AABB Annual Meeting Education Program 2014

October 25-28, 2014 | Pennsylvania Convention Center | Philadelphia, PA

Presentation Handouts

(9416-TC-PBM) Management of Bleeding Patients

October 28, 2014 ✧ 2:00 PM - 3:30 PM

Advancing Transfusion and Cellular Therapies Worldwide

Event Faculty List

Event Title: **(9416-TC-PBM)** Management of Bleeding Patients
Event Date: October 28, 2014
Event Time: 2:00 PM - 3:30 PM

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Disclosure: Yes

Target-specific Oral Anticoagulants and Anti-platelet Agents

Bleeding Management
Peri-operative Issues

Target Specific Oral Agents

- Disclosure
  - Speakers Bureau – Pfizer/BMS – apixaban
  - Advisory Board – American Red Cross
  - Speakers Bureau – Novartis – Exjade
  - TMAB – Grifols
- PI – Pharmacosmos - P – Monofer – IDA - 02
- PI – Boehringer-Ingelheim – 1321.3

Off label use: F VIIa, PCC

Anti-Thrombotic Therapy

- Anticoagulant and anti-platelet use growing as population ages – estimate 12 M with AF
- Industry is focused on developing more effective and safe agents
- Economic favors a shift to oral agents to minimize hospital length of stay
- Elimination of monitoring assays is another goal
- In recent years, three new agents have been approved – indications are expanding – additional agents, e.g., edoxaban are anticipated

Traditional Anticoagulants

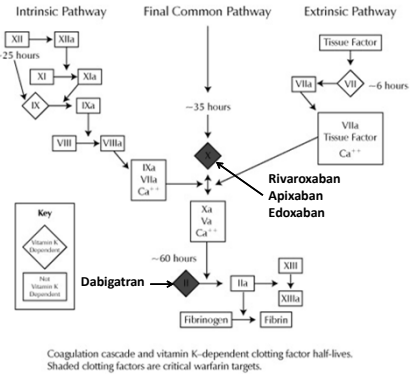
- Unfractionated Heparin (UFH): Originally isolated in 1916 from canine liver cells (cf: hepar)
- Highest negative charge (sulfated) of any known biologic molecule
- Usually purified from bovine lung and porcine intestinal sources – Mw 12-15 Kd
- Accelerates antithrombin activity (IV and subq)
- UFH monitored by PTT
- Antidote: Protamine

Traditional Anticoagulants

- Warfarin: Oral anticoagulant that reduces post-translational carboxylation of vitamin-K dependent proteins (VKA's)
- Coagulation factors II, VII, IX and X: Main vitamin K-dependent clotting proteins
- Therapeutic response usually monitored by Prothrombin Time/International Normalized Ratio (PT/INR) – TTR ~60%
- Narrow therapeutic window
- Leading agent for readmission - bleeding
- Antidote: Vitamin K, PCC or FFP

New Oral Anticoagulants

- Chemical structures designed to fit into activated coagulation enzyme active site
- Absorption from GI tract necessary before onset
- Current targets: IIa and Xa
- Monitoring for therapeutic effect not required
- Faster onset – 1-4 hours
- Unlike UFH and VKA's: no specific antidote



Coagulation cascade and vitamin K-dependent clotting factor half-lives.
Shaded clotting factors are critical warfarin targets.

New Oral Anticoagulants

	Dabigatran Etexilate (Pradaxa)	Rivaroxaban (Xarelto)	Apixaban (Eliquis)	Edoxaban
MOA	Direct Thrombin inhibitor	Direct FXa inhibitor	Direct FXa inhibitor	Direct FXa inhibitor
Manufacturer	Boehringer Ingelheim	Bayer	Bristol Myers and Squibb	
Indications	1. Reduce risk of stroke and TE in NV-AF 2. Rx of DVT/PE 3. DVT prophy	1. Reduce risk of stroke and TE in NV-AF **2. Rx of DVT/PE Rx** **3. DVT prophylaxis**	1.Reduce risk of stroke and TE in NV- AF 2. DVT/PE Rx 3. DVT prophy	**Pending**

Target Specific Oral Agents

Dabigatran

- Competitive, potent and reversible
- Binds to active site of thrombin – inhibits both free and fibrin bound
- Thrombin inhibition is dose dependent
- Peak effect 1.5 hrs
- Trough at 12 hrs
- Steady state 3 days
- Half life – 12-15 hrs
  - If Cr clearance is <30 mL/min – $t_{1/2}$ >24 hrs
  - Renal excretion accounts for 80% of clearance

Dabigatran vs Warfarin

RELY TRIAL – NEJM 2009;361:1139

(n=)	110 mg Dabi (6015)	150 mg Dabi (6076)	Warfarin (6022)	P=value
D/C at 1 yr (%)	14.5	15.5	10.2	
Primary outcome – Stroke/TE (%/yr)	1.53	1.11*	1.69	*<0.001
MI (%/yr)	0.72	0.74	0.53*	<0.48
Intracranial Bleed	27 (0.23)*	36 (0.30)*	87 (0.74)	<0.001
Extracranial bleed	299 (2.51)	342 (2.84)	315 (2.67)	NS
GI Bleed	133 (1.12)	182 (1.51)*	120 (1.02)	*<0.001
Life-threatening Bleed	145 (1.220)*	175(1.45)**	212(1.8)	*<0.001 and **<0.04

Target Specific Oral Agents

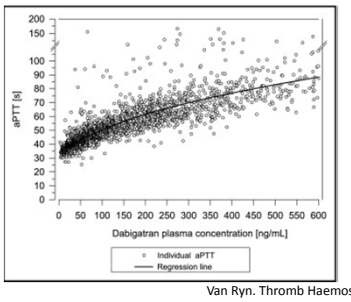
LABORATORY TESTING

- Dabigatran – bleeding cases

1. May see slightly elevated PT and elevated PTT (may use PTT for crude measure)
2. Thrombin time useful to determine if drug effect gone.
3. At usual oral doses - thrombin time too sensitive for monitoring drug effect

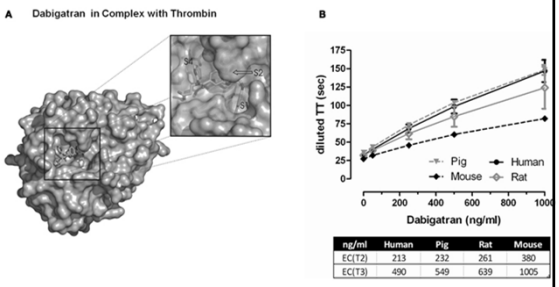
Target Specific Oral Agents

LABORATORY TESTING



Van Ryn. Thromb Haemost 2010;103:1116

Target Specific Oral Agents



ng/ml	Human	Pig	Rat	Mouse
EC(T2)	213	232	261	380
EC(T3)	490	549	639	1005

ROCKET-AF

Outcome	Rivaroxaban	Warfarin	P value
Primary outcome (Stroke/TE) %/yr	1.7	2.2	<0.001
Major bleeding %/yr	3.6	3.4	NS
ICH	0.5	0.7	0.02
GI Bleed	3.2	2.2	0.001
Hb ↓ >2 g	2.8	2.3	0.02
RBC Tx	1.6	1.3	0.04
Critical bleeding	0.8	1.2	0.007
Fatal bleeding	0.2	0.5	0.02

Rivaroxaban

- Rapidly absorbed
- 2/3rd metabolized by liver P450
- Excretion renal 2/3rd and bile 1/3rd
- Affects PT/INR more than PTT
- May be assessed by anti-Xa assay
  - Therapeutic range?

ARISTOTLE

Outcome	Apixaban	Warfarin	P value
Primary outcome (Stroke/TE) %/yr	1.27	1.60	<0.01
Major bleeding %/yr	3.6	3.4	NS
ICH	0.33	0.8	<0.001
GI Bleed	0.76	0.86	NS
Major or clinically relevant non-major bleeding	4.07	6.01	<0.001
Any bleeding	18.1	25.8	<0.001
Net clinical outcomes – stroke, TE, or major bleed	3.17	4.11	<0.001

Apixaban

- Rapidly absorbed from GI – mainly terminal ileum and ascending colon
- 87% protein bound
- Metabolized by P450 CYP3A and P-gp
- Excretion both renal (25%) and fecal (75%)
- Affects both PT/INR and PTT
- May be monitored by anti-Xa assay

TSOAC Lab Testing

- For rivaroxaban and apixaban: PT more prolonged with Xa inhibitors than dabigatran.
- Thrombin time usually not prolonged with Xa inhibitors.
- LMWH assays can be used to detect oral Xa inhibitors, but not determine therapeutic levels
- Calibrators for rivaroxaban and apixaban are available

	Warfarin	Dabigatran	Rivaroxaban	Apixaban
Onset of action	2-5 days	0.5-2 hrs	1-4 hrs	3-4 hrs
Dosing	Once a day	Twice a day	Once a day	Twice a day
Bioavailability (%)	90	4-10	60-80	50%
Prodrug	No	Yes	No	No
Variability	Common	Uncommon	Uncommon	Unknown
Therapeutic Index	Narrow	Not known	Not known	Not known
Diet/ drugs	++++	+	Not known	+
Monitoring needed	Yes	No	No	No
Test to monitor	INR	?Thrombin time	?Anti-Xa assay	?Anti-Xa assay
Elimination half life	20-60 h	12-17 hrs	6-9 hrs	12 hrs
Excretion	Liver	85% renal	66% renal	27% urine
Antidote	PCC/FFP/Vit K	None	None	None

Drug	Renal Clearance	Low bleeding risk* surgery (2-3 half lives Last dose – surgery)	High bleeding risk** surgery (4 or 5 half lives Last dose – surgery)
Dabigatran			
$t_{1/2}$ = 14-17h	Cr Cl > 50 ml/hr	Last dose 2 days PTS	Last dose 3 days PTS
$t_{1/2}$ = 16-18h	Cr Cl 30-50 ml/hr	Last dose 3 days PTS	Last dose 4-5 days PTS
Rivaroxaban			
$t_{1/2}$ = 8-9h	Cr Cl > 50 ml/hr	Last dose 2 days PTS	Last dose 3 days PTS
$t_{1/2}$ = 9h	Cr Cl 30-50 ml/hr	Last dose 2 days PTS	Last dose 3 days PTS
$t_{1/2}$ = 9-10h	Cr Cl 30-50 ml/hr	Last dose 3 days PTS	Last dose 4 days PTS
Apixaban			
$t_{1/2}$ = 7-8h	Cr Cl 30-50 ml/hr	Last dose 2 days PTS	Last dose 3 days PTS
$t_{1/2}$ = 17-18h	Cr Cl 30-50 ml/hr	Last dose 3 days PTS	Last dose 4 days PTS

*aiming for mild-moderate anticoagulant effect at surgery < 12-25%
**aiming for no or minimal anticoagulant effect at surgery < 3-6 %

Adapted From:Spyrolpoulos AC, Douketis JD.
How I treat anticoagulated patients undergoing an elective procedure or surgery.
Blood, Oct 11 2012. 120(15), 2954-2962.

Table 5. Postoperative resumption of new oral anticoagulants: a suggested management approach

Drug	Low bleeding risk surgery	High bleeding risk surgery
Dabigatran	Resume on day after surgery (24 h postoperative), 150 mg twice daily	Resume 2-3 days after surgery (48-72 h postoperative), 150 mg twice daily*
Rivaroxaban	Resume on day after surgery (24 h postoperative), 20 mg once daily	Resume 2-3 days after surgery (48-72 h postoperative), 20 mg once daily†
Apixaban	Resume on day after surgery (24 h postoperative), 5 mg twice daily	Resume 2-3 days after surgery (48-72 h postoperative), 5 mg twice daily†

*For patients at high risk for thromboembolism, consider administering a reduced dose of dabigatran (eg, 110-150 mg once daily) on the evening after surgery and on the following day (first postoperative day) after surgery.

†Consider a reduced dose (ie, rivaroxaban 10 mg once a day or apixaban 2.5 mg twice a day) in patients at high risk for thromboembolism.

From:Spyrolpoulos AC, Douketis JD. How I treat anticoagulated patients undergoing an elective procedure or surgery. Blood, Oct 11 2012. 120(15), 2954-2962.

Target Specific Oral Agents

In patients who are taking a NOAC and bleeding (e.g. intracerebral haemorrhage), can the anticoagulant effects of the direct NOACs be reversed rapidly and, if so, can NOAC-associated bleeding and bleeding-associated complications be minimised and patient outcome improved?

Hankey G. Thromb Haemst 2014;111:808.

Practical Approach

- Discontinue the drug
- Supportive care
- Activated charcoal for dabigatran
- Dialysis or PLEX
- PCC – either 3 or 4 factor non-activated may be used
- rFVIIa or plasma not recommended

Kaatz – Am J Hematol 87:S141, 2012

Experimental Dabigatran Reversal

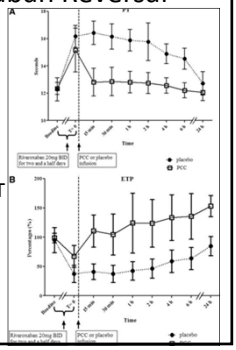
- Rat ICH model – 4.5mg/kg or 9.0 mg/kg dabigatran
- PCC significantly reduced hematoma expansion
- Mouse FFP less consistently reduced hematoma expansion in mice receiving high dose but not low dose dabigatran
- rFVIIa had no effect

Zhou - Stroke 2011;42:3594

Experimental Rivaroxaban Reversal

- Rat mesenteric vessel cutting model
  - PCC (Beriplex) – normalized bleeding time
- Baboons – rFVIIa partially reduced bleeding time and PT
- PCC – normal volunteers*

**Eerenberg Circulation 2011;124;1573*



Target Specific Oral Agents

- 91 YO F with AF admitted with aortic aneurysm (type 1 acute dissection)
- Meds: Pradaxa 75 bid, ASA 81 mg qd
- Lab: INR 1.5, PTT 58.6 secs, TT 157 secs
- OP Data EBL 2500ml, RBC 3150, Plasma 1700, Platelet 500 ml, CRYO 580, CS 505
- Meds: PCC 1000
- INR 1.7, PTT 33.6, FIB 256, TT 115, R 9 min

Target Specific Oral Agents

- ECHO Pericardial hematoma – Back to OR for evacuation of hematoma and mediastinal washout
- OP Data EBL 300 ml, RBC 600ml, FFP 378 ml, platelet 466 ml, PCC 1000 units
- Lab INR 1.7, PTT 56.5, TT 182, fib 241
- Creat 1.22 – output 10 ml/hr
- Offer of HD declined

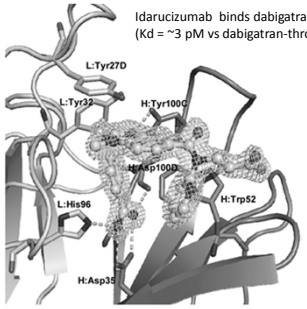
Target Specific Oral Agents

	10/2 (15:47)	10/3 (09:57)	10/3 (14:56)	10/4 (04:50)	10/5
Thrombin time	157	182	140	79.2	
INR	1.5	1.7	1.5	1.5	1.4
PTT	58.6	56.5	51.3	35	

CT output – low post op – 25, 25,66 ml; hgb stable; no other bleeding sign

Dabigatran binding to the neutralizing monoclonal antibody, aDabi-Fab.

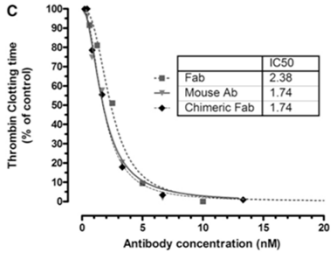
Idarucizumab binds dabigatran with high affinity (Kd = ~3 pM vs dabigatran-thrombin Kd =~7nM)



Millar C M , and Lane D A Blood 2013;121:3543-3544

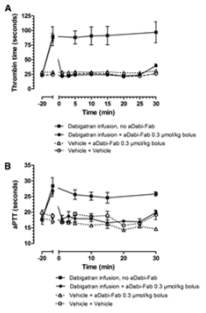
Target Specific Oral Agents

Dabigatran Antidote (aDabi-Fab)



Schiele F et al. Blood 2013;121:3554-3562

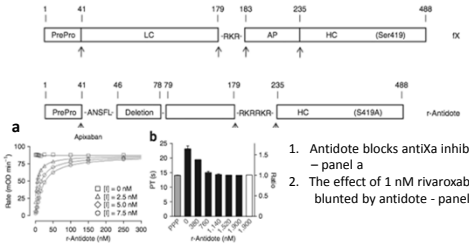
aDabi-Fab reverses the anticoagulative effects of dabigatran in vivo.



Schiele F et al. Blood 2013;121:3554-3562

Target Specific Oral Agents

Andexanet-α



1. Antidote blocks antiXa inhibition – panel a
2. The effect of 1 nM rivaroxaban on PT is blunted by antidote - panel b

Lu Nat Med 2013;19:446

Transfusion Triggers – Transfusion Algorithms

Bleeding time vs. Platelet Count

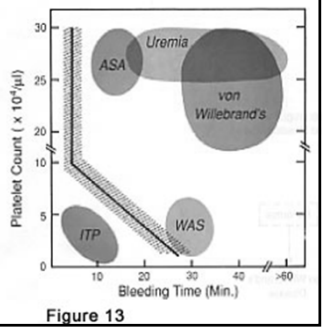
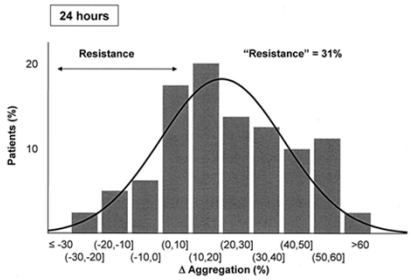


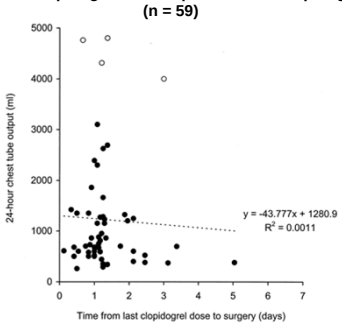
Figure 13

Interindividual variability in platelet response to clopidogrel after stenting



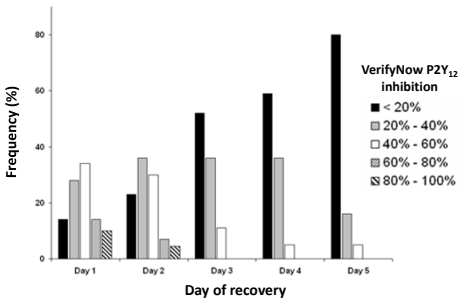
O'Donoghue, M. et al. Circulation 2006;114:e600-e606

Relationship between 24-h postoperative chest tube output and time to surgery after last clopidogrel dose in patients with clopidogrel exposure (n = 59)

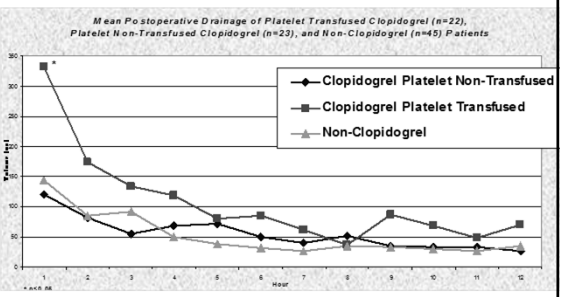


Hongo, R. H. et al. J Am Coll Cardiol 2002;40:231-237

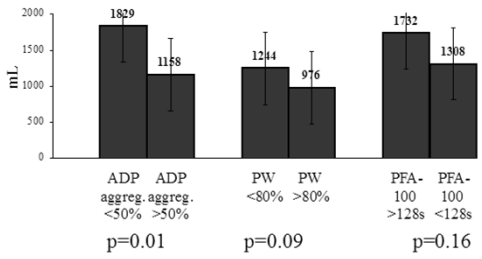
Frequency distribution of platelet inhibition after cessation of daily clopidogrel therapy



Price MJ et al. *Am J Cardiol*. 2006;98:681-684.



Total Chest Tube Blood Loss



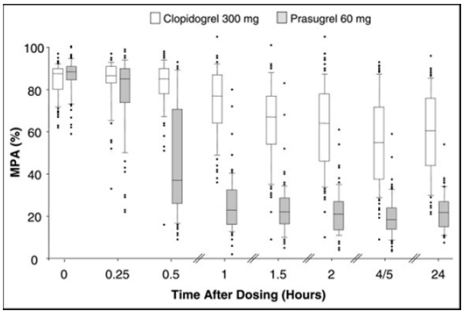
Peri-operative Anti-platelet Management

Anti-Platelet Agents

Agent	Effect	half-life	elimination	Antidote	Platelet Transfusion
ASA	irreversible inhibition -COX	P 15-20 min A 3 hr (300mg)	Urine	none	corrects defect
Clopidogrel	inhibits ADP P2Y12	P 6 hr A 30 min	U 50%; F 46%	none	corrects defect
Prasugrel	inhibits ADP P2Y12	A 7 hr	U 68%; F 27%	none	corrects defect
Brillanta	inhibits ADP P2Y12			none	??

P – Parent Drug
A – Active Drug
U – Urine
F - Feces

Peri-operative Anti-platelet Management



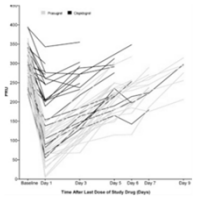


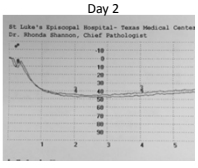
Figure Legend:

Residual Platelet Reactivity Over Time by Individual Patient and Study Group Assignment
The initial magnitude of platelet inhibition at discontinuation was an independent predictor of the time to recovery, resulting, on average, in a more prolonged recovery after prasugrel. PRU = P2Y12 reaction units.

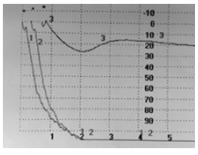
Peri-operative Anti-platelet Management

- 73 YO M S/P PCI admitted with epigastric pain
- HIDA Scan – thickened GB wall
- Meds include Effient last dose – 1 day ago
- Pre-operative consult from cardiologist

Day 2



Day 4



- Approved for surgery with platelets available on observant basis.
- Op data: EBL – 100, initial laparoscopic approach converted to open cholecsytectomy due to adhesions.

Baylor College of Medicine

Born in a Crossfire Hurricane: Management of Torrential Obstetrical Hemorrhage

Karin A. Fox, M.D.

Assistant Professor, Maternal-Fetal Medicine
Department of OB-GYN
Baylor College of Medicine/Texas Children's Hospital

Texas Children's Hospital | Pavilion for Women

DISCLOSURES

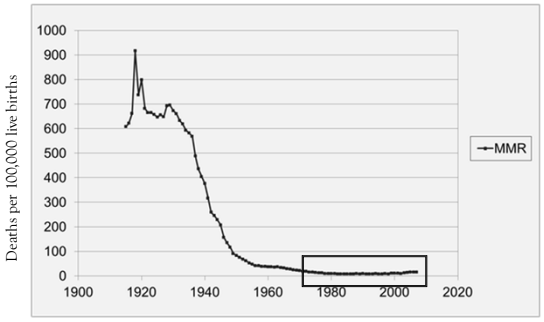
- I have no conflicts of interest to disclose
- I am NOT a Transfusion Medicine Specialist
- Discussion of Off-Label use may include:
  - Novoseven, RiaSTAP, Kcentra, Tranexamic acid

OBJECTIVES

By the end of this lecture, the participant should be able to:

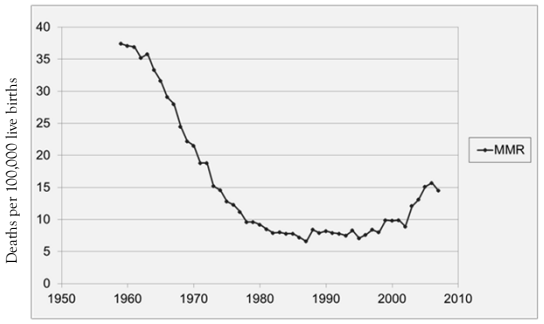
- Develop a massive transfusion protocol and communications chain for use during obstetrical emergencies,
- Provide anticipatory guidance and support to the obstetrician and anesthesiologist in cases of massive hemorrhage

MATERNAL MORTALITY RATE
United States



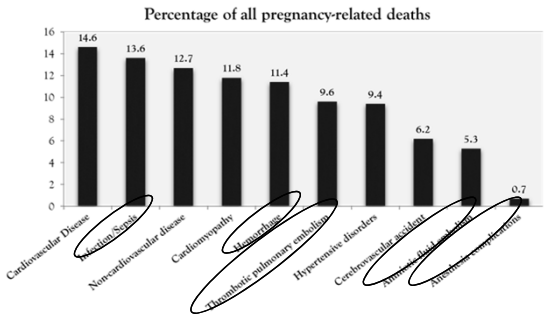
Data from various NCHS sources, including CDE Pregnancy Mortality Surveillance System

MATERNAL MORTALITY RATE
United States



Data from various NCHS sources, including CDE Pregnancy Mortality Surveillance System

HEMORRHAGE:
Leading cause of preventable death



Centers for Disease Control, Division of Reproductive Health, National Center for Chronic Disease Prevention and Health Promotion. Pregnancy Mortality Surveillance System. http://www.cdc.gov/reproductivehealth/MaternalInfantHealth/PMSS.html

Risk Factors

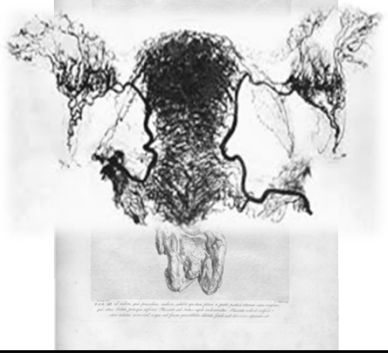
OBSTETRICAL

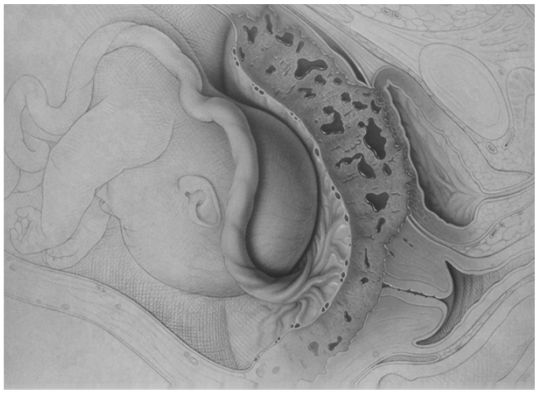
- Ectopic Pregnancy
- Preeclampsia/Eclampsia/HELLP
- Prolonged Labor/Induction
- Chorioamnionitis
- Uterine Distension
- Abruption
- Accreta/Increta/Percreta
- Amniotic Fluid Embolism

NON-OBSTETRICAL

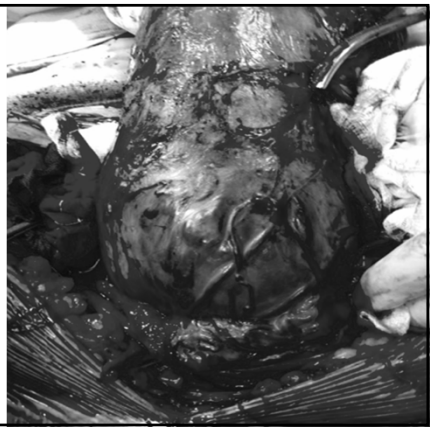
- Pre-existing anemia
- Anticoagulation
- Long-term NSAID use
- Pre-existing coagulopathy
- Liver disease
- Aneurysms/A-V Malformations
- Need for extensive surgery
- Refusal of transfusion

BLOOD SUPPLY TO UTERUS
500-700ml/min at term





Cali et al. Ultrasound Obstet Gynecol 2013; 41: 406–412



Estimating Blood Loss- How good are we?

- What is the average mean error of estimated blood loss as assessed by experienced health care workers?
  - A: 10-15%
  - B: 20-25%
  - C: 50-65%
  - D: 75-80%

-Moscati, et al. Blood loss estimation by out-of-hospital emergency care providers. Prehosp Emerg Care 1999 Jul-Sep; 3(3): 239-242.
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  - Anesthesiology Faculty
  - Nurses
  - Residents
  - None of the above

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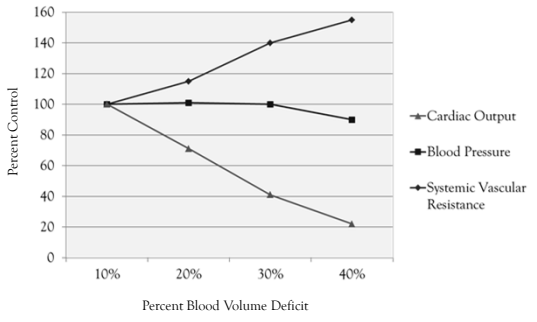
HEMORRHAGIC SHOCK



Adapted from: Gabbe: Obstetrics - Normal and Problem Pregnancies, 4th ed.

	Class I	Class II	Class III	Class IV
Blood vol. %	up to 15%	15-30%	30-40%	>40%
HR (bpm)	<100	>100	>120	>140
BP	Normal or increased	Normal (+ tilt)	Decreased (MAP < 60)	Decreased
PP	Normal	Decreased	Decreased	Decreased
Cap refill	Normal	May be Delayed	Usually Delayed	Always Delayed
RR	Normal	Mildly increased	Moderate to marked tachypnea	Marked tachypnea/respiratory collapse
Urine Outpt (ml/hr)	Over 30	20-30	5-15	Essentially anuric
Mental Status	Normal or anxious	Anxious	Confused	Lethargic, obtunded

* Class III and IV hemorrhage/shock = loss of compensatory mechanism. Survival depends on prompt replacement of crystalloid and blood products to avoid irreversible ischemia.

Hemorrhage: Leading cause of preventable death

- 10th Leading cause of death in the United Kingdom
- For every death there are nine women who develop severe maternal morbidity.
- Incidence approximately halved over the last 3 years
- High degree of emphasis on:
  - Early RECOGNITION
  - Multidisciplinary training/treatment
  - Use of "MEOWS" Score card for all pregnant women at risk
  - PREVENTION

Cantwell R, et al. Saving Mothers' Lives: Reviewing maternal deaths to make motherhood safer: 2006-2008. The Eighth Report of the Confidential Enquiries into Maternal Deaths in the United Kingdom. BJOG. 2011 Mar;118 Suppl 1:1-203.

Modified Early Obstetric Warning Score

	3	2	1	0	1	2	3
Systolic BP	<70	71-80	81-100	101-140	141-160	160-180	>180
Diastolic BP				<90	91-104	≥105	
Heart Rate	<40		40-50	51-100	101-110	111-130	>130
Resp Rate		<8		9-19	20-29	30-39	>40
SpO2%	<85	85-89	90-94	95-100			
Temp (C)		<35	35-35.9	36-37.4	37.5-38.4	>38.4	
Loss of Conscious-ness	No response	Pain	Voice	Alert	Confused		
Urine Output	<0.5ml/kg/h			0.5ml/kg/hr		>3ml/kg/hr	

Modified Early Obstetric Warning Score

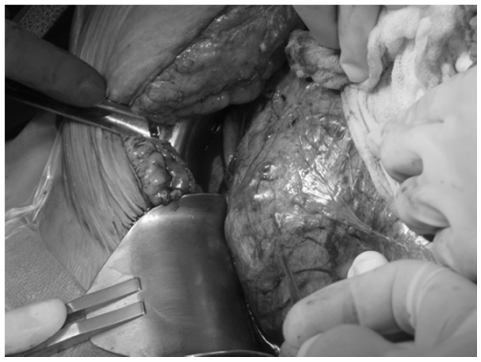
Parameter	Relative risk of morbidity	p value
Heart rate > 100 beats.min^{-1}	7.0 (4.9–10.1)	0.0001
Diastolic BP > 90 mmHg	6.6 (4.7–9.4)	0.0001
Systolic BP > 150 mmHg	5.4 (3.8–7.8)	0.0001
Respiratory rate > 22 breaths.min^{-1}	4.8 (2.9–8.0)	0.0001
Temperature > 38 °C	3.4 (2.0–5.6)	0.0003
Systolic BP < 90 mmHg	2.4 (1.5–3.7)	0.0013
Oxygen saturation < 95%	1.3 (0.2–7.9)	0.56
Pain score 2–3	2.7 (0.8–8.4)	0.17

Sensitivity 89% (95% CI 81–95%), specificity 79% (95% CI 76–82%),

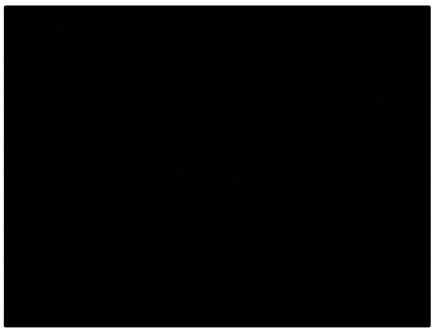
PPV 39% (95% CI 32–46%) and **NPV 98%** (95% CI 96–99%)

Singh S et. al. A validation study of the CEMACH recommended modified early obstetric warning system (MEOWS). Anaesthesia 2012, 67, 12–18

WHAT ROLE FOR TRANSFUSION MEDICINE?



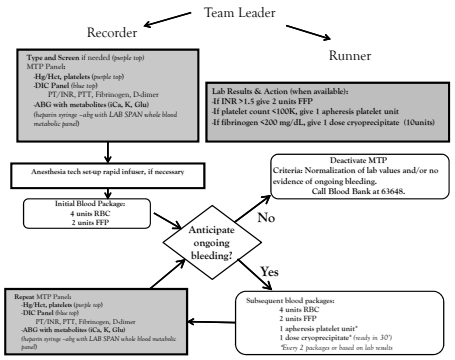
TEAM COMMUNICATION



MANAGEMENT

- Large bore I.V.s (multiple and EARLY)
- Type and Crossmatch for conditions where hemorrhage probable
- Call for assistance
- Massive Transfusion Protocols: 2:1 ratio of PRBC:FFP
- FIND and FIX the SOURCE
- Most pregnant women have physiologic reserve, until they don't– Decompensation is RAPID

MASSIVE TRANSFUSION PROTOCOL

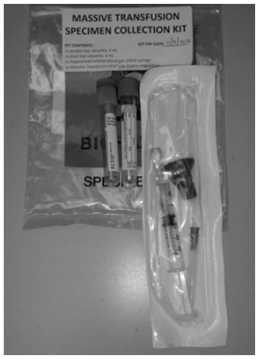


TEAM TRAINING/SIMULATON

- Studies show increase in team communication, participant attitudes with simulation*
- Structured simulation of obstetrical hemorrhage:
  - Reduced time to recognition
  - Reduced time to intervention
- Blood bank personnel key to the team/training
  - Identify systemic challenges
  - Provide invaluable insight into process improvement

*Marshall NE et al, J Matern Fetal Neonatl Med. 2014 May 29:1-5

MTP LAB PACK



- Readily available
- No need to enter labs into computer
- Simplifies process for circulators and MDs
- No need to "guess" what is needed
- Allows frequent, consistent lab draws

MASSIVE TRANSFUSION

- Need adequate lines (16 GA or bigger) to transfuse rapidly
- Hyperkalemia and hypocalcemia may ensue→ cardiac arrhythmias
  - Early identification/lab support
  - Dependent upon age of PRBC
  - Rate and Volume dependent
- Blood bank supply
  - Guidance when type specific products unavailable

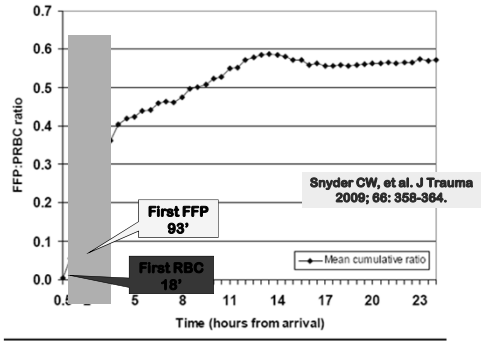
IDENTIFYING/CORRECTING COAGULOPATHY

- Coagulation profile
- TEG
- ROTEM
- Anticipate time to obtain necessary FFP/Cryo
- Role for pharmacologic products? RiaSTAP, K-Centra, TXA
- Anticipatory guidance- Who should stock pharmacologic products?

MANAGEMENT

- One of the earliest changes in coagulation profile:
  - Fibrinogen decreases
- Classically taught to keep fibrinogen > 150
- NO LONGER SUFFICIENT—better over 250-300
- Must think one step ahead of the bleeding

RBC:FFP Ratio is Time Dependent



FACTOR CONCENTRATES

All Off-Label Use

- Prothrombin complex concentrate (Kcentra™): Factors II, VII, IX, and X.
  - Coagulopathy while waiting for FFP
  - 25-50 units/kg
- Fibrinogen concentrate (RiaSTAP™)
  - Low fibrinogen <150-200 mg while waiting for cryoprecipitate
  - 70 mg/kg or [250-current fibrinogen]/1.7 = mg/kg
- Factor VIIa (Novoseven™)
  - Truly last option due to the possible thrombotic complications.* Fibrinogen has to be >200 mg/dL in order to work.
  - 30-50 µg/kg (1 mg/vial)

*Callum and Rizoli. Hematology 2012, ASH

ANTIFIBRINOLYTICS
Tranexamic Acid (TXA)

- The role for tranexamic acid in the management of postpartum hemorrhage will be clarified by the multicenter, randomized World Maternal Antifibrinolytic (woman) trial.*
  - So far 4,490 patients have been randomized – TXA or placebo.
- There is strong evidence that TXA reduces blood loss at C-section.**
- TAPP Study (tranexamic acid in placenta percreta) is being proposed to Baylor/PFW.

*Shakur, et al. Trials. 2010;11:40.
**Roberts and Ker. Int J Gynaecol Obstet. 2011;11:220-221.

TRANEXAMIC ACID

- Elective cesarean section, blood loss reduction (unlabeled use):
  - I.V.: 1-2 g over 5-15 minutes at least 10 minutes prior to skin incision (Gungorduk, 2011)
- 1 mg/kg/hour during surgery
- Half life 3 hours
- Cleared in urine
- TAPP study: loading dose 2.5-100 mg/kg, maintenance dose 0.25-4 mg/kg/hour.

Management of Massive Hemorrhage
Texas Children's Hospital
Pavilion for Women

- Follow MTP.
- Request lab testing every 20-30 min.
- Interpret the lab results.
- Manage patient according to the lab results.
- If you need assistance, page blood bank physician on service/on call. We are available 24/7.

QUESTIONS?

Management of Bleeding Patients

Jun Teruya, MD, DSc, FCAP

Professor of Pathology & Immunology, Vice Chairman for Education
Professor of Pediatrics
Professor of Medicine
Baylor College of Medicine
Chief, Division of Transfusion Medicine & Coagulation
Texas Children's Hospital
Houston, USA

Disclosure
Past 24 months

Research Support/P.I.	Department of Defense
Employee	No relevant conflicts of interest to declare
Consultant	ECMO Advisory Board, GTC Biotherapeutics Novo Nordisk
Major Stockholder	No relevant conflicts of interest to declare
Speakers Bureau	No relevant conflicts of interest to declare
Honoraria	Received honorarium from Japan Boehringer Ingelheim GmbH Immucor Gamma
Scientific Advisory Board	Gulf Coast Regional Blood Center ECMO Advisory Board, GTC Biotherapeutics

Discussion of off-label use:
Kcentra™, RiaSTAP™, Novoseven™, ROTEM™ all in one

Proposals for Division of Transfusion Medicine & Coagulation 2009

- Establish a division of transfusion medicine and coagulation in Pathology Department at Texas Children's Hospital (TCH).
- The division provides active consultation so that diagnostic and therapeutic options are immediately available to meet the individual patient's needs based on coagulation and blood bank test results.

Projected Outcomes of Division of Transfusion Medicine & Coagulation

- High quality care of actively bleeding patients in an expedited and cost-effective manner.
  - Expedited work-up of coagulopathy and initiation of appropriate therapies.
- Better adherence to transfusion guidelines.
- Minimize empiric evidence based blood transfusion therapy.
- Better utilization of blood component therapy and institution of therapies appropriate to the individual patient's needs.
- Better patient outcome in mortality and morbidity.

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Current Scope of Clinical Consultation at Texas Children's Hospital

- Acute bleeding, massive transfusion, bleeding of unknown etiology, liver failure, pre-spinal surgery, ECMO anticoagulation, and hemolytic anemia.
  - On site assistance for massive bleeding if needed.
- Further work up for abnormal coagulation results.
- Management of patients who are receiving anticoagulant for invasive procedures.

Integration of the transfusion medicine and coagulation service. TRANSFUSION 2014;54:1440-1441.

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Daily Activities of Transfusion Medicine & Coagulation

- Morning Rounds: everyday at 7:00 -7:30 am.
  - Review lab data of patients with residents and fellows we are following.
  - Go to see those patients and discuss with the treating team. Most of them are in PICU, CVICU, or NICU.
- Sign-out in the morning and afternoon with residents and fellows.
- ECMO rounds at 10 am everyday.
- Get consultation 24/7.
- Sign-out and rounding patients on weekend without residents or fellows.

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Sign Out in Coagulation

- DIC panel (PT, PTT, fibrinogen, D-dimer, thrombin time, and platelet count) : Good to know most sick patients in the hospital.
- PFA-100
- TEG™ → ROTEM™
- Lupus anticoagulant
- Prolonged PT/PTT consultation: Receive 3 tubes and we decide what assays are needed.
- Hypercoagulation panel
- ECMO coagulation panel
- Easy bruisability screening panel
- Whole blood platelet aggregometry
- Von Willebrand panel
- ADAMTS 13 panel
- MTP (massive transfusion protocol) panel

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Sign out and Consults in Blood Banking

- Red cell antibody
- Transfusion reaction
- Deviation from standard practice
- Granulocyte transfusion consult
- Platelet refractoriness
- HDFN and NAIT
- Transfusion suggestion for ABO incompatible stem cell transplant
- Administration of Rh immune globulin
- T antigen

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Example: 16 year old female

- Severe menorrhagia caused severe anemia (Hgb 5.5 g/dL)
- DIC panel:
  - PT 36.3 sec, INR 3.7, PTT 106.2 sec, fibrinogen 380 mg/dL, D-dimer 0.24 μg/mL, platelet count 123,000/mm3
- Plasma was transfused repeatedly for "coagulopathy".
- Von Willebrand panel:
  - Factor VIII >178% (non-specific inhibitor pattern), vWF:Ag 195%, vWF:RCo 152%

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Example: 16 year old female

- No previous bleeding history.
- Severe menorrhagia caused severe anemia (Hgb 5.5 g/dL).
- DIC panel:
  - PT 36.3 sec, INR 3.7, PTT 106.2 sec, fibrinogen 380 mg/dL, D-dimer 0.24 mg/mL, platelet count 123,000/mm3.
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- Von Willebrand panel:
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STAT Coagulation Factor Assays

- Factor VII 71%
- Factor V 62%
- Factor II 2%

1. What is the diagnosis?
2. What is the optimal treatment at this time?

LAHPS

- Lupus anticoagulant hypoprothrombinemia syndrome (LAHPS).
- Prothrombin complex concentrate (Kcentra™) 25 units/kg was given. By next morning menorrhagia stopped.
- Lupus anticoagulant assays: DRVVT ratio 1.42 (positive) and hexagonal phase phospholipid neutralization test +149.9 sec (positive).
- Antiprothrombin antibody IgG 128.2 units (strongly positive) and IgM 9.3 units (negative).

Managing Bleeding Patients

1. **Jun Teruya, MD, DSc:** Professor, Departments of Pathology & Immunology, Pediatrics, and Medicine, Baylor College of Medicine, Chief of Division of Transfusion Medicine & Coagulation, Texas Children's Hospital, Houston
   - Role of Transfusion Medicine for Pediatric Liver Failure
2. **Karin Fox, MD:** Assistant Professor, Department of Obstetrics, Maternal Fetal Medicine, Baylor College of Medicine, Houston
   - Born in a Crossfire Hurricane: Management of Torrential Obstetrical Hemorrhage
3. **Arthur Bracey, MD:** Director of Clinical Pathology, Director of Transfusion Medicine, Baylor St. Luke's Medical Center, Houston
   - Peri-operative Issues of Bleeding Management – Target-specific Oral Anticoagulants and Anti-platelet Agents

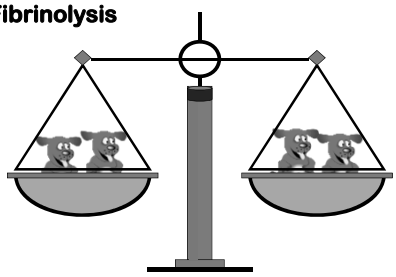
Role of Transfusion Medicine for Pediatric Liver Failure

Consult Transfusion Medicine

- Once patient with liver failure is listed for liver transplant, Transfusion Medicine is consulted.
- Our role is to prevent bleeding and keep the patient alive until liver transplant surgery.
- Acute liver failure: coagulopathy without thrombocytopenia
- Acute-on-chronic liver failure: coagulopathy and thrombocytopenia
  - Failed Kasai procedure after biliary atresia
  - TPN induced
  - Alagille syndrome

Normal Hemostasis

- Normal Coagulation Factors
- Normal Coagulation Inhibitors (AT, proteins C & S)
- Normal Platelets
- Normal Fibrinolysis



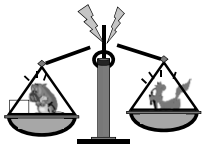
Hemostatic Derangement in Acute Liver Failure and Acute-on-Chronic Liver Failure

- Decrease of pro-coagulants and anti-coagulants.
- Factor VIII, factor XIII, and vWF are not decreased.
- Hyperfibrinolysis due to low TAFI and antiplasmin.
- Thrombocytopenia

Evidence of managing bleeding pediatric patients with liver failure is extremely limited.

Solution

- Extrapolation of adult data.
- Experience based practice.
- Expert opinion.



Bleeding Thrombosis

Myth

INR (international normalized ratio) is useful in liver failure to assess liver status and predict bleeding

Reality

- There is no evidence of predicting bleeding based on INR.
- Formula: $INR = (PT^{patient}/PT^{control})^{ISI}$
- ISI was established by patients receiving warfarin.
- Calibration of ISI of PT reagents for stable warfarin patients (INR_W) is different from patients with liver disease.
- INR_{LD} using ISI_{LD} is most appropriate PT reporting style in patients with liver disease.
- MELD/PELD score* (prioritize patients for liver transplantation) should use INR_{LD}, not INR_W.
- Of note, INR_{LD} does not predict bleeding, either.

*Model for end-stage liver disease/Pediatric end-stage liver disease

[Hepatology Research 2014;44:92-101., Hepatology 2007;46:520-527.]

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Myth

The longer the PTT, the more risk for bleeding.

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Reality: PTT does not predict bleeding.

- Severe hemophiliacs have PTT of 80-90 sec and experience spontaneous bleeding.
- PTT of 90 sec in the presence of lupus anticoagulant does not cause any bleeding.
- PTT of >150 sec associated with homozygous prekallikrein deficiency (<1%) does not cause bleeding. [Unal, S, Jariwala, P, Mahoney, D, Teruya, J. Lab Medicine 2010;41:271-274.]
- PTT of 40 sec associated with type 1 von Willebrand disease causes excessive bleeding.
- PTT of 100 sec due to heparin therapy does not cause bleeding.

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Myth

Fibrinogen level of 100 mg/dL (1.0 g/L) is enough for hemostasis.

Truth

- It is true for congenital hypofibrinogenemia without any other coagulation or platelet abnormalities.
- In the setting of liver failure, patients have multiple coagulation factor deficiency and may have thrombocytopenia.
- We recommend fibrinogen level of >150-200 mg/dL for patients with liver failure.

Crit Care 2013;17:R76 (trauma)
J Thromb Haemost 2007;5:266-273. (post partum hemorrhage)
TRANSFUSION 2014;54:1389-1405.

Role of Therapeutic Plasma Exchange (TPE)

- Acute liver failure is ASFA Category III.
  - Optimum role of apheresis therapy is not established. Decision making should be individualized.
- Indications at TCH.
  - Uncontrollable coagulopathy, or
  - Hepatic encephalopathy
- Since patients commonly have hepato-renal syndrome, TPE is performed with CRRT (continuous renal replacement therapy).
- Side effect: citrate lock
  - Hyper-total calcemia and hypo-ionized calcemia

J Clin Apheresis 2013;28:161

Myth

Therapeutic plasma exchange (TPE) improves survival rate of patients with liver failure.

Reality

- TPE does not prevent brain swelling and herniation.
- TPE will not improve survival rate in 6 months.
- TPE is used as a bridge to liver transplant surgery.
- TPE using plasma as replacement fluid makes coagulation and platelet management easy.
- My institution started to perform MARS (molecular adsorbent recirculation system). It removes albumin-bound toxins (bilirubin, bile acids, phenols, ammonia, etc) and improves hemodynamics. MARS and TPE may be performed on alternate days.

Pediatr Nephrol 2013;28:1763-1769.
Ann Hepatol 2011;Suppl 1:S21-28.
Ann Surgery 2001;234:418-424.

"New" Hemostatic Drugs

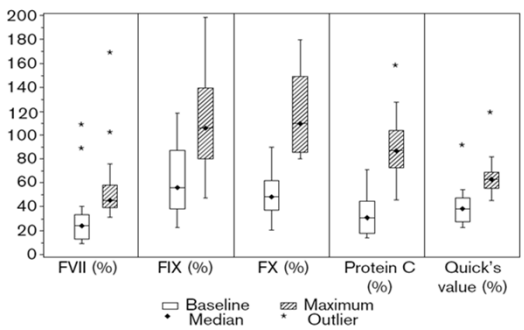
Factor Concentrates
All Off-Label Uses

- **Prothrombin complex concentrate (Kcentra™*): Factors II, VII, IX, and X, protein C, and protein S.**
  - **Coagulopathy while waiting for FFP**
  - **Lower volume than FFP**
- **Fibrinogen concentrate (RiaSTAP™**)**
  - **Low fibrinogen <150-200 mg while waiting for cryoprecipitate**
  - **70 mg/kg or [250-current fibrinogen]/1.7 = mg/kg**
- **Factor VIIa (Novoseven™)**
  - **Truly last option due to the possible thrombotic complication.*** Fibrinogen has to be >100 – 200 mg/dL in order to work.**
  - **30-50 μg/kg (1 mg/vial)**

*** Average wholesale price $815/vial (= 500 units)**
****Average wholesale price $1,021/vial (= 1,150 mg)**
*****Callum and Rizoli. Hematology 2012, ASH**

Prothrombin Complex Concentrate (PCC) Kcentra™

Factors	Amount per Vial (500 units)
Factor II	380-800 mg
Factor VII	200-500 units
Factor IX	400-620 units
Factor X	500-1,020 units
Protein C	420-820 units
Protein S	240-680 units
Heparin	8-40 units
Antithrombin	4-30 units
Total protein	120-280 mg
Human albumin	40-80 mg



Lorenz R et al. Efficacy and safety of a prothrombin complex concentrate with two virus-inactivation steps in patients with severe liver damage. Eur J Gastroenterol Hepatol. 2003;15:15-20.

Use of Antifibrinolytics

- Use of antifibinoytics is empirical in the setting of active bleeding.
- TEG™ or ROTEM™ may help decision making.
- Risk of occlusion of hepatic artery after anastomosis should be carefully balanced with the benefits. During liver transplant surgery, surgeon's opinion really matters.
- ε-aminocaproic acid (Amicar™) – 100 mg/kg bolus, 30 mg/kg/hour continuous IV. Half-life 2 hours.
- Tranexamic acid – 10 mg/kg bolus, 1 mg/kg/hour continuous IV, if needed. Half-life 3 hours.
- Decrease the dose in the setting of renal failure.

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Utility of ROTEM

- Individual tests do not predict bleeding.
  - PT, PTT, fibrinogen, D-dimer, platelet count.
- ROTEM shows primary hemostasis (platelet hemostasis), secondary hemostasis (coagulation hemostasis) and fibrinolysis.
- Patients with cirrhosis have a coagulopathy that is associated with decreased clot formation capacity. [J Thromb Haemost 2014;12:1647]
- ROTEM is not appropriate for hemostatic assessment of patient with liver cirrhosis. [Thromb Haemost 2014;111:447.]

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Myth

If ROTEM or TEG is normal, bleeding risk is low.

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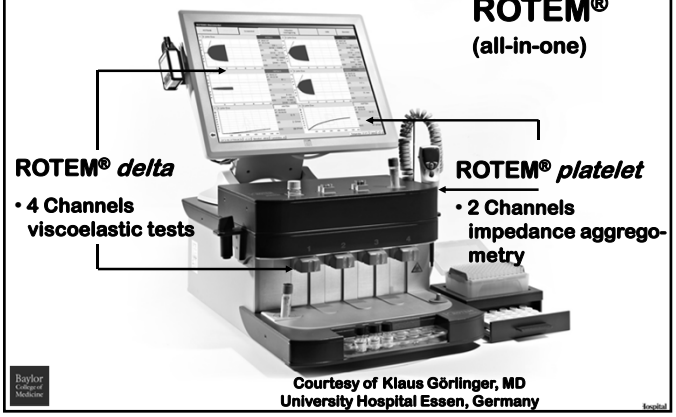
Limitations of Current Methods in ROTEM Analysis

- Low sensitivity for platelet function defects and antiplatelets.
- No detection of low von Willebrand factor.
- Low sensitivity to mild hyperfibrinolysis.*

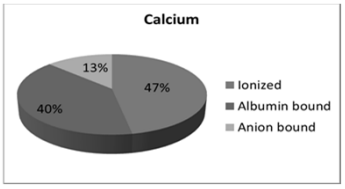
*ROTEM™ sensitivity to tPA-induced fibrinolysis in vitro. XXVIIth International Symposium on Technological Innovations in Laboratory Hematology. Hague, Netherlands, May 2014.



Courtesy of Klaus Görlinger, MD
University Hospital Essen, Germany

Calcium Homeostasis

- In normal individuals
  - 40% albumin bound
  - 13% small endogenous anions (such as phosphate and lactate)
  - 47% free in solution as ionized calcium.



Myth

Transfusion will result in hypocalcemia

Truth

- **Citrate chelates calcium and magnesium reversibly.**
- **Transfusion, especially therapeutic plasma exchange using FFP, and CRRT requires substantial amount of citrate.**
- **Citrate causes hypocalcemia, but it is hypo-ionized calcemia.**
- **Since liver metabolizes citrate to bicarbonate, in the setting of liver failure, citrate bound calcium continues to be circulating causing hyper-total calcemia = citrate lock.**

4 month old Full Term Baby with Biliary Atresia Receiving TPE and CRRT

	Reference range	9/27/13	10/6/13	10/7/13	10/8/13
Na	133-142	126	127	139	146
K	3.7-5.6	5.4	6.9	2.5	3.6
Cl	95-105	99	89	101	105
CO2	20-28	17	27	22	18
Glucose	50-120	95	72	183	120
BUN	8-28	10	12	8	2
Creatinine	0.12-1.06	0.29	0.22	0.25	0.36
Calcium	8.0-10.7	9.7	10.0	16.1	19.9
Ionized calcium	0.95-1.50		0.71	0.90	0.93
Mg	1.6-2.6	2.1	1.6	1.5	1.2
Phosphorus	3.8-6.7	5.8	5.4	3.7	2.9

Summary

- Pediatric patients with acute liver failure have coagulopathy.
- Patients with acute-on-chronic liver failure also have thrombocytopenia.
- When those patients have bleeding symptoms such as oozing around catheter insertion sites and bleeding from endotracheal tube, aggressive therapy is necessary: PT INR <2.5, fibrinogen >200 mg/dL, platelet count >50,000-100,000/mm3
- Management of bleeding includes blood component therapy, medication (e.g. antifibrinolytics, PCC), and TPE.
- Post liver transplant surgery, bleeding and occlusion of hepatic artery has to be carefully balanced.

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(Research Associate of Division of Transfusion Medicine & Coagulation)

Thank you.

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