The Making of a CLOTT

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UCSF AND ACS
Coalition of Leaders in the study of Traumatic Thromboembolism (CLOTT)

- Initiated through a meeting at the AAST 2013
- Group of surgeons with interest/previous publications in VTE
- Subsequent survey of the group of “experts”: we all practiced VTE prevention and treatment after injury differently!*
- Second publication: Surveillance bias with assessment of lower extremity ultrasound-increased the DVT rate by >5 times!**

*Bandle et al: Variability is the standard; JTACS 2014

**Shackford et al: Determining the magnitude of surveillance bias...JTACS 2016
The Search for Research Topics and Funding

- ASA Presentation: 3738 Posttraumatic Pulmonary Emboli*
- Suggested a disconnect: DVT and PE
- Pulmonary clots: inflammatory
- Velmahos: pulmonary clots seen on admission: not associated with DVT**

*Knudson et al: Annal Surgery 2011

**Velmahos et al: Arch Surg 2009
Knudson’s Trauma Triad

Knudson, et al., J Trauma, 1994
Background for CLOTT Studies: Military Experience

- Casualties from Iraq/Afghanistan
- High rates of DVT: blast injuries and amputations
- Selective surveillance; 1.4% PE
- Universal surveillance: 4.42% (most asymptomatic)
- High risk of full anticoagulation “en route”
- Do all pulmonary clots need to be treated?
Main Hypothesis: Peripheral asymptomatic pulmonary thrombi (PT) seen on chest computed tomography can be safely observed.

Secondary Hypothesis: Risk factors for PT will differ from risk factors for PE (pulmonary clot associated with DVT).

Tertiary Hypothesis: Patients who develop a hypercoagulable state detected by fibrinolytic shutdown will be at increased risk for PE and DVT.
17 CLOTT CENTERS and PIs

- OHSU: Lazlo Kiraly
- Christiana HS: Cipolle/Sixta
- MUSC: Bruce Crookes
- JHU: Elliot Haut
- UF: JAX-Andy Kerwin
- DGH: Gene Moore
- U. Utah: Ram Nirula
- Scripps Mercy: Shackford/Martin
- UCSF: Knudson/Kornblith
- Stanford: Spain/Knowlton
- UMM: Scalea/Bruns
- UCSD: Costantini
- Harvard: Velmahos
- MCW: Mila
- UF Gainesville: Mohr/Brakenridge
- UT Houston: McNutt/Wade
- LGH: Rogers
Study design: Prospective, observational study at all 17 Centers

Main Outcome Measure: Presence, location, timing of any pulmonary clot

Secondary Outcome Measure: Presence of DVT

Definition: PE=DVT plus pulmonary clot; De novo PT=no DVT

Methods: Specifically designed CRF collected in RECap at UCSF

Data collected: demographics, mechanism of injury, injury characteristics (ISS, AIS), operations, transfusion data, prophylactic measures and missed doses, lab studies, imaging studies (duplex exams, CT scans), complications, outcomes
Study Design: CLOTT Part 1

- Prophylactic measures and treatment of clots left to the discretion of the treating surgeons

- Entrance criteria:

  1. Deployable age group: 18-40 years
  2. Expected to be hospitalized for at least 48 hours
  3. At least one VTE risk factor*: AIS >3 head, chest, abdomen
     - shock on admission  - spinal cord injury  - pelvic, lower extremity fx  - INR > 1.5
     - venous injury  - femoral catheter  - major operation on Day #1

CLOTT 1: RESULTS

- 7880 patients enrolled: 2018-2020
- 277 pts with DVT: 3.5%
- 40 pts with PE: 0.5%
- 117 with PT: 1.5%

Factors *independently* associated with PT but not DVT or PE:
- Shock on admission (OR=2.74; p< 0.001)
- Major chest injury (OR 1.72; p=.007)
Of the 117 patients with PT, 52.1% had clot on same side of injury

- Location: 8 main, 25 lobar, 28 segmental, 21 subsegmental, 34 multiple
- 23.9% had clot evident on the admitting CT scan
- Factors associated with PT on admission included:
  - major chest injury
  - major venous injury
PROPOSED TREATMENT ALGORITHM

Knudson et al: JAMA Surg 2021
ARE ALL POST-TRAUMATIC PULMONARY CLOTS EMBOLIC?

**STUDY POPULATION**
7880 injured patients aged 18-40yrs with VTE risk factors

Admitted to one of 17 trauma centers in the “CLOTT” research group

**METHODS**
Prospective observational study; main outcome of interest: de novo pulmonary thrombi (PT)

Secondary outcomes of interest: Presence of PE (with DVT)

**OUTCOMES**
277 with DVT; 40 PE; **117 primary PT**; risk factors for PT only = chest trauma and shock

De novo PT are distinct from traditional VTE paradigm
tPA Resistance: An Early Predictor of Post-traumatic VTE

KNUDSON, MOORE, MOORE, CHAPMAN, KORNBLITH, KIRALY, MCNUTT, WADE, BRUNS, SAUAIA: CLOTT-2 STUDY GROUP
Trauma Induced Coagulopathy

- Acute traumatic fibrinolysis: 40% mortality
- Lead to wide-spread use of TXA
- Failure to lyse clot: 5x increased mortality

Brohi et al J Trauma 2003

Moore et al 2016
FIBRINOLYSIS SHUTDOWN (SD)

- First described in 1964 in surgical patients
- Associated with myocardial infarction and trauma
- Post-op hip surgery: SD associated with VTE
- COVID-19 patients with SD: VTE and Renal Failure
- Associated with increased levels of PAI-1
  - Most severe form: resistant to tPA (tPA-R)
Purpose: To Describe the injury patterns associated with early SD and tPA-R

Hypothesis: Early SD and/or tPA-R: independent risk factor for the development of post-traumatic VTE complications
STUDY DESIGN

- Prospective, observational study: 5 CLOTT-2 Centers*
- Patients with VTE Risk factors requiring ICU care
- Paired samples of TEG assays (kaolin and tPA): 12 and 24 hrs.
  - **SD:** kaolin TEG Ly30% < 0.3%
  - **tPA-R:** tPA 75ng Ly30%<2.1%
- Duplex ultrasound exam at day 4

UCSF, U Colorado/DGH, U Texas Houston, Oregon HSC, U of Maryland
RESULTS

- 141 patients with paired samples
- SD at 12 hours: 52%; SD at 24 hours: 44%
- tPA-R at 12 hours: 45.4%; tPA-R at 24 hours: 34.3%
- Factors significantly associated with early SD:
  - > 4 units FFP/first 24 hours
  - brain or pelvic fractures
  - major surgery on day of admission
- Factors significantly associated with early tPA-R
  - > 4 units RBCs/24 hours
  - chest injuries or long bone fractures
RESULTS

- DVT detected in 15 patients; pulmonary clots in 5 (1=both)
- Overall VTE rate: **14.2%**
- tPA-R at 12 hours: independent risk factor for VTE (hazard ratio of **5.57**, 95% CI 1.39-22.39)
CONCLUSIONS

▪ Patients with injury patterns associated with early tPA-R: high risk for VTE
▪ In these patients, prophylactic measures should be started early
▪ As platelets are one source of PAI-1, consideration should be given to anti-platelet agents as prophylactic measures
▪ The timing of initiation of prophylactic measures may be more important than the agents utilized!
▪ tPA-R represents for the first time a potentially modifiable post-injury risk factor for clot development
### Study Population

**CLOTT-2**: Prospective, observational study across 5 Trauma Centers

- Risk Factors: Venous Thromboembolic Event
- Role of Fibrinolysis

### Results

- **141 Patients Serial Coag Assessment**
  - Time from ICU Admit: 12 hours
  - Lysis < 2.1%

### Conclusions

- **tPA resistance**
- Early quantifiable risk factor for VTE in ICU

**HR VTE 5.57**

95% CI 1.39-22.39
## Secondary Analyses of CLOTT-1 Data

<table>
<thead>
<tr>
<th>Authors</th>
<th>Study</th>
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<tbody>
<tr>
<td>Lombardo, Nirula: Presented at WTA; paper under review at JTACS</td>
<td>Weight based enoxaparin was not associated with reduced VTE rate compared to Standard dosing</td>
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<tr>
<td>Bokenkamp, Velmahos: Abstract submitted to AAST</td>
<td>Early versus late (&gt;24 hours) chemical prophylaxis in pts. With solid organ injury; VTE rates were high (3-6%) but were reduced with early prophylaxis without concern for bleeding</td>
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<tr>
<td>Godat, Costantini: Abstract submitted to AAST</td>
<td>Rates of thromboembolic events in patients with spinal cord injury are high (8.7% DVT, 0.9% PE, 3.2% PT) but lower in those who received prophylaxis within 48 hours (6.7% vs 12.5%)</td>
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<tr>
<td>Haut</td>
<td>CLOTT-3: missed doses; education</td>
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## OTHER PLANNED STUDIES: CLOTT

<table>
<thead>
<tr>
<th>Proposed PI</th>
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<tr>
<td>Kerwin</td>
<td>Vena Cava Filters</td>
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<tr>
<td>Martin/Moore</td>
<td>Prophylaxis in head injuries</td>
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<tr>
<td>Martin</td>
<td>Race, ethnicity as risk factors for clot</td>
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<td>Martin</td>
<td>Enoxaparin versus heparin</td>
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<td>Bruns</td>
<td>Use of an Ortho Predictive tool for clot</td>
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<td>Brakenridge</td>
<td>Bleeding complications with chemical prophylaxis</td>
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<td>Knowlton/Spain</td>
<td>TXA and post-traumatic clotting</td>
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<td>Kornblith</td>
<td>Platelet biology : CLOTT-2</td>
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<tr>
<td>Moore</td>
<td>Plasma assays: tPA, PAI-1, plasminogen, thrombin activated fibrinolysis inhibitor etc.</td>
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One final comment……

- A plea for a change in terminology
- Suggest that the term **VTE be “retired” (sorry Dr. Virchow)**
- Most pulmonary clots are not embolic
- Those that embolize lodge in the pulmonary artery (not vein)
- **Replacement terms:**
  - DVT=deep vein thrombosis
  - PT= primary pulmonary artery thrombosis
  - PE=pulmonary artery thrombosis associated with DVT
Study Arms

Post-traumatic pulmonary clot identified on CTA in first 24h, asymptomatic

BLE DVT US negative for above knee clot

No exclusion criteria, consents to study

Recommended algorithm 1: LMWH based prophylactic AC

If develops symptoms related to PT, clot progresses or additional clot, switch to LMWH based therapeutic AC for remainder of hospitalization

Clinician determines post-discharge treatment and followup

If no development of symptoms or clot progression or additional clot, continue LMWH based prophylactic AC until discharge

Clinician determines post-discharge treatment and followup

Recommended algorithm 2: LMWH based therapeutic AC

Continue through discharge

Clinician determines post-discharge treatment and followup
Primary: There will be equivalent adherence of clinicians to recommended algorithms for prophylactic dosing of LMWH anti-coagulation compared to recommendation for therapeutic dosing of LMWH anti-coagulation for treatment of pulmonary thromboses.

Secondary: Prophylactic LMWH anti-coagulation dosing is non-inferior to therapeutic LMWH anti-coagulation dosing in the treatment of pulmonary thrombosis for in-hospital VTE progression, VTE recurrence, and mortality.
Please use QR code to let us know if you are interested in participation or email us at:

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