Transfusion, Cirrhosis, Liver Transplantation and Portal Hypertension

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A. Coagulation Changes - Chronic Liver Disease

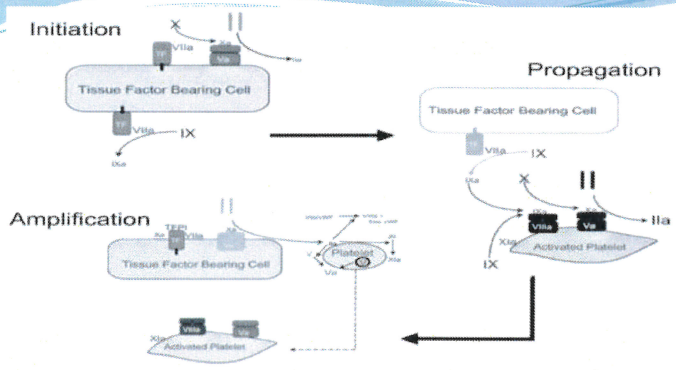
Understanding evolved - appreciation 'Cell-based theory' coagulation

1. Initiation: TF –VII dependent → low level thrombin
2. Propagation: Thrombin activates platelets/cofactors on platelet surface
3. Amplification: Accelerated production large amt thrombin
4. Termination: inhibitor systems (AT, protein C, TFPI) limit amt/duration thrombin

Key: *Thrombin generation*

No conflicts to declare apart from .....

- University Texas academic physician ceiling earning power .....
- Discuss potential hemostatic therapies:
  - European data
  - Some indications in liver disease fall outside current FDA approvals
- USA rugby fan



Outline and Objectives

- Clinical dilemma bleeding and transfusion in cirrhosis/LT
  - Review coagulation abnormalities, new paradigms, monitoring
  - Review risk of bleeding cirrhosis/LT and possible prediction
  - Review risks of BP transfusion cirrhosis/LT
  - Discuss current, potential hemostatic options – cirrhosis/LT
- Some manifestations Portal Hypertension (may see in main OR, GI lab)
  - Porto-pulmonary hypertension
  - Hepato-pulmonary syndrome

- ↓ activity/levels procoagulants (II, V, VII, IX, X, XI), including Vit K dependent (malabsorption, poor nutrition)

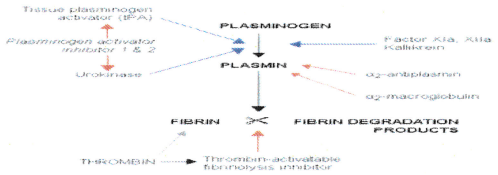
  Also, ↓ activity natural (Vit K) dependent coagulation inhibitors (protein C/S, antithrombin)

- Dysfibrinogenemia (up 70%)
  - Abnormal structure/function – abnormal; sialic acid residues

- Thrombocytopenia - < 150K (76%)
  - Sequestration spleen
  - ↓ production thrombopoietin
  - Autoimmune destruction
  - BM suppression (cause cirrhosis – alcohol, hep B, C)
- Platelet function
  - May retained or disturbed - ↑ vWF, VIII
  - ↓ ADAMTS13 – enzyme maintains normal distribution vWF

- Plasma pts with cirrhosis generates = thrombin as plasma normals, *provided* thrombin measured methods reflect pro/anti-coagulants
- Severity preop coagulation disturbance NOT uniformly predict intraop blood loss
- Correction abnormal CCT's not routinely ↓ blood loss
- Should we be measuring/monitoring in another way?

- Deranged fibrinolysis
- ↑ tPA (compromised clearance)
- ↓ fibrinolysis *inhibitors* (alpha2 antiplasmin, TAFI [thrombin-activatable fibrinolysis inhibitor])
- ↑ expression TF bearing cells



Alternate Coagulation Assessment

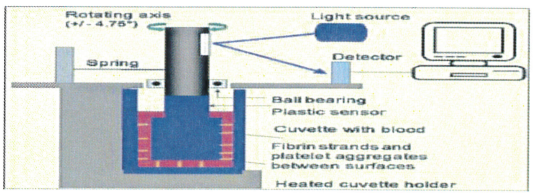
Point of Care Coagulation Monitors

- Rapid results
- May predict bleeding/cause
- NOT always correlate traditional lab analyses
- NOT exclusive – usually incorporated into transfusion algorithm
- ↑ appreciation limitations isolated, plasma based lab tests
  - PT – sheep thromboplastin
  - Inter-lab variation INR for MELD score (Lisman 06)

- 'Re-Balanced', tenuous coagulation status (Lisman 2010)
- Often better than traditional coagulation tests suggest
  - Designed monitor anticoagulants
  - NOT reflect parallel changes anticoagulants
  - Fail predict bleeding outcomes – variceal bleeding, liver biopsy
- Less robust coagulation, > prone abnormal bleeding AND thrombosis (!)
  - Portal vein thrombosis 8-26% in LT
  - Cirrhosis independent risk factor DVT/PE

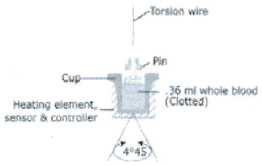
RoTEM® (Rotational Thrombelastometry, Pentapharm)

- Europe → USA - FDA approved 2011
- Disposable pin fixed tip rotating axis
- Axis rotates ball bearing system, connected spring → measure elasticity, detected reflection of light on mirror
- Changes elasticity → change axis rotation



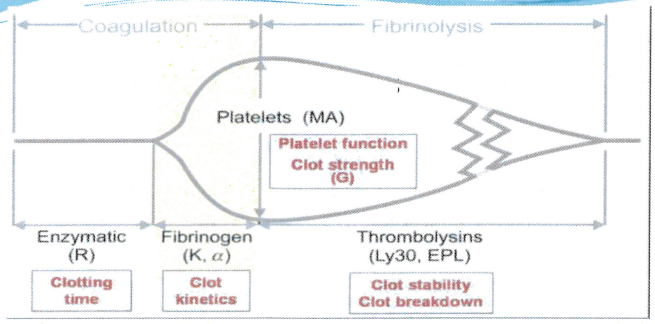
Traditional TEG (Haemanetics)

- Global visco-elastic whole blood monitor
- Complements cell-based theory coagulation
- Follows dynamic clot formation
  - Initial fibrin formation
  - Fibrin-platelet interaction
  - Clot strength/platelet function
  - Fibrinolysis



Potential Limitations

- Standardization, quality control (Chitlur 2011)
  - International working group (9 labs) - PRP, pooled normal plasma. CV:
    - R: 8 - 17% K: 31- 59% Angle: 3-47% MA: 14-21% G: 21-33%
- Sample analysis
  - Operator influence
  - Anesthesia technicians vs credentialed lab
- Device maintenance
  - CLIA requirements (> manufacturer's)
  - Dedicated anesthesia tech daily QC's
- Blood collection
  - Tissue trauma, contamination heparin flush



Liver Transplantation Data

- ↓ BP use (historical controls)(Kang 85, 95)
- Reperfusion coagulopathy, heparin-like activity (endogenous or exogenous) (Kettner 98, Pivalizza 98)
- Fibrinolysis (Kang 87, Porte 89, Grosse 91, Steib 94, Avidan 01)
- Survey – 62 % routinely used LT centers (Schumann 13)
  - 25 – 26% on-site availability or stat lab
- Prospective observational study transfusion triggers – TEG vs. ROTEM vs. Conventional (20)
  - Fair agreement TEG/ROTEM - plt transfusion (k = 0.33), ROTEM better - fibrinogen (FIBTEM) (Coakley 08)

Modifications relevant LT

- Heparinase
  - Bacterial derived enzyme, simultaneous regular + heparinase samples
  - Little quantification: algorithms recommend intervention if ↑ 20-50%
- Functional Fibrinogen
  - Address limitation TEG 'mono-analysis'
  - Abciximab-inhibited plt activation → fibrinogen contribution clot strength
  - Cytochalasin D (ROTEM) > plt inhibition, > fibrinogen estimation FF vs FibTEM (in vitro) (Solomon 12, Lang 04)
  - Initial description LT (Lu 14)
    - Excellent correlation plasma fibrinogen baseline (r = 0.9)
    - Less well post reperfusion (r = 0.58)
- Tissue Factor
  - Rapid TEG (kaolin + TF)
  - R/K times short - replaced by ACT
  - Initial description LT

- Cochrane review/Meta-analysis - LT (Wikkelsoe 11)
  - Only 1 RCT included (high risk bias)(Wang 10)
  - 28 pts – TEG^R vs std labs
  - Algorithm driven
  - R > 10: FFP MA < 45 – plt Angle < 45 – cryo
  - < FFP (8 U) - TEG group

- Preliminary data ESLD (some transplant): (Pivalizza 12 - abstract)
  - All TEG parameters WNL despite abnormal conventional tests (36):
  - PT 18.1 ± 6.2 INR 1.5± 0.7
  - PTT 39.5 ± 12.5
  - Plt 114.3 ± 135.4

- Follow-up report (77):
- Unblinded, historical, NOT have been included meta-analysis (Wang 12)
- Abnormal TEG values may not predispose ↑ BL
- Led them revising protocol (R > 15, MA < 40) ↑
- New group: < FFP (4 vs 11), plts (2 vs 4) with similar RBC, EBL

Can we Predict Bleeding?

- Accepted donor and recipient variables – 'surgical'
- Cywinski (2014)
  - 804 pts, retrospective
  - ↓ plts, ↑ MELD components (including INR) predicted intraop BP use
  - Despite complex statistical model, NOT reliably predict high users (> 20 – 30 units RBC + CS)
- Massicotte (2012)
  - 500 consecutive pts
  - Strongest associated factor - preop Hb
  - No relationship INR, plt count

Summary TEG/ROTEM

- Multiple reports use in LT
- Increasingly incorporated monitoring/transfusion algorithm
  - Wisconsin:
    - Pre-anhepatic: MA > 45
    - Neo-hepatic: R 2 x > heparinase, MA > 45, Lysis 8%
- Insufficient prospective level I evidence
- Potential role functional fibrinogen

- Rana (2013) - retrospective, 233 pts
  - WIT (OR 1.12)
  - Bilirubin (1.04)
  - Previous abdominal surgery (1.7)
  - Duration of hepatectomy (1.01)
- Massicotte (2004)
  - Predict RBC transfusion high probability 3 factors
  - Inability phlebotomy, > FFP, lower Hb
  - Low overall rate transfusion (20%) – difficult apply other centers

B. Risks Bleeding in LT

- Historically, transfusion rates 20-96%
- Suggestion rates ↓ even as MELD ↑ (Makroo 13)
  - Better surgical techniques, expertise
  - ↑ appreciation *risks* BT
  - Proactive hemostatic management
- Added stresses:
  - Hypocalcemia
  - Hypothermia
  - Heparin/heparin-like substances from donor organ
- Significant institutional variation
  - 8 centers France – variation persisted after adjustment Hb loss (Ozier 03)

C. Risks of Transfusion in LT

- Coagulation status at risk even in 're-balanced' state
- *Some* predictors ↑ EBL with ↑ MELD
- Meta-analysis (2008)
  - Mean RBC: 2-14 U Mean FFP: 1-28 U

Problem: Transfusion RBC, FFP, plts ∞ ↑ morbidity and mortality
- Association rather than causal effect
- LOS - ICU, hospital
- Transplant center effect

Storage lesion RBCs

- ↑ osmotic fragility
- ↓ deformability
- Depletion ATP, 2,3-DPG
  - Impaired RBC transit through capillaries
  - ↓ oxygen-carrying capacity
- Depletion NO – may promote vasoconstriction, plt aggregation, thrombosis, pro-inflammatory factors
- Changes within 2 to 3 weeks storage
  - Is 14-20 day-old blood debate relevant? Should be wider range than that ...

Pediatric data

- Retrospective, 243 pts, Italy (Nacoti 2012)
- FFP and RBC transfusion independent risk mortality
- HR 3.15 for > 3 RBC (compared < 1)
- HR 3.35 > 3 FFP (compared < 1)

- Rana (2013)
  - 253, retrospective, single surgeon, 3 yr follow-up
  - ↓ survival:
    - HCC (HR 1.9)
    - Intraop transfusion (1.01 per unit)
  - Threshold analysis: > 28 U (HR 2.5)

- Cywinski (2014)
  - 804 pts, retrospective, single center
  - Significant BP use: > 8 RBC, 5 CS, 10 FFP, 3 plt packs
  - F/U > 3 years
  - 'Early' hazard (< 9 months):
    - > RBC + CS use
    - Higher preop INR
    - Older donor
    - Donor not African-American or Caucasian

Age of Blood?

- Cardiac, ICU, trauma – suggested, not proved, ↑ RBC storage duration may ↓ outcomes
- Dunn (2012) – Liver: similar outcomes, retrospective
  - 531 pts (2001-10)
  - Only # RBCs associated risk (MV regression)
  - Define threshold - 10 RBCs (HR 0.33 if < 10 RBCs)
  - Duration NOT significant but difference survivors/death 15.5 vs 14.5 days storage (none > 20 days) – not really 'old'

- De Boer (2008)
  - Retrospective, 433
  - ↓ % pts receiving transfusion 100- 74 % (1989-2004)
  - 3 dominant factors 1 yr survival:
    - Indication transplant
    - Transfusion RBC (HR 1.06/U)
    - Transfusion plts (HR 1.38/U)
- De Boer (2009)
  - Retrospective, 449
  - Plt transfusion predicted ↓ pt (74-92%), graft (69-85%) survival
  - > early mortality due pulmonary injury

- Cywinski (2013)
  - 1,123 pts (2001-11) – 667 analyzed after exclusions (incomplete data, age blood straddled cut-off)
  - Defined 15 days storage (median 12 vs 19 days)
  - MV analysis predictors death/dysfunction – 2 yrs: HR (p value):
    1. Donor race (other than white) – 2.46 (0.03)
    2. Donor risk index – 1.89 (0.002)
    3. Age blood – 1.65 (0.004)
    4. # RBC units (per 5U increase) – 1.35 (< 0.001)

- Current debate fueled trauma, critical care, cardiac, pediatric cardiac surgery
- Data limited thus far for LT, driven by debate and public opinion
- Your patient may ask you how old the blood is that you will give!
- Blood banks face critical supply-demand imbalance
  - FDA change 1 week storage limit → significant shortages in TX (Merlyn Sayers, MD - Carter Blood Care - personal communication)
  - Risk of old blood vs. No blood .....
- Stay tuned .....

Anti-Fibrinolytics

- Numerous case reports/series TE events ∞ anti-fibrinolytic Rx
- Systematic review - no ↑ risk (may not detect high-risk sub-groups) (Molenaar 2007)
- Current practice: EACA/TXA - lysis + clinical bleeding (> 7.5% - 15%)
- Cochrane analysis (Gurusamy 2011) -limited studies:
  - No difference transfusion - TXA vs aprotinin

D. Current and Potential Hemostatic Options

- Bleeding is bad for LT recipients .....
- Transfusion appears to be bad for LT recipients .....
- What do we do?
  - Can we mitigate risks of transfusion?

- Retrospective analysis after withdrawal aprotinin 2008 (Schofield 2014)
  - 110 propensity matched pts (> 15% TEG^R)
  - After withdrawal:
    - ↑ fibrinolysis (23%), majority received TXA
    - NO difference RBC, FFP plt or cryoprecipitate transfusions

- Current practice (survey – 2013):
  - Routine practice 50 – 60% (TXA, EACA)
  - Ramsay (Dallas) – only Rx if see lysis TEG

Low CVP

- Data - benefits EBL inconsistent
- Concerns delayed renal dysfunction
- Massicotte (2004) - proponents (institutional effect)
- Survey – practiced 54% centers USA (Schumann 2013)

Dedicated anesthesia team

- Hevesi (2012): Requirements RBC/FFP ↓ 2- 3-fold:
  - Anesthesia team
  - Protocol (low CVP)
  - Goal-directed transfusion (TEG^R)

Recombinant factor VIIa

- Cochrane meta-analysis (11)
  - May potentially reduce EBL (Lodge 2005)
  - No significant differences mortality, TE episodes, SAEs
  - Insufficient level 1 data (3 trials, < 200 pts)
    - Niemann (11), Gala (7) – retrospective
- Bosch – variceal bleeding (14)
  - Better labs, no difference bleeding, mortality, ↑ TE events
- Planinsic – multicenter PRCT 82 (05)
  - Single dose 0, 20, 40, 80 mcg/kg not ↓ RBC transfusion
- Current practice (survey 13):
  - 9% programs protocol
  - 54% use post-reperfusion coagulopathy or rescue therapy

Prothrombin Complex Concentrates (PCC)

- FDA approved (Kcentra®, CSL Behring 13):
  - Urgent reversal acquired coag factor deficiency induced vit K antagonist, adults needing urgent surgery/procedure
  - Local MHH protocol: 'liver disease' exclusion (!)
- 4 factor (II, VII, IX, X) + antithrombotic protein C and S
- Reports TE complications post-marketing surveillance
- Cost, hematology consultation
- *Off-label use* cardiac, trauma, neurosurgery
- No evidence ↑ risk thrombosis (Sorensen 2011, Hanke 2013)
- LT - European data .....

How Provide Fibrinogen?

- Plasma
  - 1-3 g/L (4 U FFP)
  - Studies - > 33.5 ml/kg - ↑ 1g/L (impractical, TRALI, TACO)
- Cryoprecipitate
  - 15 g/L (100 ml = 1.5g)
  - Multidonor product, no antiviral processing
  - Unavailable Germany
- Fibrinogen concentrate
  - Human derived, pasteurized, lyophilized
  - Reconstitution – 1 g (0.9-1.3)/vial
  - RiaSTAP (CSL Behring): FDA approved – acute bleeding pts *congenital fibrinogen deficiency* (a/hypofibrinogenemia, NOT dysfibrinogenemia)

- Lorenz (2003) – 22 pts – non-transplant surgery ESLD

Gorlinger (Germany):

- Retrospective (266 pts) – all *with* clinical bleeding
- 2009-10: 156 with concentrates – 110 without
- EXTEM (ROTEM) > 80: PCC 25U/kg
- Hyperfibrinolysis: TXA 25 mg/kg
- Rescue: FFP 15-20 ml/kg
- 35% received PCC (57% - fibrinogen)
- ↓ RBC, FFP and platelets concentrate Rx group
- No difference TE or safety events

Fibrinogen Concentrate

- Manufacturer: 1-2 g
- Dose = desired ↑ (g) x plasma volume (L)
- Dose = target – actual FIBTEM MCF (mm) x weight (kg/70)
- Normal FIBTEM 9-22 mm
- Concerns:
  - Cost
  - Anaphylaxis
  - Thrombotic events
  - Although ↓ transmissible viral agents, potential

Fibrinogen

- Critical role maintaining hemostasis
- First factor fall critically low levels major bleeding
- Cross-linking XIIIa essential clot stability
- What level?:
  - Historical 1 g/L
  - European trauma guidelines 1.5-2
  - Obstetric population > 2.0
  - Liver Transplantation ?

Preliminary Data

Gorlinger (2014):

- Protocol with PCC, TXA
- Mean 6 G (153 pts – 57% cohort)
- ↓ RBC, FFP and platelets concentrate Rx group
- No difference TE or safety events

Suggested Strategies Liver Patient in GI Lab

- Restrictive transfusion
- Variceal bleeding related local vascular abnormalities, ↑ portal pressure
- Lower CVP → lower portal pressure
- Platelets
  - AASLD suggests transfuse < 50K (limited high quality evidence)
  - Splenomegaly – 90% radiolabeled plts sequestered 5 minutes!
  - Plts redistributed from spleen after epinephrine
  - Disappointing results thrombopoeitin agonist (Eltrombopag) – thrombotic events, no improved outcome
  - Consider lower thresholds *lower risk* procedures (30K – endoscopy without biopsy, endoscopic management varices, screening colonoscopy)
  - 50K for higher risk procedures (ERCP, biopsy)
  - Educate anesthesiology, GI and radiology colleagues!

- Strategies mitigate risk:
  - Anesthetic, surgical technique
  - Hemostatic adjuncts (anti-fibrinolytics)
  - Coagulation factor concentrates (PCC, fibrinogen, XIII)
    - NOT FDA approved yet
    - Proof of concept
    - Early positive/preliminary data Europe
  - Allied with guided, algorithm driven therapy WHEN bleeding .....
  - Don't treat the test result alone

- RBCs
  - AASD recommends Hb 8
  - Evidence restrictive (Hb < 7) better for bleeding, mortality than > 9 (lower hepatic venous pressure gradient)

- Cryoprecipitate
  - Consensus if fibrinogen < 100 mg/dl

- Plasma
  - 30% all plasma one facility hepatobiliary disease (Wells 09)
  - AASLD discourages arbitrary PT/INR values influence plasma transfusion
    - Consider TEG^R
  - Plasma little effect *thrombin generation* (Tripodi 12)
  - Some use INR 2.5 low risk procedures (Yates 16)

Porto-Pulmonary Hypertension (PPH)

- 5 - 6% cirrhosis, ↑ in those screened for LT
- Not necessarily related severity liver disease
- Dx – R heart cath:
  - MPAP > 25 mmHg
  - PVR > 3 Wood units (x 80 = dynes/sec/cm^5)
  - Normal L-sided pressures (PCWP/LVEDP < 15, TPG > 12)
- M/M: 60% 1-yr survival without Rx
  - MPAP > 50 = 100% periop mortality
  - 35-50 = ↑ mortality if PVR > 250 [Krowka 00, 04]

Conclusions

- Well known risks for bleeding with LT
- Shift understanding coagulation balance pts ESLD
- May necessitate different approach monitoring
- Increasing appreciation risks transfusion in LT
  - Cautious transfusion thresholds
  - PRCTs in LT needed

Treatment Options

- General measures pulmonary hypertension
  - Control AWP, avoid hypoxia, hypercarbia, acidosis (when can)
- Endothelin antagonists (PO)
- PDE-5 inhibitors (PO + IV)
- Prostacycline analogs
  - IV epoprostenol/inhaled Iloprost
- Inhaled NO
  - Theoretical concern methemoglobinemia
- Other

How are we doing for LT?

- Candidates applied exception points (06-12) [Goldberg 2014]
  - Liver disease not severe enough to ↑ MELD, but PPH severe
- Of 174, 155 least 1 application approved:
  - Only 47.1% met OPTN criteria
  - 17.5% met initial criteria, not post-Rx
    - Of this 100, 63 transplanted
  - 35.4% insufficient data/volume overload
    - Of 55, 44 transplanted

Unanswered Questions

- Can refine ability TTE (intraop TEE) predict PPH and implications?
- Who/when gets RHC?
- How will this affect anesthetic Mx 'presumed or possible' PPTN?
  - Do we treat intraop if diagnosis unconfirmed?
    - PDE inhibitors, NO, PO meds in NG tube?
  - If so, what risks/benefits?

Outcome

- Response Rx positive:
  - ↓ PVR 3.2, ↓ MPAP 17

IF HDs consistent with PPH:

- < likely transplanted (63 vs 80%)
- > likely removed waitlist - death/deterioration (23 vs 9%)
- Unadjusted post-transplant outcomes 'similar' but I'm not so sure:
  - 3 yr survival 64.3 vs 77.3% (p = 0.08)
  - 12/100 died – PPH group (3 same day) – HR 2.46
  - 6/55 died – insufficient data/overload group – HR 1.6

Hepato-Pulmonary Syndrome

- 10% liver disease pts
- Lack hepatic clearance vasoactive substances produced splanchnic territory
- Cause inappropriate intrapulmonary shunts with hypoxemia
- Orthodeoxia (orthostatic desaturation)

Diagnostic criteria:

1: Chronic liver disease

2: A-aDO_2 ≥ 15 - 20 mmHg (PaO_2 60-80 = mild)

3: Intrapulmonary vascular dilatation (contrast enhanced echo < 3 vs 4-6 beats, technetium labelled albumin lung perfusion scan)

VD 40%, hypoxemia 15%, LT candidates 10%

How valuable is Transthoracic Echo?

- Undetermined cut-off for unnecessary R heart cath
- Reasonable - MPAP > 35?
- Predict outcome [Kia 2013]?
  - Retrospective 216 pts (2007-10)
  - Only > mild TR predicted mortality (HR 3.91) and graft failure (HR 3.7)
  - PASP and MELD correlated ICU LOS
  - Majority 'severe' pts excluded transplant
    - Only 3.7% had RHC
  - 1 prior study correlated TR jet velocity – survival [Ford 2009]

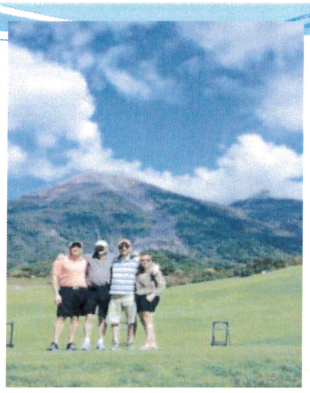
- Severe, MELD exception points, prioritized on LT waiting list
- Increased risk – exclude other causes
  - ↓ FRC – ascites, pleural effusion
  - Pulmonary edema/hydrothorax
- Medical treatment disappointing
  - Pentoxyfillin (PDE-4 inhibitor), methylene blue (blocks effect NO), garlic
- TIPS controversial
- Definitive Rx LT (previously contra-indication)
- Anesthesia:
  - NOT over-PEEP or over-diurese (won't fix)
  - Lung protective strategy(6-8 mL/kg, 6-8 cm PEEP, regular recruitment)
  - Slow resolution (weeks – months)

Severe post-op hypoxemia

- Trendelenburg position
- Extracorporeal membrane oxygenation
- Embolization abnormal pulmonary vessels

HPS References

1. Aldenkortt F. PPH and HPS. World J Gastroenterology 2014:20;8071
2. Lv Y. HPS. Dig Dis Sci 2015: 60; 1914
3. Najjar D. Proposed management algorithm for severe hypoxemia after LT in HPS. Am J Transplant 2015; 15; 903
4. Raevens S. HPS and PPH: recent knowledge in pathogenesis and overview of clinical assessment. Liver Int 2015: 35; 1646



Coagulation References

1. Caldwell SH. Coagulation disorders and hemostasis in liver disease: pathophysiology, critical assessment current management. Hepatology 2006:44;1039
2. Lisman T. Hemostatic alterations in liver disease: Review pathophysiology, clinical consequences, treatment. Dig Surg 2007:24;250
3. Lisman T. Normal to increased thrombin generation in pts undergoing liver transplant despite prolonged conventional coagulation tests. J Hepatol 2010:52;355
4. Lisman T. Rebalanced hemostasis in pts with liver disease; evidence and clinical consequences. Blood 2010:116;878

PPH References

1. Kia L. Role of pre-transplant echo evaluation in predicting outcomes following LT. Am J Transplant 2013:13;2395
2. Goldberg DS. MELD Exceptions for PPH: Current policy and future implementation. Am J Transplant 2014:14;2081
3. Krowka MJ. Pulmonary contra/indications and MELD exceptions for LT. J Hepatol 2013:59;367
4. Aldenkortt F. PPH and HPS. World J Gastroenterology 2014:20;8071
5. Krka MJ. MELD exception for PPH. Liver Transept 2006:12; S114
6. Saddar Z. PPH: update. Liver Transept 2012:18; 881

5. Tripodi A. Abnormalities of hemostasis in chronic liver disease: reappraisal of clinical significance, need for clinical and laboratory research. J Hepatol 2007:46;727

6. Tripodi A. Coagulopathy of chronic liver disease. N Engl J Med 2011:367;145

7. Aldawood A. Incidence of venous thromboembolism and practice of deep venous thrombosis prophylaxis in hospitalized cirrhotic patients. Thromb J 2011:9;1

8. Lu S. Clinical applicability rapid TEG and Functional Fibrinogen TEG in adult LT. Liver Transpl 2014: 20; 1097

9. Massicotte L. Transfusion rate for 500 consecutive liver transplants: Experience of one LT center. Transplantation 2012:93;1276

10. Massicotte L. Coagulation defects do not predict BP requirements during LT. Transplantation 2008:85;956

11. De Boer M. Minimizing blood loss in LT: progress through research and evolution of techniques. Dig Surg 2005:22;265

12. De Boer M. Impact of intraoperative transfusion of platelets and RBCs on survival after LT. Anesth Analg 2008:106;32

13. Pereboom ITA. Platelet transfusion during LT is associated with increased postoperative mortality due to acute lung injury. Anesth Analg 2009:108;1083

14. Massicotte L. Survival rate changes with transfusion of blood products during LT. Can J Anaesth 2005:52;148

15. Benson A. Differential effects of plasma and red blood cell transfusions on acute lung injury and infection risk following LT. Liver Transpl 2011:17;149

16. Lisman T. Anemia as a potential contributor to bleeding in patients with liver disease – neglected but not forgotten. J Hepatol 2011:594

17. Osier Y. Institutional variability in transfusion practice for LT. Anesth Analg 2003:97;671

18. Massicotte L. Transfusion predictors in LT. Anesth Analg 2004:98;1245

19. Hevesi Z. Designated LT anesthesia team reduces blood transfusion, need for mechanical ventilation and duration of intensive care. Liver Transpl 2009:15;460

20. Walia A. Anesthesia for LT in US academic centers: institutional structure and perioperative care. Liver Transpl 2012:18; 737

21. Cywinski JB. Prediction of intraop transfusion requirements during orthotopic LT and influence on postop patient survival. Anesth Analg 2014;118:428

22. Glance LG. Association between intraop blood transfusion and mortality/morbidity in patients undergoing non-cardiac surgery. Anesthesiology 2011:114;283

23. Cywinski JB. Transfusion of older red blood cells is associated with decreased graft survival after orthotopic LT. Liver Transpl 2013:19;1181

24. Dunn LK. Duration of RBC storage and outcomes following orthotopic LT. Liver Transpl 2012:18; 475

25. Schofield N, et al. No increase in blood transfusions in LT since withdrawal aprotinin. Liver Transpl 2014:20; 584

26. Levy JH. Fibrinogen as therapeutic target for bleeding: review of critical levels and replacement therapy. Transfusion 2014:54; 1389

27. Kirchner C. Coagulation management with factor concentrates in LT: single center experience. Transfusion 2014: 54; 2760

28. Rana A. Blood transfusion requirement during liver transplantation is an important risk factor for mortality. J Am Coll Surg 2013: 216; 902

29. Yates SG. How do we transfuse blood components in cirrhotic pts undergoing GI procedures? Transfusion 2016: epub ahead of print

30. Jairath V. Modern-day management upper GI hemorrhage. Transfusion Medicine 2015: