Goals for Today’s Brief Talk

• State current recommendation for anti-coagulation in SARS-COV-2 patients
  - Pharmacological prophylaxis remains standard of care
  - There is no current evidence to support empiric full dose anticoagulation for any d-dimer

• Understand proposed role of immunosuppressants
  - Convalescent serum is an old-school, difficult to scale, reasonable approach
  - Anti-IL-6 is being used as rescue therapy; there is not robust evidence for this
Tissue injury precedes dry cough and fever, with peripheral GGOs near pleura

Edema with proteinaceous exudates leading to intra-alveolar organization and fibrosis (rather than accumulation of granulocytes and fibrin)

Increased lymphocytes in BAL of COVID-19 patients
Beyond Lymphopenia Limited Data For Hematological Complications

- Lymphopenia in up to 80% of patients, and may be predictive of severity (esp <5% lymph)
- Thrombocytopenia ~30% in most series, usually mild (>100), associated with severity
- Case control series of 94 patients with SARS-CoV-2 vs healthy controls

Table 1: Comparison of coagulation function between SARS-CoV-2 patients and control group (X ± s).

<table>
<thead>
<tr>
<th>Parameters</th>
<th>SARS-CoV-2 patients (n=94)</th>
<th>Controls (n=40)</th>
<th>t-test</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>APTT, s</td>
<td>29.01 ± 2.93</td>
<td>28.65 ± 3.03</td>
<td>0.648</td>
<td>0.518</td>
</tr>
<tr>
<td>AT, %</td>
<td>85.46 ± 14.43</td>
<td>98.82 ± 12.91</td>
<td>-5.054</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>D-dimer, mg/L</td>
<td>10.36 ± 25.31</td>
<td>0.26 ± 0.18</td>
<td>3.871</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FDP, mg/L</td>
<td>33.83 ± 82.28</td>
<td>1.55 ± 1.09</td>
<td>3.803</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FIB, g/L</td>
<td>5.02 ± 1.53</td>
<td>2.90 ± 0.53</td>
<td>11.88</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PT, s</td>
<td>12.43 ± 3.00</td>
<td>12.08 ± 3.28</td>
<td>0.419</td>
<td>0.678</td>
</tr>
<tr>
<td>PT-INR</td>
<td>1.07 ± 0.09</td>
<td>1.05 ± 0.49</td>
<td>0.244</td>
<td>0.809</td>
</tr>
<tr>
<td>PT-act, %</td>
<td>80.59 ± 12.77</td>
<td>96.86 ± 26.92</td>
<td>-3.651</td>
<td>0.001</td>
</tr>
<tr>
<td>TT, s</td>
<td>18.00 ± 1.80</td>
<td>18.34 ± 0.92</td>
<td>-1.495</td>
<td>0.137</td>
</tr>
</tbody>
</table>

The coagulation parameters were compared using Student’s t-test. APTT, activated partial thromboplastin time; AT, antithrombin; FDP, fibrin/fibrinogen degradation products; FIB, fibrinogen; PT, prothrombin time; INR, international normalized ratio; PT-act, prothrombin time activity; TT, thrombin time.

Han et al. Prominent changes in blood coagulation of patients with SARS-CoV-2 infection. Clinical Chemistry and Laboratory Medicine. March 2020. DOI: https://doi.org/10.1515/cclm-2020-0188
What is a D-Dimer?

▶ In words “Thrombin cleaves fibrinogen into fibrin which is then cross linked by Factor XIII. Plasmin cleaves cross linked fibrin creating D-Dimers. D-dimers of cleaved fibrin can only be formed from cross linked fibrin. D-dimers are cleaved by liver. Increased dimers reflect increased micro or macrovascular thrombus and/or decreased liver function”

▶ FYI we measure D-Dimers at HUP by a latex bead test
  • Our prior test was an ELISA and had maximum value >10 (20xULN), we now go much higher…
As COVID continues, we’re settling into high D-Dimers…
Consult question is “h/o HIT”

78 year-old woman with atrial fibrillation on rivaroxaban, h/o provoked saddle pulmonary embolism (2010), HIT, p/w acute hypoxic respiratory failure requiring intubation, found to have Severe ARDS 2/2 COVID 19.
- Saddle PE POD 5 s/p lap hernia repair 2010
- Seen at TJUH 2010; neg hypercoag panel, no documented HIT ELISA nor SRA

LFTs: WNL
D-dimer: 3.81 ug/mL FEU
IL-6: 21 pg/mL
Ferritin 912
D-Dimer Correlates with Mortality in COVID-19

D-Dimer Correlates with Mortality in COVID-19

Some sources argue for full anticoagulation if D-Dimer is 4-6x upper limit of normal based on opinion, and if clot…

Anticoagulation is probably an easy decision…

But some have argued Italians empirically anti-coagulating

- Tang et al series has been proposed by some as justification…
  - 449 patients with severe COVID-19 in Tonji Hospital
  - 99 heparin (22%) of which 95% had prophylactic lovenox
  - No difference in mortality between heparin users and non-users
  - Stratifying by SIC score > 4 or D-dimer shows subsets with possible benefit (SIC >4 or D-dimer > 3.0 ug/mL)
ASH and others have guidance… punchline is stick to the basics

1. D-dimer*
2. Prothrombin time
3. Platelet count
4. Fibrinogen**

---

1. D-dimer not markedly raised***
2. Prothrombin time normal
3. Platelet count normal
4. Fibrinogen elevated

---

Admit (even if no other concerns)
Monitor once or twice daily

If admitted for other clinical reasons, Monitor daily

If discharged, use as baseline for if re-presenting with symptoms

---

Start prophylactic dose low molecular weight heparin

In all patients

Worsening

Blood products as per protocol (see box on the right)
Consider experimental therapies

---


There are more aggressive approaches…

- COVID-19-induced ARDS who have a P/F ratio 60 despite prone positioning and maximal mechanical ventilatory support
- “same exclusion criteria currently in place for stroke and MI treatment could be used”
- 25mg of tPA over 2 hours followed by a 25mg tPA infusion administered over the subsequent 22 hours
- For the bull argument of heparin see Thachil “The Versatile Heparin in COVID-19”
Goals for Today’s Brief Talk

• **State current recommendation for anti-coagulation in SARS-COV-2 patients**
  - Pharmacological prophylaxis remains standard of care
  - There is no current evidence to support empiric full dose anticoagulation for any d-dimer

• **Understand proposed role of immunosuppressants**
  - Convalescent serum is an old-school, difficult to scale, reasonable approach
  - Anti-IL-6 is being used as rescue therapy; there is not robust evidence for this
A Typical Heme Consult?

68 year old woman with rheumatoid arthritis on abatacept, hypertrophic cardiomyopathy who is transferred to HUP with septic shock complicated by hypoxemic respiratory failure, atrial fibrillation, progressive anuric AKI, pancytopenia, hypogammaglobulinemia.

- No recent baseline
- Admission 6 days ago:
  WBC: 7, Hgb: 10.6 Pt: 110
- Diff: Abs Lymph 0.04  ANC 2.60

Quantitative Igs: IgG <300, IgM 18, IgA 95
- BCx, UCx negative

Rheumatology team calls to discuss the role of IVIG?

Is this COVID?
Severe Cases Develop ARDS, Cytokine Storm

- 80% older than 60; median age 72
- 77% w/ comorbidities: HTN 56%, DM 18%, CVD 12%, Cancer 7%
- On admission neutrophilia (74%) and lymphopenia (89%) and thrombocytopenia (24%) - neutrophil to lymphocyte ratio of >5 (95%); elevated LDH (93%), and D-dimer (97%); high levels of IL-6 in 100%
- Death from respiratory failure (70%), sepsis/MODS (28%), cardiac 15%, hemorrhage 6% renal failure 4%
- Respiratory, cardiac, hemorrhage, hepatic, and renal damage in 100%, 89%, 81%, 78%, and 32%
- Time from symptom to death 15d (IQR 11-20)

Clinical Characteristics of 82 Deaths of CoVID

- Zhang et al. BMJ 2020

- 201 pts retrospective cohort (21-83 yo), dx by PCR
- Median age 51 (IQR 43-60)
- 10% DM, 20% HTN, 4% CVD
- WBC 6 (nl.No, lymphopenia) plt down
- CRP > 42, nl LFTs, d-dimer

- 90% fever, 80% cough (40% productive), 95% bilateral CXR infiltrate
- 80% supplemental O2, 30% NIVV; 98% abx, 85% antivirals, 53% antioxidants, 30% methylpred, 35% IVIG
- Median length of stay 13 days
- 42% ARDS, 50% of those died

Risk Factors for ARDS and Death

Wu et al. JAMA Internal Medicine

Figure from Siddiqi and Mehra. COVID-19 Illness in Native and Immunosuppressed States: A Clinical-Therapeutic Staging Proposal. Journal of Heart and Lung Transplantation. 2020. DOI: https://doi.org/10.1016/j.healun.2020.03.012
Hydroxychloroquine and azithromycin as a treatment of COVID-19

A Trial of Lopinavir–Ritonavir in Adults Hospitalized with Severe Covid-19


ABSTRACT

No therapeutics have yet been proven effective for the treatment of severe illness caused by SARS-CoV-2.

METHODS

We conducted a randomized, open-label trial enrolling hospitalized adults with confirmed SARS-CoV-2 infection, which causes the respiratory illness Covid-19, and an oxygen saturation (Sao₂) of 94% or less while they were breathing ambient air or a ratio of the partial pressure of oxygen (PaO₂) to the fraction of inspired oxygen (Fio₂) of less than 300 mm Hg. Patients were randomly assigned in a 1:1 ratio to receive either lopinavir–ritonavir (400 mg and 100 mg, respectively) twice a day for 14 days, in addition to standard care, or standard care alone. The primary end point was the time to clinical improvement, defined as the time from randomization to either an improvement of two points on a seven-category scale or discharge from the hospital, whichever came first.
There are centers using tocilizumab or sarilumab…

Tocilizumab

Case reports abound ("101-year-old Italian man who survived the 1918 Spanish flu pandemic and World War II, recovered from COVID-19," or 20 pt case series), the phase III is pending…
Some centers have fully incorporated tocilizumab into algorithms
Major argument is for convalescent serum, see Shen et al JAMA Treatment of 5 Critically Ill Patients with Convalescent Plasma

- Hypogammaglobulinemia described in septic shock (small series by Taccone et al. Shock 2009 found 76% of pts)
- Only large randomized trial to look at IVIG administration in septic shock found no benefit in mortality (Werdan et al. Critical Care Medicine 2009).
- Meta-analyses have some possible benefit but not risk of bias
- Linked to transfusion reactions and a controversial risk of increased thrombosis
But wait did our patient have HLH?

- HScores greater than 169 are 93% sensitive and 86% specific for reactive HLH (calculator: http://saintantoine.aphp.fr/score/)

If your patient has COVID doubt it will be the time for a bone marrow biopsy and high dose dexamethasone and etoposide...

\[ \Sigma 142 \quad (~16\% \text{ chance of HLH}) \]
Goals for Today’s Brief Talk

• **State current recommendation for anti-coagulation in SARS-COV-2 patients**
  - Pharmacological prophylaxis remains standard of care
  - There is no current evidence to support empiric full dose anticoagulation for any d-dimer

• **Understand proposed role of immunosuppressants**
  - Convalescent serum is an old-school, difficult to scale, reasonable approach
  - Anti-IL-6 is being used as rescue therapy; there is not robust evidence for this
Goals for Today’s Brief Talk

• State current recommendation for anti-coagulation in SARS-COV-2 patients
  - Pharmacological prophylaxis remains standard of care
  - No current evidence to support empiric full dose anticoagulation for any d-dimer

• Understand proposed role of immunosuppressants
  - Convalescent serum is an old-school, difficult to scale, reasonable approach
  - Anti-IL-6 is being used as rescue therapy; there is not robust evidence for this

• If you were to curbside me…
  - Thrombocytopenia and lymphopenia may predict worse outcomes
  - Lovenox for everyone unless bleeding or plt < 25
    - If obese (not renal failure) 40mg BID
  - DIC associated with worse survival (71% non-survivor with DIC vs 0.6% of survivors), goal plt >25, fibrinogen > 150 and would continue prophylaxis
  - Trend PT/PTT, D-dimer, fibrinogen every 2 days minimum
  - Tocilizumab may be useful rescue therapy