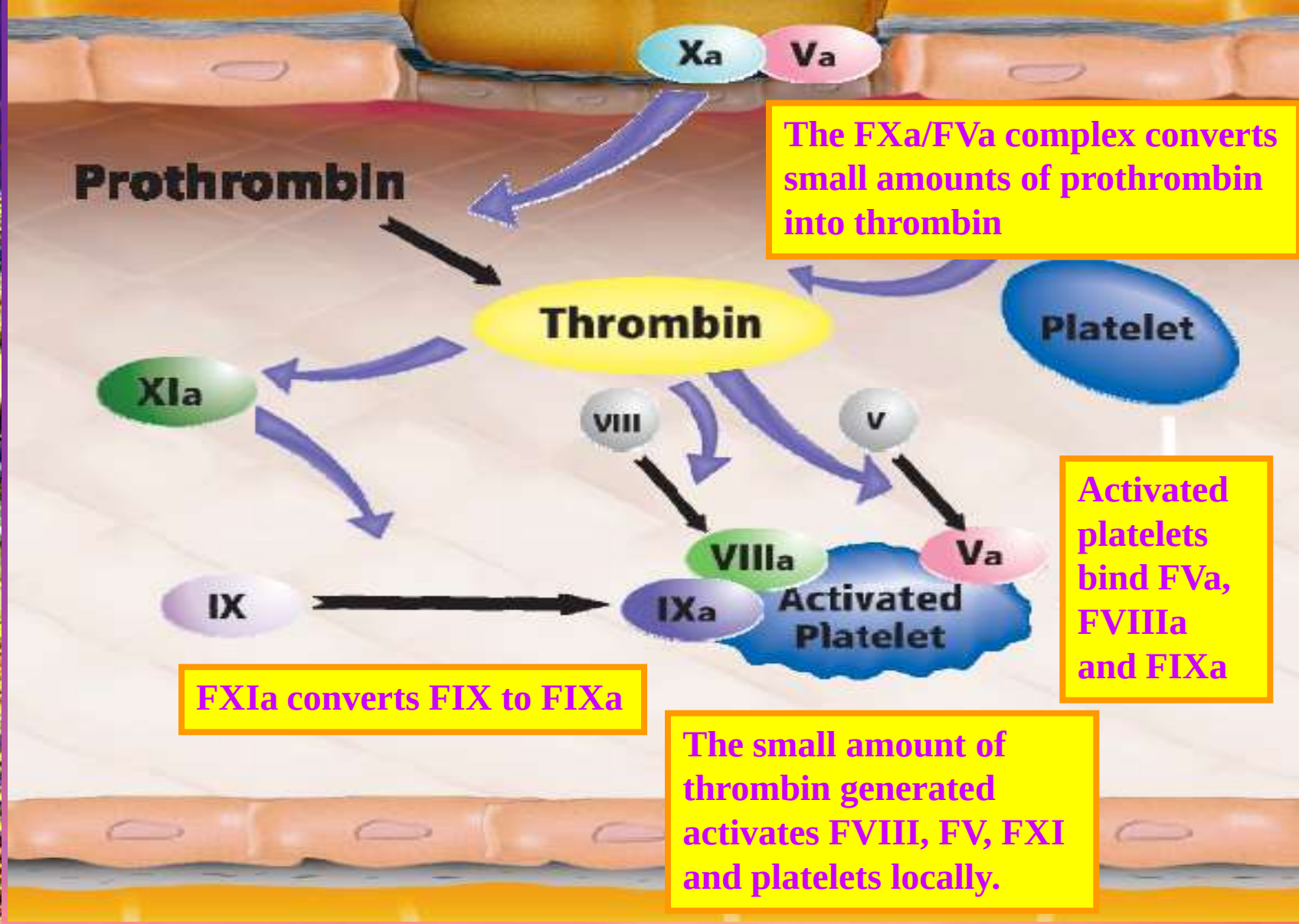
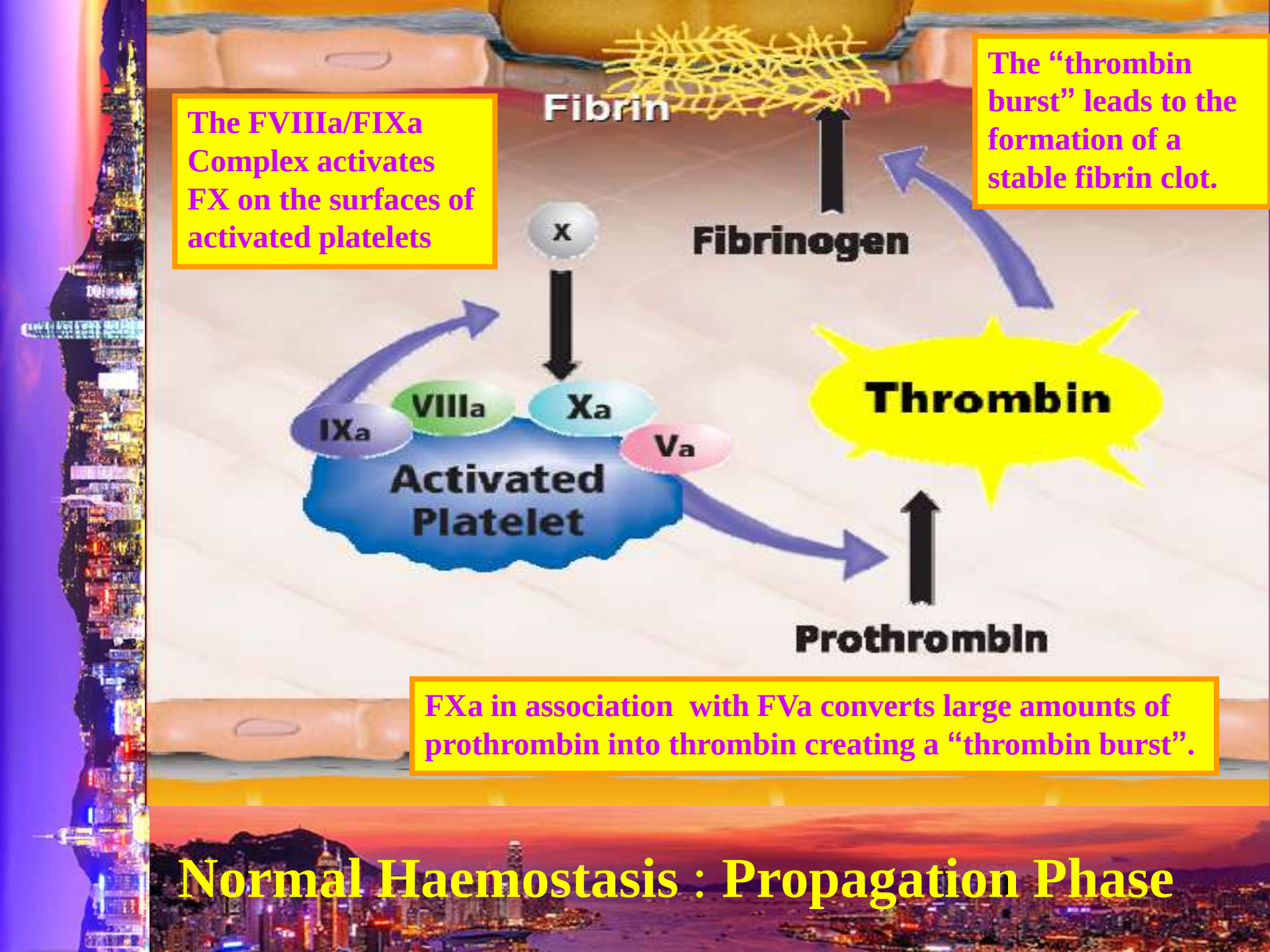


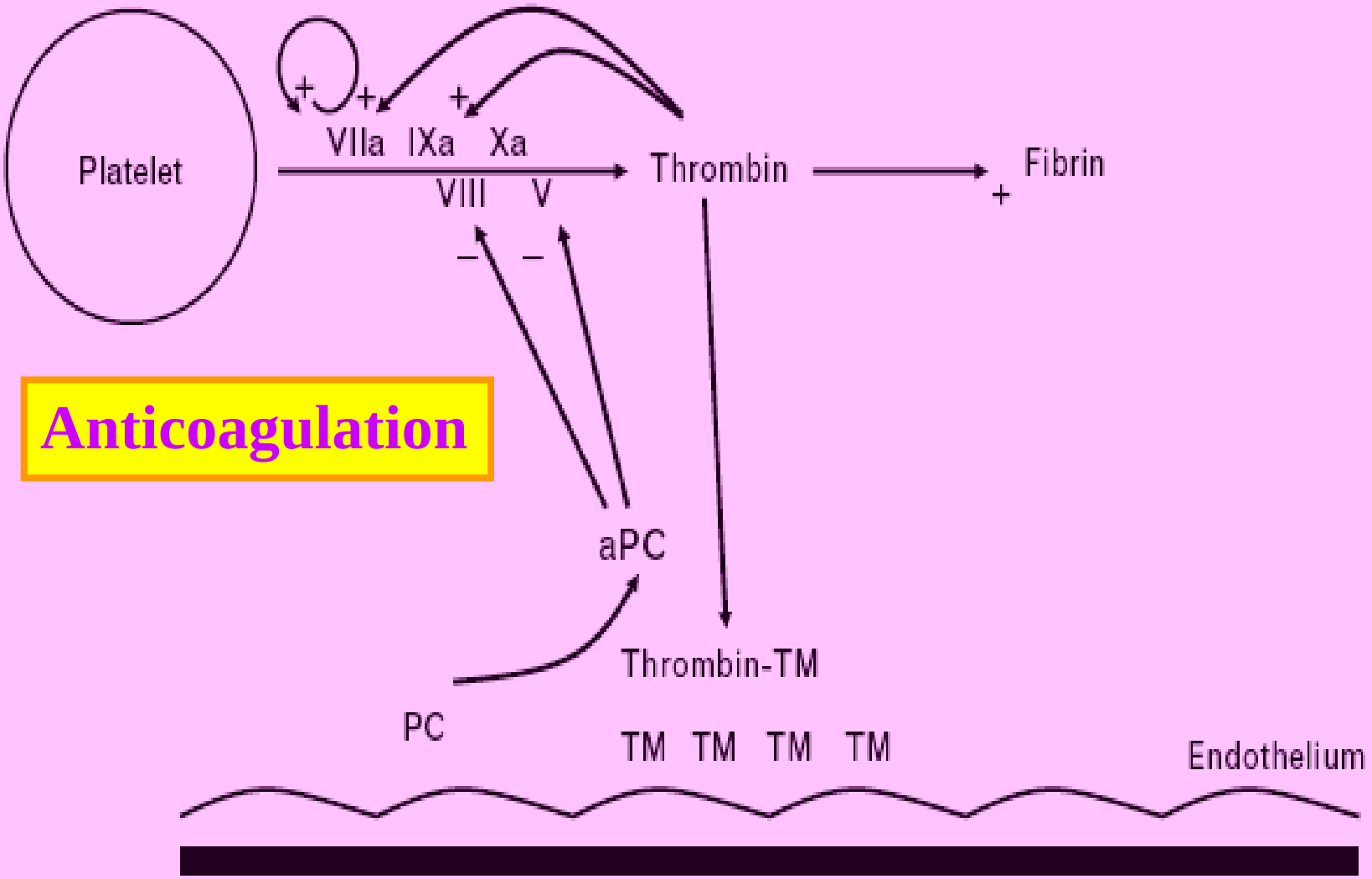
Normal Haemostasis: Initiation Phase



Normal Haemostasis: Amplification phase

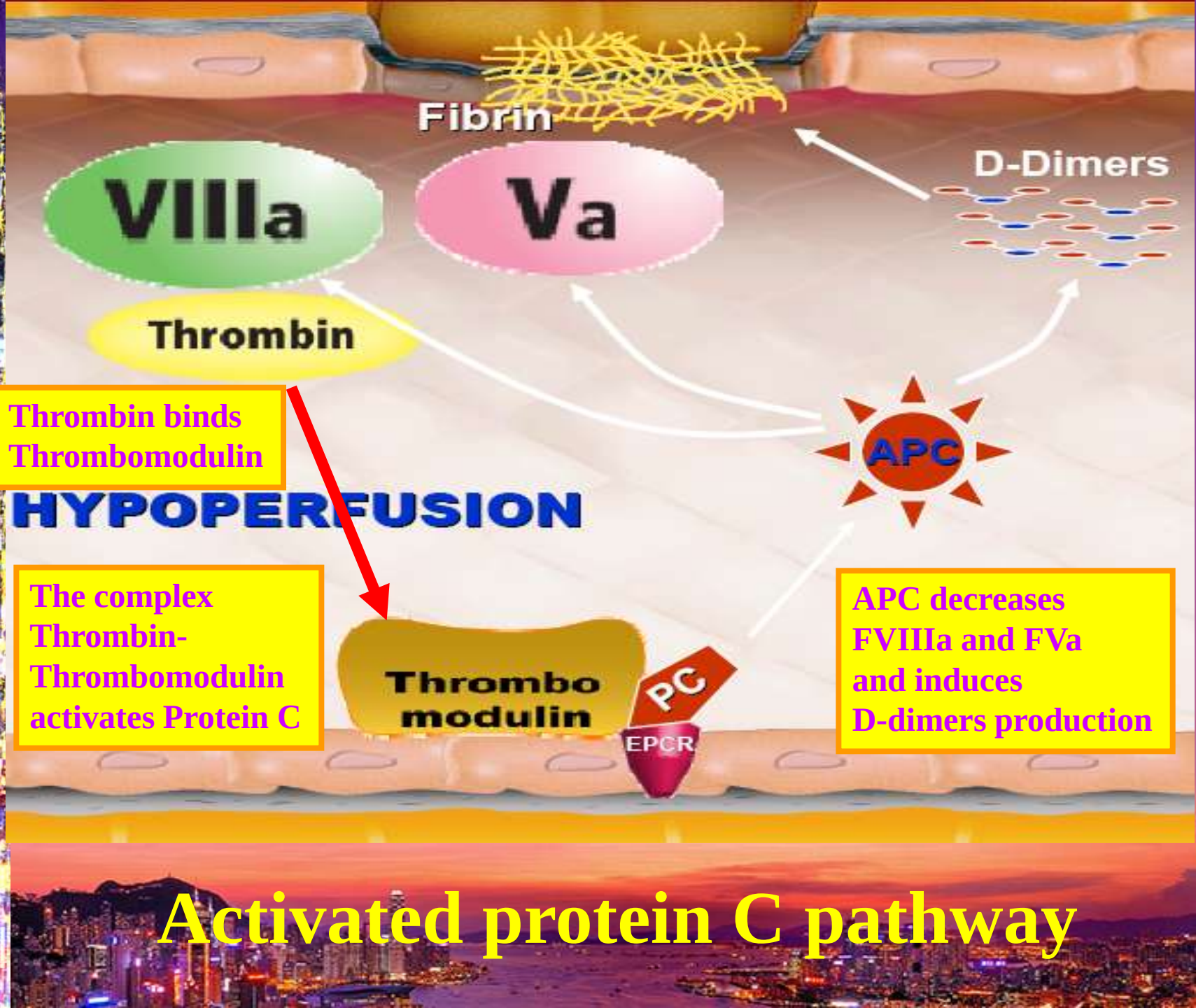


Normal Haemostasis : Propagation Phase



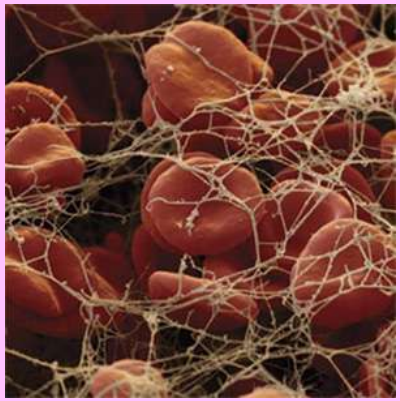
Anticoagulation

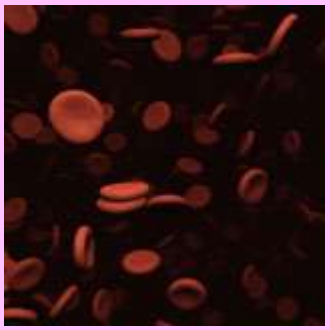
Thrombin is generated primarily via the 'extrinsic' pathway with multiple feed-forward loops. When thrombomodulin (TM) is presented by the endothelium, it complexes thrombin which is no longer available to cleave fibrinogen. This anticoagulant thrombin activates protein C which reduces further thrombin generation through inhibition of cofactors V and VIII.



Activated protein C pathway

Hyperfibrinolysis





Platelet

VIIa IXa Xa

VIII V

Thrombin

Fibrin

FDPs

Plasmin

PAI-1

tPA

aPC

Thrombin-TM

PC

TM TM TM TM

Endothelium

Tissue plasminogen activator (tPA) is released from the endothelium by injury and hypoperfusion and cleaves plasminogen to initiate fibrinolysis. Activated protein C (aPC) consumes plasminogen activator inhibitor-1 (PAI-1) when present in excess, and reduced PAI-1 leads to increased tPA activity and hyperfibrinolysis.

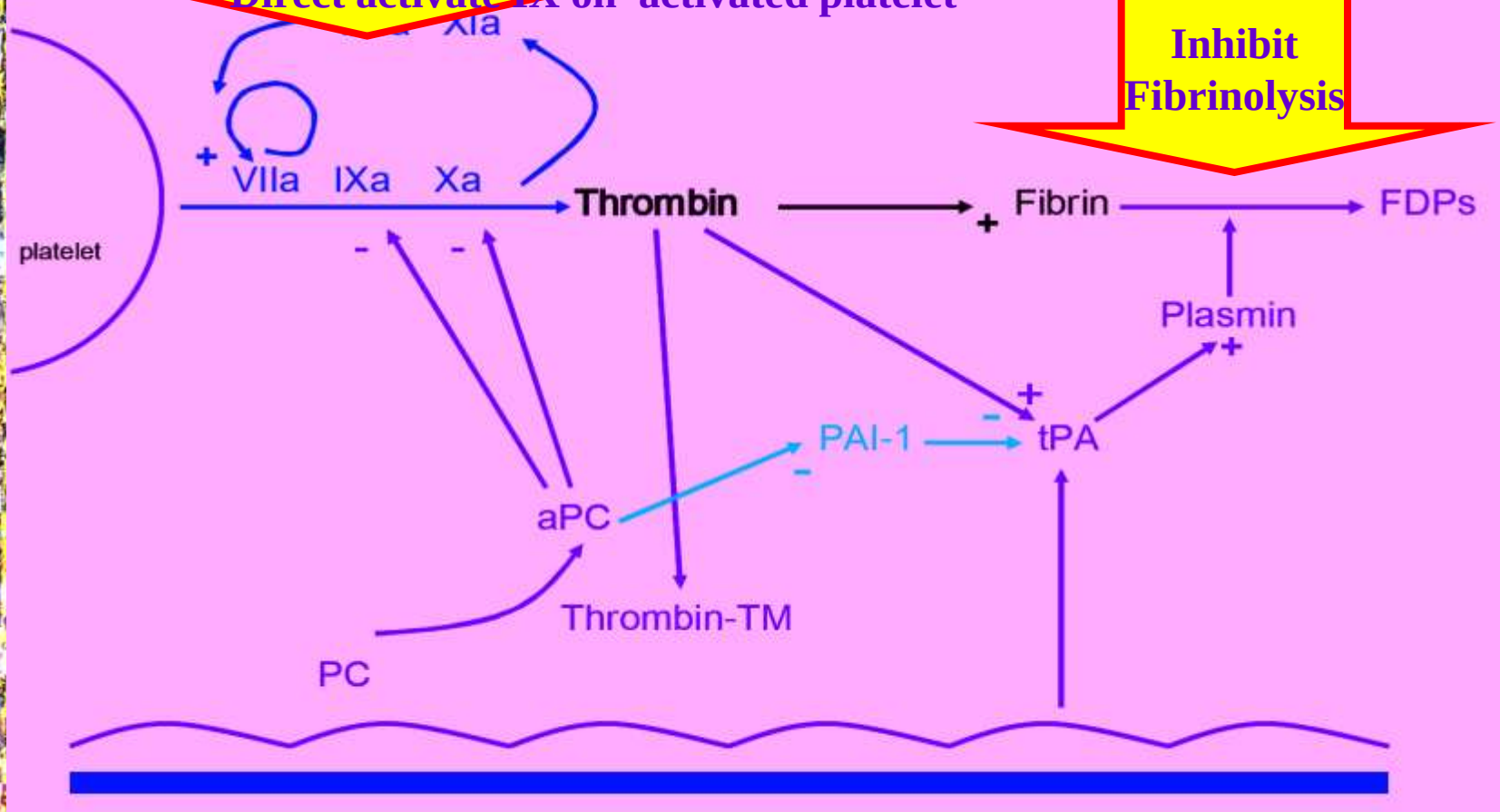
Direct thrombin generation even in the absence of F VIII & F IX

Increase Xa

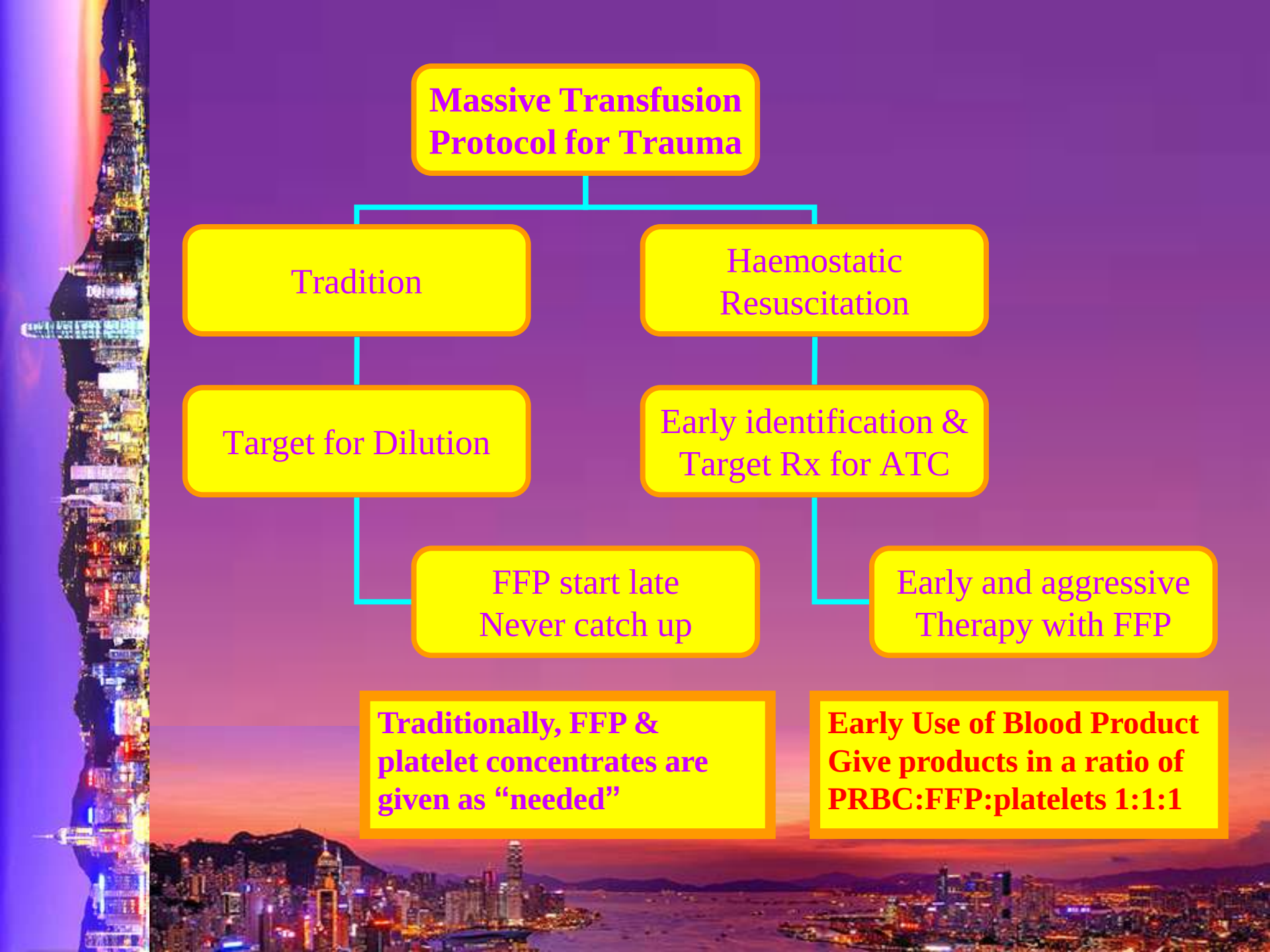
Direct activate IX on activated platelet

FVIIa

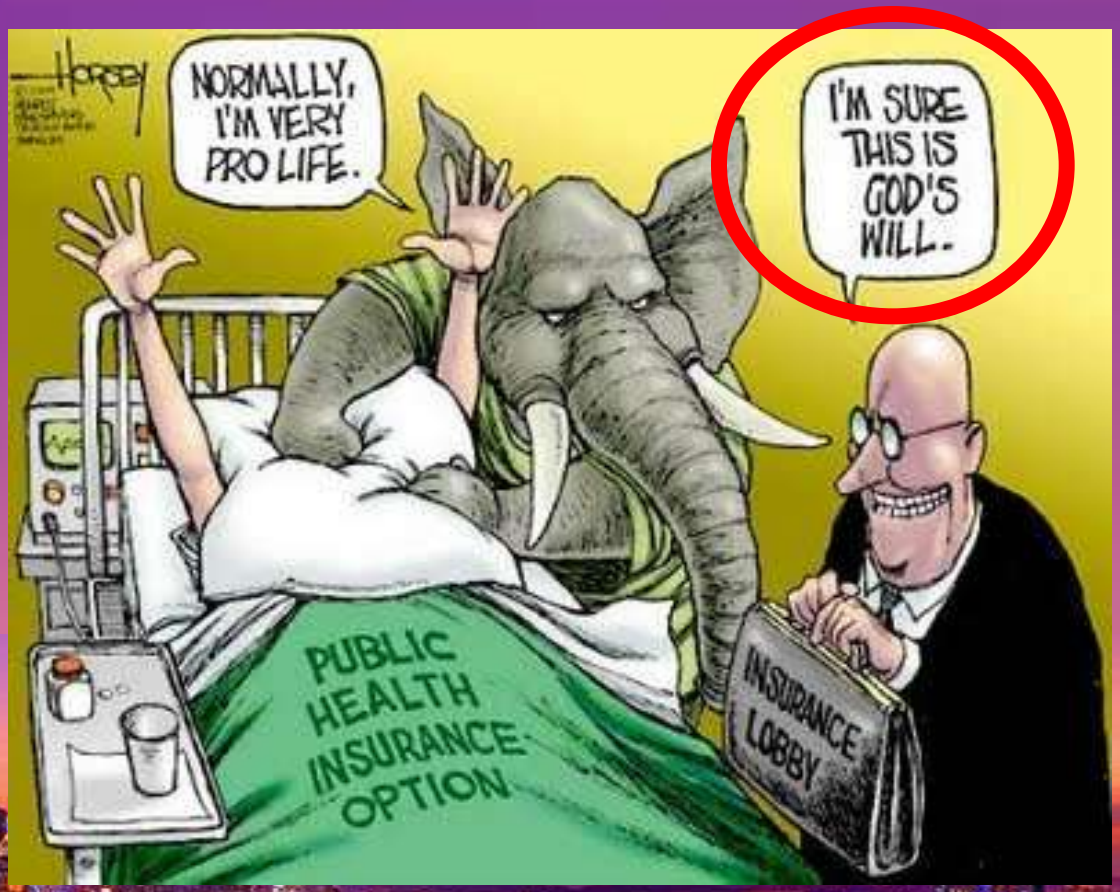
Inhibit Fibrinolysis



Potential Role of FVIIa in Acute Traumatic Coagulopathy


Massive Transfusion Protocol for Trauma
Tradition
Haemostatic Resuscitation
Target for Dilution
Early identification & Target Rx for ATC
FFP start late Never catch up
Early and aggressive Therapy with FFP
Traditionally, FFP & platelet concentrates are given as "needed"
Early Use of Blood Product Give products in a ratio of PRBC:FFP:platelets 1:1:1

What is the Natural Role of aPC in Acute Traumatic Injury ?



Animal Model of Trauma/Hemorrhage

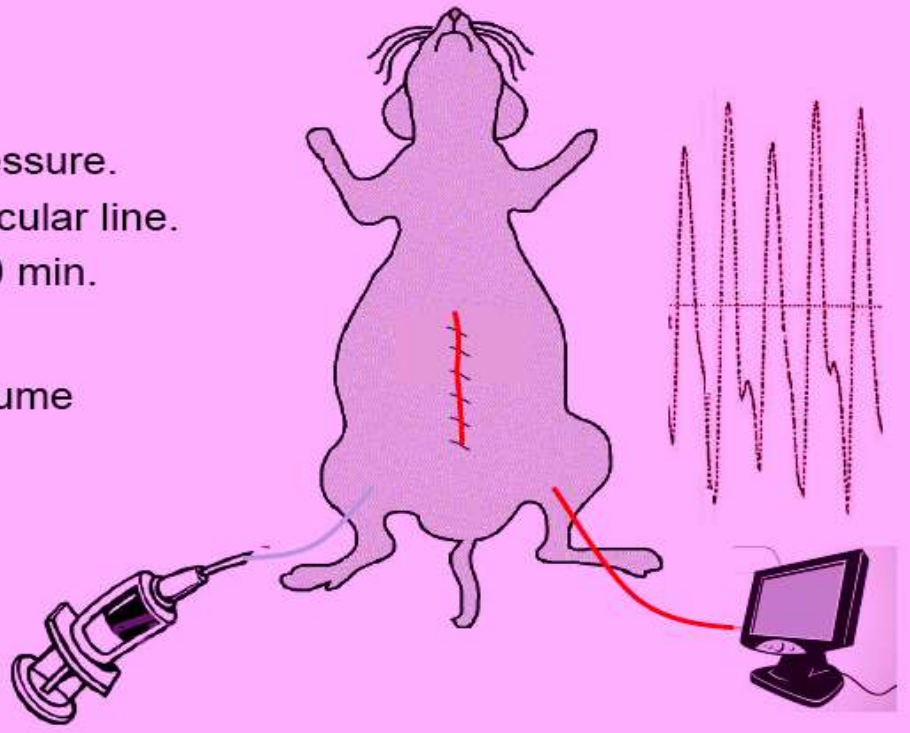
Soft-Tissue Trauma

Hemorrhagic shock:

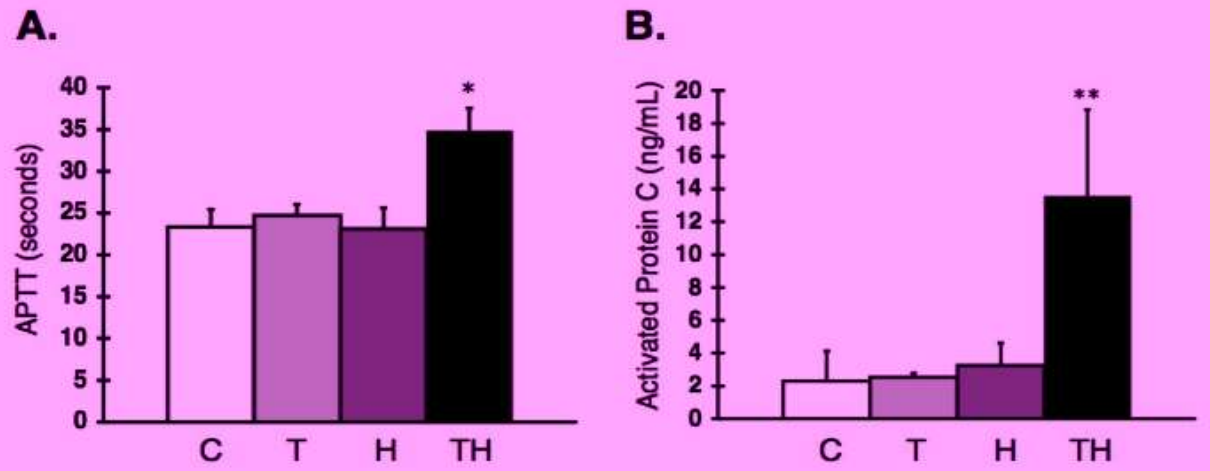
- Non-ventilated, fixed-pressure.
- Blood withdrawn via vascular line.
- MAP 35 +/- 5mmHg x 60 min.

Fluid Resuscitation:

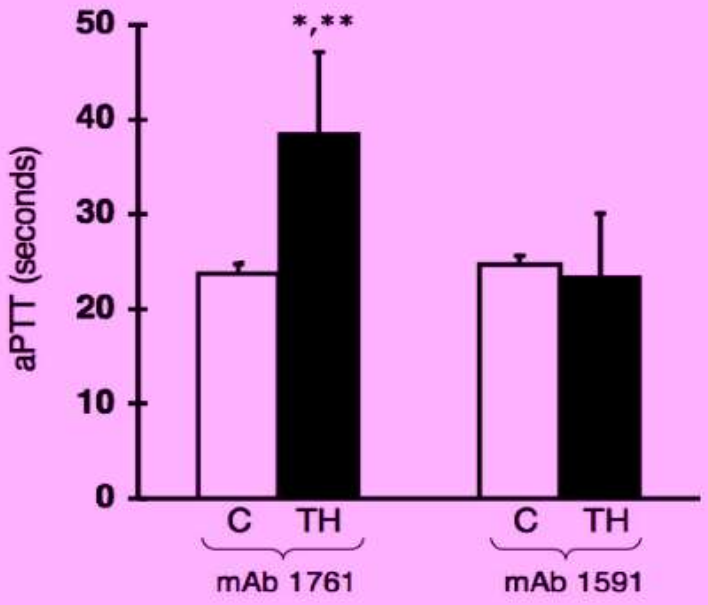
- LR @ 2x shed blood volume
  + shed blood

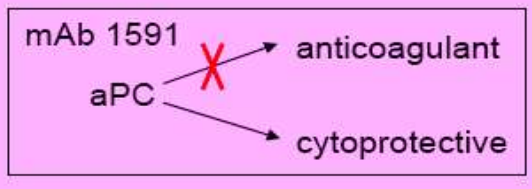


Acute Traumatic Coagulopathy in Mice

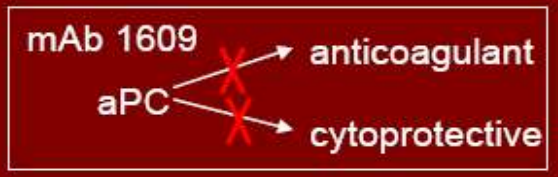


Acute Traumatic Coagulopathy is Mediated by aPC Anticoagulant Function

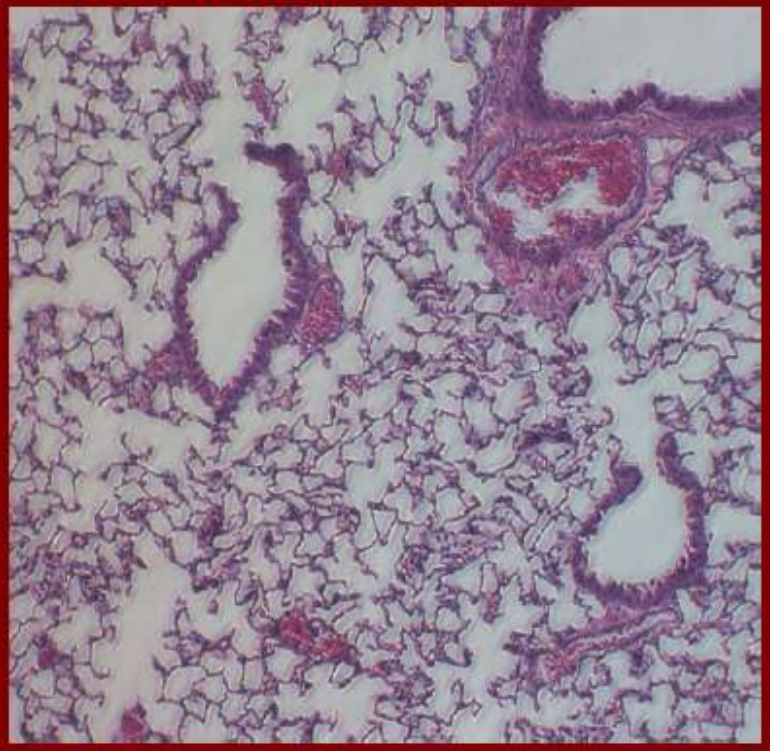




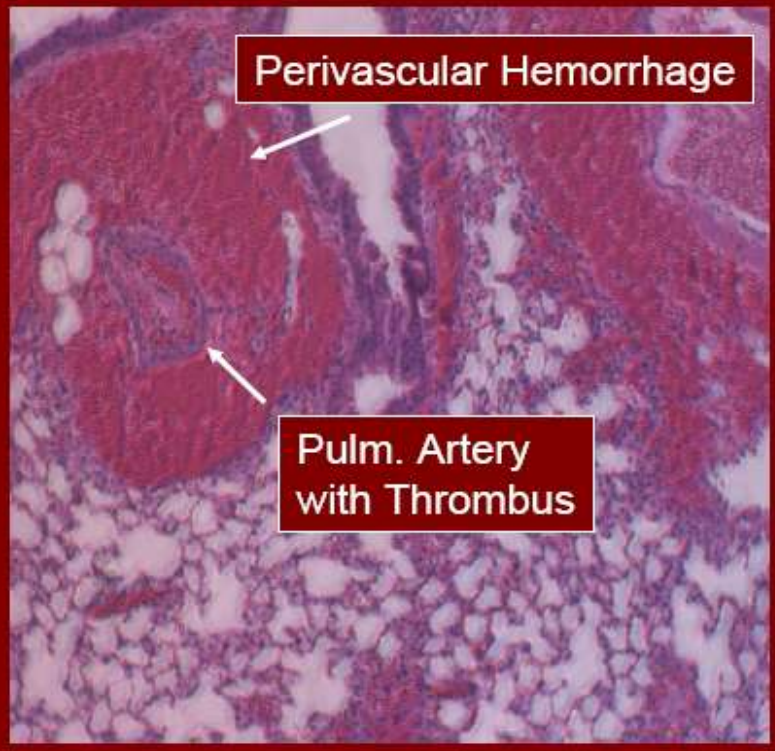
Inhibition of the Cytoprotective Domain of Protein C Causes Diffuse Intravascular Coagulation Lung Injury



A. Control mAb

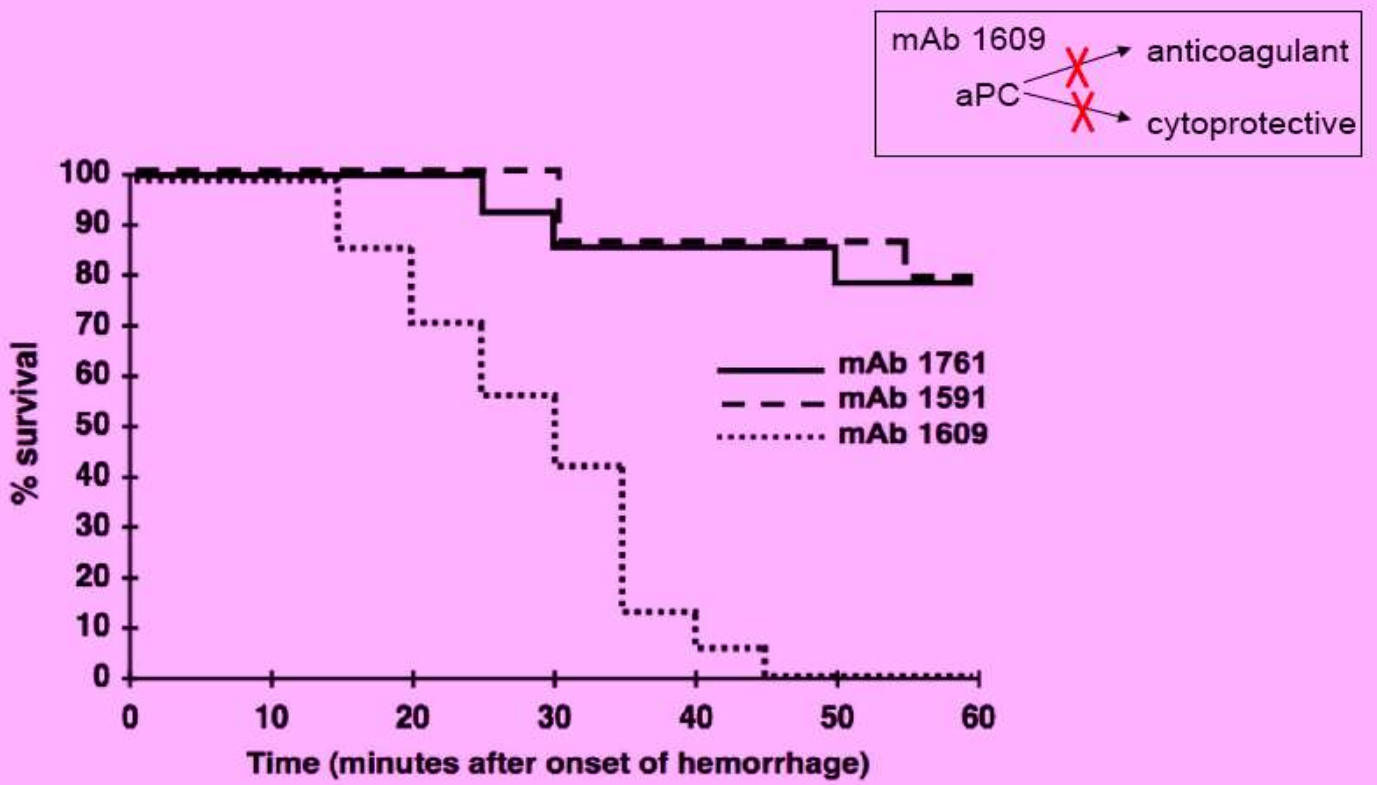


B. mAb 1609



Jean-Francois Pittet Cardiovascular Research Institute University of California San Francisco

Acute Traumatic Coagulopathy in Mice:



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Summary

- *First* Animal Model of Acute Traumatic Coagulopathy
  - Mimics human response to trauma/hypoperfusion
- Role of Activated Protein C in Trauma/ Hypoperfusion

aPC function Required for	Acute Traumatic Coagulopathy	SURVIVAL/ Prevention of DIC
Anticoagulation	+	-
Cytoprotective	-	+

Jean-Francois Pittet Cardiovascular Research Institute University of California San Francisco

Clinical Implications

- Inhibition of anticoagulant function of Protein C could become a NEW, mechanistic treatment for Acute Traumatic Coagulopathy in trauma patients.
- Role of protein C in **organ dysfunction** in traumatic shock: recombinant mutant non-anticoagulant protein C…potential treatment in humans ?

Conclusion (I)

- Data are starting to support changes in transfusion approaches and policy:
  - Trauma is a leading case of death worldwide and 30-40% of trauma patients die secondary to bleeding and coagulopathy
  - Early trauma induced coagulopathy occurs in ~25% of trauma patients and predicts four fold increased in mortality
  - Implementation of a MTP with aggressive use of plasma/cryoprecipitate/platelets may reduce mortality and may reduce blood product usage.
  - Increased amount of coagulation products relative to RBC products transfused improves mortality
  - Until results from prospective trials, current data support a target ratio of plasma:red blood cell:platelet transfusions of 1:1:1. during massive blood loss

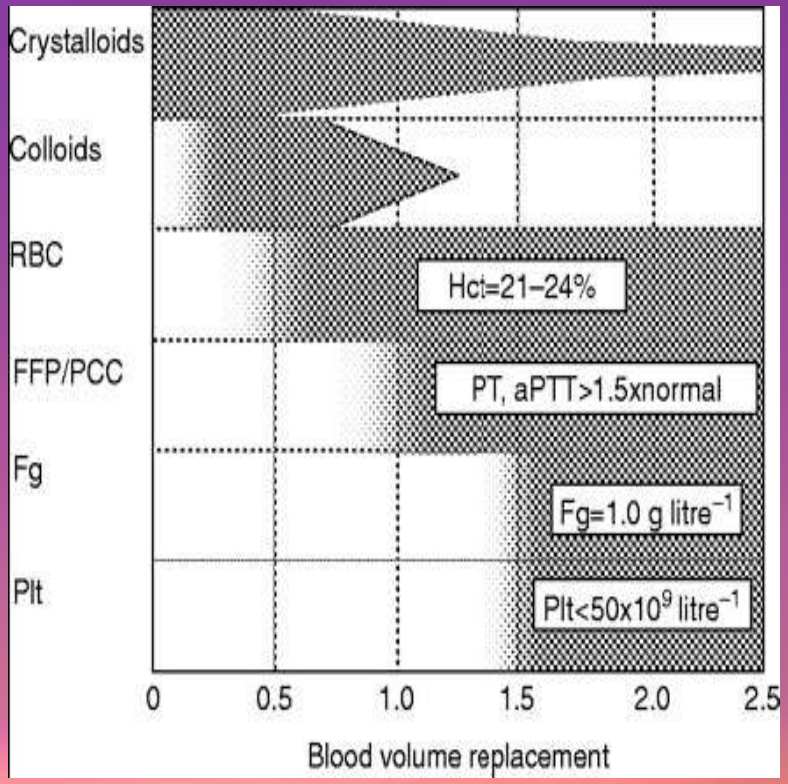
Conclusions (II)
Goal for Resuscitation - Early

- Expedite control of hemorrhage with damage control surgery
- Maintain blood pressure 80-100 mmHg systolic!
- Limit crystalloid infusion and consider vasopressors early!
- Give blood products early and often: pRBC: FFP:Platelet at 1:1:1 ratio
- Frequent laboratory studies!

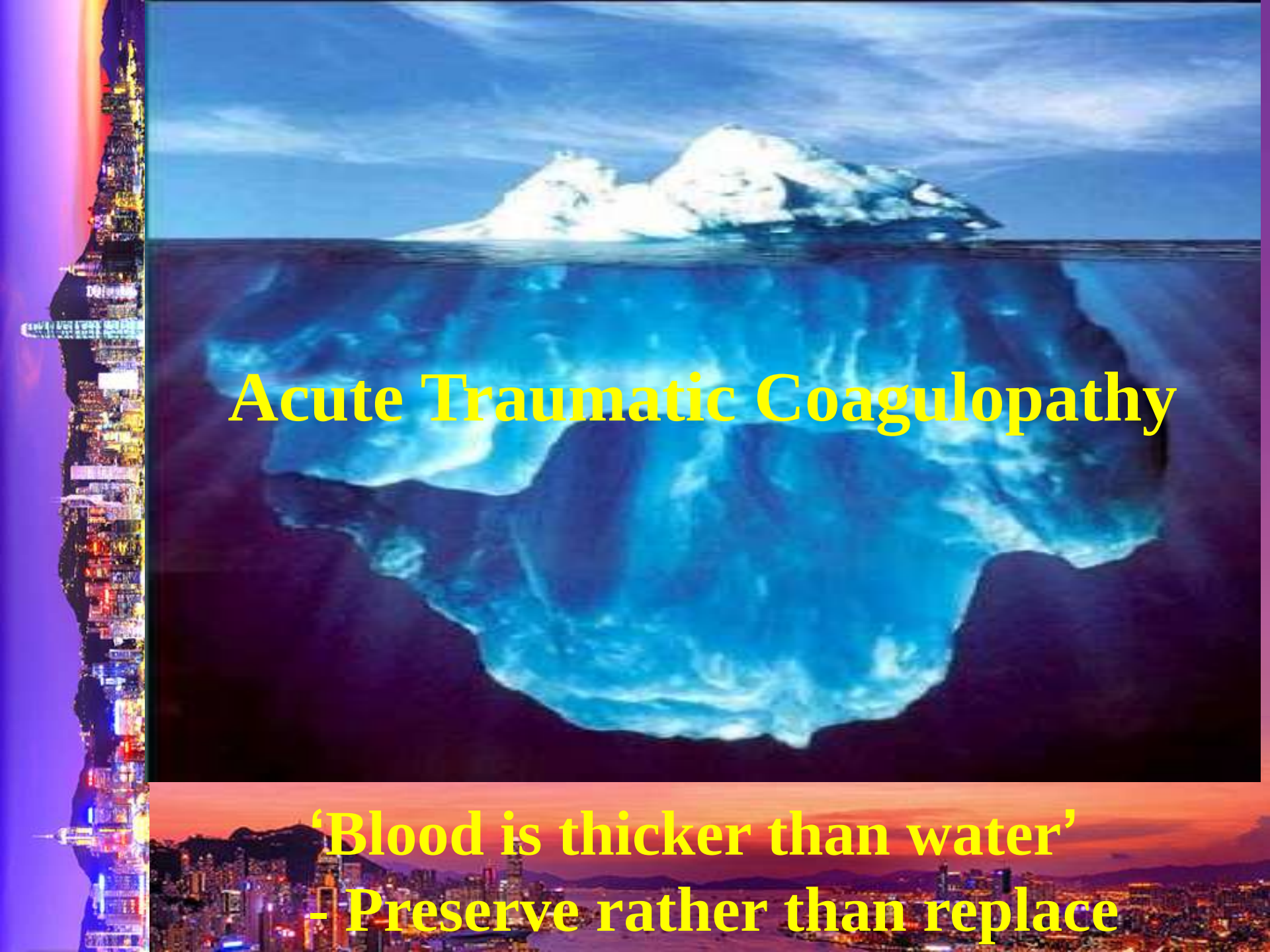
Conclusions (III)

Key Goals for the Management of critical bleeding in the Trauma Patient : 8 Steps to Support Coagulation

1. Achieve normothermia
2. Achieve normal pH
3. Achieve normal Ca2++
4. Treat with FFP, if PT or aPTT abnormal
5. Treat with platelets, if < 80 x 109
6. Treat with Fibrinogen, if < 1g/l
7. Treat with Antifibrinolytics,if hyperfibrinolysis
8. Treat with rFVIIa, if all else fails Plt > 50x109, Fg > 1g/l, Hct >24, pH > 7,2



Modified from Spahn D, Roissaint R, Br J Anaesth 2005; 95(2): 130-139


Acute Traumatic Coagulopathy
‘Blood is thicker than water’
- Preserve rather than replace

Any Questions ?

Risk of Transfusion

Dr. Lai Kang Yiu
Intensive Care Unit
Queen Elizabeth Hospital

Risks of Transfusions
(Dzieczkowski and Anderson)

- **Reactions (Frequency: unit)**
  - Febrile (FNHTR) 1–4:100
  - Allergic 1–4:100
  - Delayed hemolytic 1:1,500
  - Acute hemolytic 1:12,000
  - Fatal hemolytic 1:100,000
  - Anaphylactic 1:150,000
  - TRALI: 1:5000
- **Miscellaneous**
  - RBC allosensitization 1:100
  - HLA allosensitization 1:10
  - Graft vs. host disease Rare
- **Infections**
  - CMV 3-12:100
  - Hepatitis C 1:103,000
  - Hepatitis B 1:200,000
  - HIV-1 1:490,000
  - HIV-2 Unknown
  - HTLV-I (II) 1:641,000
  - Malaria 1:4,000,000
- Immunomodulation
  - Postoperative sepsis
  - Tumour relapse

Possible Mechanisms of Transfusion-Associated Immunomodulation

- Anergy
- Tolerance
- Cytokines released during blood storage
- Iron-mediated immune suppression
- Suppressor cell network inhibition
- Anti-idiotypic and anti-clonotypic antibodies
- Clonal deletion

Any Questions ?