Managing the Coagulopathy of Liver Disease

Bradford Sherburne MD
Medical Director
Hartford Hospital Laboratories
THE BLACKOUT: This was New York City, a city that knows no darkness. Office towers, tall apartment houses, the United Nations, the Empire State Building, spire of a skyscraper, lights visible made by cars.

THE BIG CITY LIVED BY THE LIGHT OF THE MOON
Objectives of our discussion

• Know the limitations of the INR in patients with End Stage Liver Disease (ESLD)

• Understand the derangements of hemostasis that occur in the anhepatic environment.

• Be comfortable using Thromboelastography (TEG) to guide transfusion therapy in ESLD patients

• P.S. I have no conflicts to disclose; I may mention off-label use of activated factor 7 and 4-factor PCC
This is why you don’t like coagulation

- Practices are handed down by “oral history”
- Most practitioners know that the (a)PTT reflects heparin effect
- Most practitioners know that the INR is used to dose warfarin
- **BUT MOST HAVE NO IDEA WHY!!!!**
...and, there is the horrible specter of math:

- To back-calculate the PT from the ISI and the INR:
  - \[ \text{INR} = \frac{\text{PT/Mid NL Range}}{\text{ISI}} \]
  - [Midpoint NL Range = 12 seconds]
  - \[ 10^{\text{INR}} = \text{ISI}(\text{PT}) - \text{ISI}(12) \]
  - \[ 10^{\left[\frac{\text{INR}}{\text{ISI}}\right]} = \frac{\text{ISI}(\text{PT})}{\text{ISI}} - \frac{\text{ISI}(12)}{\text{ISI}} \]
  - \[ \frac{\text{INR}}{\text{ISI}} = \text{PT} - 12 \]
  - \[ \log \left(\frac{\text{INR}}{\text{ISI}}\right) = \log (\text{PT}) - \log (12) \]
    \[ \text{Note: } \log 12 = 1.08 \]
  - \[ \log \left(\frac{\text{INR}}{\text{ISI}}\right) = \log (\text{PT}) - 1.08 \]
  - \[ 10^{\log \left(\frac{\text{INR}}{\text{ISI}}\right)} + 10^{1.08} = 10^{\log (\text{PT})} \]
  - Therefore, \[ 10^{\left[\log \left(\frac{\text{INR}}{\text{ISI}}\right) + 1.08\right]} = \text{PT} \]
Has this ever happened to you?

- Everyone expects the ESLD patient to **BLEED**!

- You ask neurosurgery to put in an ICP monitor

- But they won’t, because the INR is 5.7, and they assume they will **bleed** like someone on warfarin who has an INR of 5.7…
What’s the difference?

- Virtually ALL coagulation factors are synthesized in the liver. But you cannot make a clot without **FIBRINOGEN**

- Warfarin inhibits Vitamin K dependent factors: 2,7,9,10, Proteins C & S, BUT has NO effect on fibrinogen, which is why the elevated INRs are completely different

- To add insult to injury, ESLD may have Dysfibrinogenemia
But doesn’t the INR correlate with synthetic function, like albumin?

• Indeed, we do use the INR as a component of the MELD score, which validates a false belief that INR relates to hemostatic integrity.

• But there is a HUGE difference between a high INR on warfarin versus a high INR in cirrhosis.
Vitamin K-dependent gamma carboxylation

Diet & Intestinal microbes → Vit K Quinone

Vit K epoxide → Vitamin K epoxide reductase → Vit K Quinol

Coumadin

Coagulation protein precursor → γ-carboxylated Glutamic acid on clotting protein
Sometimes it’s hard to be a Eukaryote

- The INR is a (crappy) surrogate test to measure Vitamin K antagonists

- Your liver doesn’t CARE if its zymogen proteases get carboxylated or not

- So the INR is an indirect (even crappier) surrogate test of synthetic function
FFP and Warfarin reversal

- We DO tend to under-dose plasma: Standard dose is 10-20 ml/kg TO REVERSE WARFARIN

- If time permits, give I.V. (I.V. please) Vitamin K

- There is NO edict to give EVEN numbers of FFP, why do we do that?
So you try to get the INR down…

Since the INR is so high, use $20 \times 85 \text{ kg} = 1700 \text{ ml}$.

Here’s what happens when you give 8 units of plasma:

At least their INR went down.

There is a special place in hell for who those who treat numbers, and not patients!
Maybe I’ll try something else…

But there’s not a lot else out there. How about:

some Novo-7?
some K-centra?

those will decrease the INR

But remember, you’re NOT ON WARFARIN!! Oops…
Screening tests: the PT and the aPTT
plasma drawn into citrate, calcium added back, time until clot forms

- **activated Partial Thromboplastin Time**
  - Kaolin, activator, P-lipid
  - Intrinsic pathway
  - All factors involved EXCEPT for 7 (VII)
  - Unfractionated heparin inhibits serine proteases via Anti-Thrombin 3

- **Prothrombin Time [INR]**
  - Human or rabbit brain (provides tissue factor)
  - Extrinsic pathway
  - Factors 1,2,5,7 and 10:
  - 7 has shortest in vivo $t_{1/2}$
  - But, INR WAS NEVER INTENDED TO BE A SCREENING TEST!!!!
Percent total factor activity versus the PT or INR (like GFR vs. creatinine...)
% Coagulation Factors

100 %

0 %

INR and Coagulation Reserve

Zone of Normal hemostasis

Zone of therapeutic anticoagulation

PT (sec) 12 13 15.5 19 21.8 24 30 32
INR 1.0 1.3 1.7 2.0 2.2 3.0

Feb 2007 [slide courtesy of Dr. Sunny Dzik]
Changing paradigms over a generation #1

• The historical criterion for dosing warfarin was a TARGET PROTIME of 1.3 to 1.7 times the patient’s baseline or the PT “control”

• Do any of you remember how the PT and aPTT were reported for both “patient” and “control”?

• Our technology has come a long way; our way of looking at this is pretty much arrested in the ‘90s
Changing paradigms over a generation #2

• The time-honored method for measuring PT was the “tilt-tube”; end-point was observer dependent

• Lab technology evolved to yield accurate and precise values, but reagents remained insensitive through their therapeutic range

• So more and more sensitive (and expensive) reagents were introduced to titrate warfarin
INR = \{ \text{PT/Mid Normal Range} \}^{\text{ISI}}

[Midpoint Normal Range = 12 seconds]

1994: ISI = 2.5 (brain extract)

- Normal PT was 11-13 sec
- Therapeutic target was 1.3x – 1.7x of baseline
- Therapeutic PT range = 15.6 to 20.4 seconds
- INR equates to 1.9 to 3.8

2017: ISI = 1.0 (synthetic agent)

- Normal PT still 11-13 sec
- Therapeutic target is now expressed as INR 2.0-3.5
- Corresponding PT range is now 24 to 42 seconds
- PT range 18 vs. 4.8 sec!
Changing paradigms over a generation #3

• When the therapeutic value had a “tight” response range, it felt different to us as doctors

• We dosed FFP to get the PT less than 1.5 times normal, generally 17 seconds, and we audited transfusion practice based on this “consensus”

• PT of 1.5 x “normal” is NOTHING like an INR of 1.5, BUT that is what “they” chose
Factor activity versus PT, high ISI (insensitive reagent, as used in the past)

Steep parabolic curve – clinician is sensitized to numbers over 17 seconds, oblivious to the INR
Factor activity versus PT, low ISI (sensitive reagent as now in use, adopted over 10+ years).

Shallow parabolic curve – values once therapeutic are now basically normal: “24 is the new 17”
PT versus INR for different ISI values

Left column, ISI=1.0 (current); Right column, ISI=2.2 (Circa 1999)

In the span of one generation, we manage to screw everything up…
INR and Coagulation Reserve

% Coagulation Factors

- Normal hemostasis
- Zone of therapeutic anticoagulation

PT (sec)
- 12
- 13
- 15.5
- 19
- 21.8
- 24
- 30
- 32

INR
- 1.0
- 1.3
- 1.7
- 2.0
- 2.2
- 3.0

Feb 2007 [slide courtesy of Dr. Sunny Dzik]
O.K., you’ve convinced me to forget about the INR, but my platelets are only 60,000!

Once again, there is a special place in hell for practitioners who treat NUMBERS instead of PATIENTS

Going to hell:
Radiologists
Cardiologists
Orthopedic Surgeons
Quantitative Platelet Defects

Remember, as long as you are actively synthesizing platelets, they usually work pretty well (check the blood smear, MPV, IPF)

Acquired
- Immune
  - Drugs: Heparin, Quinine
  - ITP, PTP, [TTP]
- Non-Immune
  - Drugs: anti-anything!
  - Consumption due to sepsis or clotting
  - Post-massive transfusion
  - Sequestration (ESLD)

Congenital
- Alport Syndrome
- Bernard Soulier
  - also a prototypical qualitative disorder
- May-Hegglin anomaly
- Wiskott-Aldrich
- Chediak Higashi

Unless you’re a pediatric hematologist, it’s not these
Anatomy of your basic platelet

if you’re a real coagulation nerd, you can tell me something that will mess up every receptor site….
Thromboelastography: TEG

- Cup with recalcified whole blood plus kaolin; heparinase
- Transducer measures resistance during angular acceleration
- Dynamic formation of clot is recorded like a seismometer
TEG is on the right
TEG sample cup design (with permission from Deltamed SA)

Dynamic quantification of clot formation and clot lysis

- R, K, alpha angle, MA and LY30 parameters
- R measures “enzymatic stage” of clot (like PT/PTT)
- Alpha angle and K reflect fibrinogen quality and quantity
- MA indicates contribution of platelets to clot strength
- LY30 (percentage) is an indicator of fibrinolysis

Figure 1
Analytical software graphical representation of a TEG tracing.
Clotting in Real Time: TEG Split Point

No resistance up to this time
Very first “blip” occurs just as fibrin monomers anneal
This is analogous to the end point on the old fibrometer

“Enzymatic” stage of clotting ends with the thrombin burst
Split Point = Fibrin polymer
Resistance increases on the rotating sensor

• Unlike a PT or aPTT, this is whole blood, with red cells, plasma and platelets

• Like stirring a pot as the contents gradually thicken, to use the cooking analogy
Enzymatic stage is standardized: the **R-time**

- The excursion of the white line from the baseline is measured.
- When it reaches **2 mm.**, that’s the **R-time**.
- The **R-time** gets longer if you don’t have enough clotting factor, or if there’s an inhibitor (like heparin).
As resistance increases, so does the amplitude

- Now we are into the realm of whole blood, or “visco-elastic”, clotting

- Analogous to platelet aggregometry, but red cells along for the ride

- The steeper and faster it gets, e.g. “harder to stir”, the more robust the clot
Next measure of clot strength: **K-time**

- Asterisks around number indicate that the software is figuring out the “final” values, and:
- **K-time** is the time in minutes from the R-time that it takes in order to reach **20 mm** of total amplitude (K = Kinetics)
- **REFLECTS THE CRITICAL ROLE OF FIBRINOGEN**
Cross-linking fibrin monomers: alpha-angle

- Measuring fibrinogen’s contribution to clot strength
- **Alpha-angle** is essentially the same as the **K-time**, but in the old days you used a protractor to measure it, and that made everyone take you very seriously!
Fibrin and platelets combine to make the composite clot: the **MA** (Maximal Amplitude)

The MA is the ultimate indicator of total clot strength: it reflects the action of thrombin on the platelets. Thrombin is the strongest natural agonist of platelet activation.
Still waiting for a final MA (*asterisks*)

- Notice how you have watched a clot develop in real time; not just a test, it’s live entertainment!
- More importantly, it’s easier and quicker to decide what blood product to administer (if any)
Remote TEG viewing: can you think of another lab test you watch in real time?
MA completed; clock starts on LY30

- This measures fibrinolysis and reflects the action of plasmin degrading fibrinogen and cross linked fibrin (FDPs and fdps):
- Seen after tPA and in anhepatic phase of OLT
Alas, the **LY30** is normal, no fibrinolysis

- Note how the TEG continues for 30 minutes after the MA is reached (horizontal axis)
- No longer any *asterisks* around LY30 parameter; test is complete
### TEG patterns and Transfusion Therapy

<table>
<thead>
<tr>
<th>Pattern</th>
<th>Description</th>
</tr>
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</table>
| a | **Normal**  
| R; K; MA; Angle=Normal |
| b | **Anticoagulants/hemophilia**  
| Factor deficiency  
| R; K=Prolonged; MA; Angle=Decreased |
| c | **Platelet blockers**  
| Thrombocytopenia  
| Thrombocytopeny  
| R - Normal; K=Prolonged; MA=Decreased |
| d | **Fibrinolysis (UK, SK, or t-PA)**  
| Presence of t-PA  
| R - Normal; MA=Continuous decrease  
| LY30>7.5%; WBCLI30<97.5%; Ly60>15.0%; WBCLI60<85% |
| e | **Hypercoagulation**  
| R; K=Decreased; MA; Angle=Increased |
| f | **DIC**  
| Stage 1  
| Hypercoaguable state with secondary fibrinolysis |
| g | **Stage 2**  
| Hypocoaguable state |

- Remote viewing of TEG: guide therapy in real time
- Heparin: Protamine
- Low **MA**: platelets
- Long **R**: plasma, etc.
- Long **K, low alpha**: cryo
- High **LY30**: TXA, EACA
- Early DIC: heparin
Direct Thrombin Inhibitors
versus indirect acting inhibitors (AT3)

*IV*: argatroban, hirudin, bivalirudin; *Oral* (DOAC): Dabigatran [Pradaxa]

Pentasaccharide depicted below in green = Fondaparinux
Inhibitor of the enzymatic phase

- This is the heparin effect, neutralized by heparinase
- Inconsistently reflected with the new DOACs—so check alternate tests:
  - Dabigatran (Pradaxa)
    - Prolonged Thrombin Time
  - Eliquis (Apixaban)
  - Xarelto (Rivaroxaban)
    - Elevated Anti-Xa activity (heparin assay)
Bleeding post-op CT surgery: heparin neutralized INR=1.3
In retrospect, R-time at end of bypass WAS prolonged
[This was when we were correlating TEG and conventional tests]
Heparin neutralized INR almost normal at 1.3, but:

PTT was 54 (no one checked it)

Contact factor deficiencies are detected by TEG ("hemophilia C")
Does the TEG correlate with routine coagulation tests, e.g., the PT/INR?

Our “involuntary” Randomized Clinical Trial went live at HH:

\[ R^2 = 0.0046 \]

![Graph showing R time versus Protime with linear relationship and a correlation coefficient of 0.0046.](image)
General approach using the TEG to address coagulopathy in the ESLD patient even if they’re not bleeding, how to get a smart radiologist or neurosurgeon to touch them

- **DON’T** MEASURE THE INR; this should be clear by now.
- Check a TEG and fibrinogen level every 12 hours
- Assess, in this order, the TEG parameters: R, K, MA, LY30
  - If R is long, you DO need cascade factors [FFP, “etc”]
  - If K is long, need fibrinogen*
  - If MA still low: platelets
  - If LY30 high: consider EACA
    - *Fibrinogen >150: one dose cryo
    - *Fibrinogen <150: 2 or more
ESLD patient with enlarging hypertensive basal ganglia hemorrhage

Address abnormal R, K, and MA values in that order. Here, R is normal, K long, MA decreased:

Pre-cryoprecipitate
- K 4.9 min; MA 34mm
- Fibrinogen 59 gm/dL

Post-cryoprecipitate
- K 1.2 min; MA 58mm
- Fibrinogen 151 gm/dL
Would you give this ESLD patient about to have her liver transplant some FFP? [R-time normal]
What if I told you that her INR was 7.6 (PT of 82) and aPTT 73 sec.

If you just had those numbers, you would probably give her empiric FFP (or something worse...)

Even if her surgical field was hemostatic? Really?

TEG allows you to believe what you are SEEING CLINICALLY!

So you can treat the patient, not the number.

(you remember why!)
**TEG in massive hemodilution**

All products needed; principle of “massive transfusion”

<table>
<thead>
<tr>
<th>R</th>
<th>K</th>
<th>Angle</th>
<th>MA</th>
<th>PMA</th>
<th>G</th>
<th>EPL</th>
<th>A</th>
<th>CI</th>
<th>LY30</th>
</tr>
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<tbody>
<tr>
<td>min</td>
<td>min</td>
<td>deg</td>
<td>mm</td>
<td></td>
<td>d/sc</td>
<td>%</td>
<td>mm</td>
<td></td>
<td>%</td>
</tr>
<tr>
<td>14.4</td>
<td>15.6</td>
<td>15.9</td>
<td>26.6</td>
<td>1.0</td>
<td>1.8K</td>
<td>0.0</td>
<td>29.7</td>
<td>-18.6</td>
<td>0.0</td>
</tr>
<tr>
<td>4 — 9</td>
<td>1 — 3</td>
<td>59 — 74</td>
<td>55 — 74</td>
<td>5.3K — 13.2K</td>
<td>0 — 15</td>
<td></td>
<td></td>
<td></td>
<td>0 — 8</td>
</tr>
</tbody>
</table>

Sample: 4/11/2012 10:29AM-11:43AM
VAD patient on Warfarin clotting their device with an INR of 3.7 – are you surprised?
ECMO patient - sudden acrocyanosis, filter clot, new bleeding – what treatment now?
TEG showing primary fibrinolysis

Viscosity decreases as the clot “dissolves” (plasmin)

Could treat with a lysine analog = competitive inhibitor (EACA, TXA)

Plasma NOT thrombogenic; a source of the natural anti-coagulants (a2AP, PAI-1) as well as clotting factors!
Blocking the action of Plasmin
It’s the only lab test of the coagulation cascade that can show you this
(Does anyone remember the Euglobulin Lysis Time? No? Good!)
Fibrin and fibrinogen degradation products

When increased, help to impede platelet aggregation

Degradation products mimic fibrin monomer, but are not functional

They act as competitive inhibitors; block 2b3a receptor (like ReoPro)
Fibrin and fibrinogen degradation products
-are cleared by the liver, so they accumulate readily in ESLD patients

Plasmin cleaves fibrin monomer and cross-linked fibrin (latter: d-dimer)

Cross-linking of normal clot is disrupted by fibrin split products
TEG during liver transplantation

- Start of case, note long K, low alpha angle and low MA. Platelets 50K; Fibrinogen is 74 mg%; orderly dissection without significant blood loss (HCT = 25%).

- What product does anesthesia decide to give?
TEG during liver transplantation

- Start of case, note long K, low alpha angle and low MA. Platelets 50K; Fibrinogen is 74 mg%; patient is bleeding like a stuck pig and surgeons have trouble visualizing where the bleeding is coming from (HCT =15%)
- What product does anesthesia decide to give?
TEG during anhepatic phase of OLT

• It’s that magic moment when they are about open up the clamps and re-perfuse. Anesthesiologist is reciting the Rosary (they’re Jewish); has bicarb & 5 pressors ready.

• Should you give cryo? TXA? 4-factor PCC? Novo-7?
TEG during OLT, new graft in, ready for biliary anastomosis

- Anesthesiologist left to go hang out at the front desk, perfusionist is packing up, surgical residents laughing about weekend plans, HCT 28%, INR 1.4, Platelets 48K

- What products would you give at this point?
TEG during OLT, new graft in, ready for biliary anastomosis

- Anesthesiologist calls second attending into the room, perfusion calls for more reservoirs, Blood Bank issues fifth MTP pack. HCT 28%, INR 1.4, Platelets 40K

- What products would you give at this point?
So, the next time you feel truly compelled to treat an abnormal lab value or something else that really doesn’t need to be treated, try to remind yourself:

“WE DON’T SEE THE THINGS THE WAY THEY ARE. WE SEE THINGS THE WAY WE ARE.”

- TALMUD