Hematologic Considerations in the COVID-19 Pandemic

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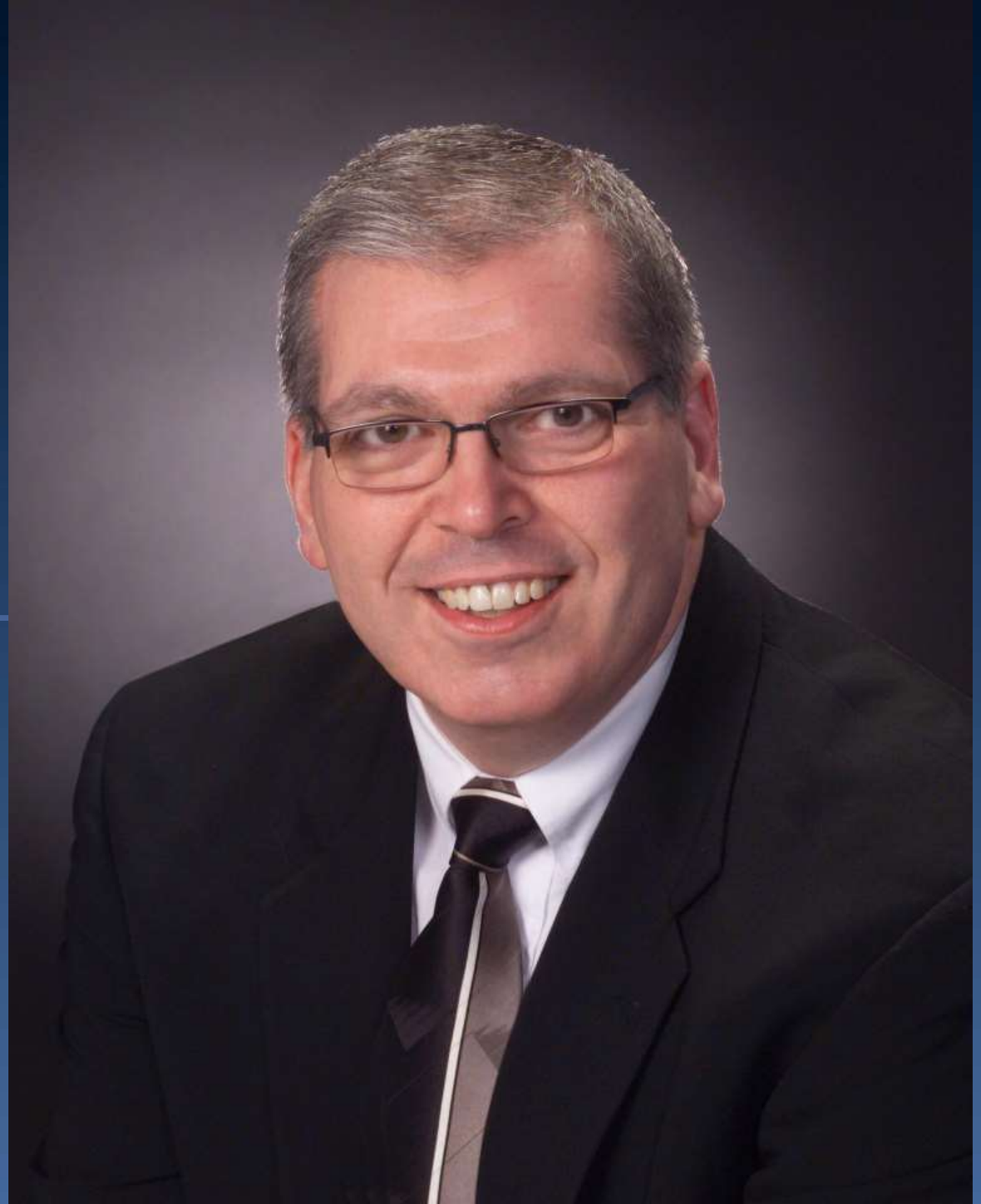


Disclosue of Financial Relationships

I have no financial relationships that would affect this presentation and will not be promoting any products for which I have a financial interest.

Biographical Information

- Saint Luke’s Health System - Kansas City
  - Palliative Care Division
  - Associate Hospice Medical Director - Saint Luke’s Hospice
- Board Certifications
  - Internal Medicine, Hematology, Oncology, Hospice and Palliative Medicine
  - Certified Hospice Medical Director

Objectives

- Recognize the possibility for hematologic complications of COVID-19
- Implement new approaches to management
- Develop strategies for early identification of both bleeding and clotting problems

Outline

- Introduction
- Thromboembolic considerations
- Cytopenias 
- Management concepts
- FAQ
- Conclusion

Introduction

- Challenges
  - Most initial studies are small, single-institution observational studies
    - Limited population, but small number of individuals interpreting data, thus less variability
  - Emerging data sets now involve prospective randomized trials and multiple institutions
    - Larger population, but larger numbers of individuals interpreting data, and added variability in institutions (not all hospitals are created equal)

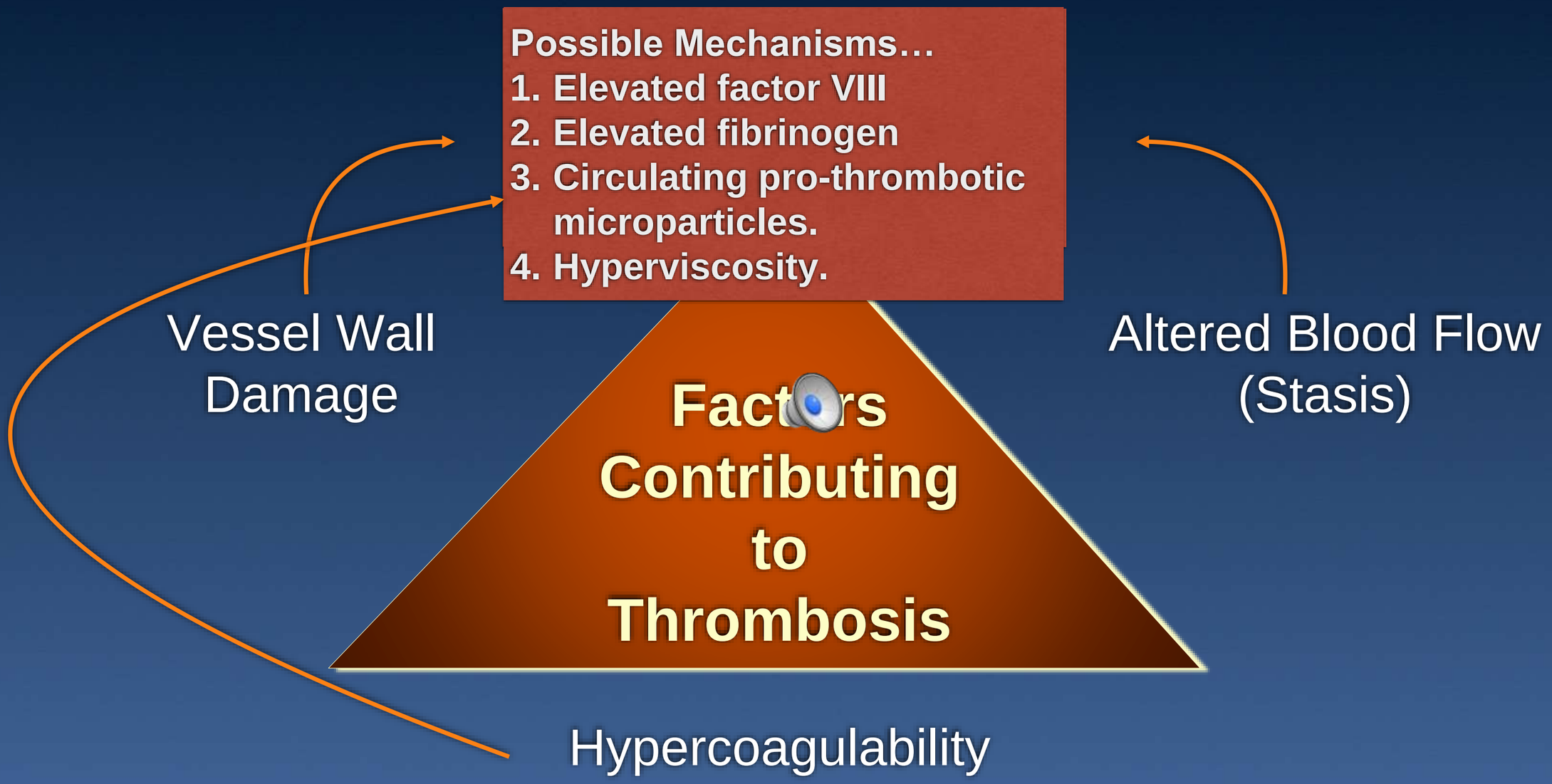
Definition of Severity of Illness

- Mild - able to be managed as an outpatient
- Moderate - sick enough to require admission, but not the ICU
- Severe - ICU admission

Thromboembolic Considerations

- Patients with COVID-19 have complex and varied coagulation abnormalities
- Pathogenesis is not clear…we've known about COVID for a little more than two years
- General theme is that COVID-19 infected patients have a hypercoagulable state

Virchow's Triad



Thromboembolic Considerations

- Hyperviscosity - can promote hypercoagulable state
  - Initially described in 15 patients in the ICU at Emory University (https://doi.org/10.1016/S0140-6736(20)31209-5)
    - All patients had COVID-induced ARDS, encephalopathy, were intubated, 12 had shock and were on vasopressors, 11 had AKI and were on CRRT
    - All patients were anticoagulated per institutional guidelines
    - All patients had serum viscosity exceeding 95% of normal

Thromboembolic Considerations

- Marked elevation of D-dimer
  - Surrogate marker for illness severity
  - High levels in acutely ill patients with many different infectious and inflammatory diseases

Thromboembolic Considerations

- To DIC, or not to DIC? *…with apologies to William Shakespeare*
  - Similarities to DIC…
    - Often prolongation of PT/  TT
    - Elevated D-dimer (often significantly elevated)
    - Mild thrombocytopenia in some patients

Thromboembolic Considerations

- To DIC, or not to DIC?
  - Differences from DIC…
    - Fibrinogen normal to elevated
    - Factor VIII normal to elevated
    - PT/PTT may be normal

Consumption of clotting factors is not occurring

Thromboembolic Considerations

- To DIC, or not to DIC? (A little more food for thought…)
  - Acute (decompensated) DIC
    - Initial thrombotic stage (often not seen) followed by bleeding
  - Chronic (compensated) DIC
    - Minimal to no accentuated bleeding
    - Chronic thrombosis

“DIC-ish?”

Classic, acute DIC

Subacute, smoldering DIC

Thromboembolic Considerations

- Antiphospholipid Antibodies
  - Transient presence of APAb known in viral diseases
    - Does not usually cause APS 
  - Lupus anticoagulant subtype has been reported in COVID-19 patients (88-91% in two small observational studies)
  - These are usually of the IgA subclass

Thromboembolic Considerations

- Correlation of Lupus Anticoagulant with thromboembolism in COVID-19 patients (Gill MR, et al.; *JAMA Netw Open.* 2020;3(8):e2017539. doi:10.1001/jamanetworkopen.2020.17539)
  - Retrospective review study at Montefiore Medical Center of 187 patients with COVID positivity who had LA testing performed
  - Association between LA positivity and thromboembolic rate (Odds ratio 4.39, p=0.01)

Thromboembolic Considerations

- Clinical features
  - Venous thromboembolism
    - Up to 1/3 of hospitalized 🔊OVID patients
    - Risk post-discharge for COVID-infected patients only slightly greater than non-COVID-infected patients

Thromboembolic Considerations

- Clinical features
  - Venous thromboembolism
    - Risk factors: high BMI (>28.7 kg/m^2), age (>75 years), concomitant medical problems (CV disease, COPD, HTN, DM, CKD, malignancy, others)
    - Autopsy findings
      - DVT/PE, thrombotic microangiopathy (Menter T, et al; ***Histopathology***. 2020;77(2):198. Epub 2020 Jul 5.)
      - DVT/PE, lungs with diffuse alveolar damage, endotheliolitis (Ackermann M, et al; ***N Engl J Med***. 2020;383(2):120. Epub 2020 May 21)

Thromboembolic Considerations

- Clinical features
  - ICU
    - Several studies correlate ICU admission with a 1.5-3.5 fold increase in development of DVT/PE

Thromboembolic Considerations

- DVT/PE in the non-ICU COVID admission…
  - Incidence is higher in patients screened prophylactically vs evaluating only symptomatic patients (Santoliquido A, et al; *J Thromb Haemost*. 2020;18(9):2358. Epub 2020 Aug 27)
  - 3% in a study of over 6500 patients, most in general medical units (Hill JB, et al; *Blood Adv.* 2020;4(21):5373)
  - 3.6% in a study of 2505 patients (Bilaloglu S, et al.; *JAMA*. 2020;324(8):799)

Thromboembolic Considerations

- Cytokine Release Syndrome (“cytokine storm”)
  - Exuberant inflammatory response
  - Fever, elevated inflammatory markers and pro-inflammatory cytokines
  - Associated with poor prognosis

https://cdn1.neoskosmos.com/uploads/sites/2/2018/07/Thunderstorm.jpg

Thromboembolic Considerations

- Cytokine Release Syndrome (“cytokine storm”)
  - Pro-inflammatory cytokines have been implicated in myocardial injury
  - May have role in thromboembolic risk

https://cdn1.neoskosmos.com/uploads/sites/2/2018/07/Thunderstorm.jpg

Thromboembolic Considerations

- Arterial events
  - Stroke - 1.6-3.7%
  - Myocardial infarction - 8.9%
  - Limb ischemia 3-15%; occurs about 70% of the time in lower extremities
  - Microvascular thrombosis - typically affects the lung; mechanism unknown

Thromboembolic Considerations

- Arterial events - patient characteristics (Etkin Y, et al.; *Ann Vasc Surg*. 2021;70:290. Epub 2020 Aug 28; Bellosta R, et al.; J *Vasc Surg.* 2020;72(6):1864. Epub 2020 Apr 29)
  - Age > 60; risk highest if age > 75
  - BMI > 25
  - HTN
  - PAD
  - DM
  - Prior MI
  - ↑ D-dimer

Thromboembolic Considerations

- Laboratory findings in patients with COVID-19 (Panigada M, Bottino N, Tagliabue P, et al., *J Thromb Haemost.* 2020;18(7):1738. Epub 2020 Jun 24)
  - Coagulation testing
    - PT/aPTT normal to slightly prolonged
    - Platelet count normal or increased (mean 348K/µl)
    - Fibrinogen increased (mean 680 mg/dl)

Cytopenias

- Thrombocytopenia
  - COVID-associated ITP
- Lymphopenia

Thrombocytopenia

- Definition: platelet count < 150,000/μL
  - Subdivided into…
    - Mild: 100,000 - 150,000 🔉
    - Moderate: 50,000 - 99,000
    - Severe: ≤ 49,000

COVID-19 Associated ITP

- Has been reported, but no clear data on incidence
- Most often occurs during acute phase of illness
- Management Considerations
  - Many hospitalized patients already on dexamethasone; but dosing is different in COVID-19 compared to ITP
  - IVIG is non-immunosuppressive and has been effective
  - Anti-CD 20 agents (rituximab, others) may be helpful but more expensive and potentially impair immune response for as long as 6 months (or more)

Lymphopenia

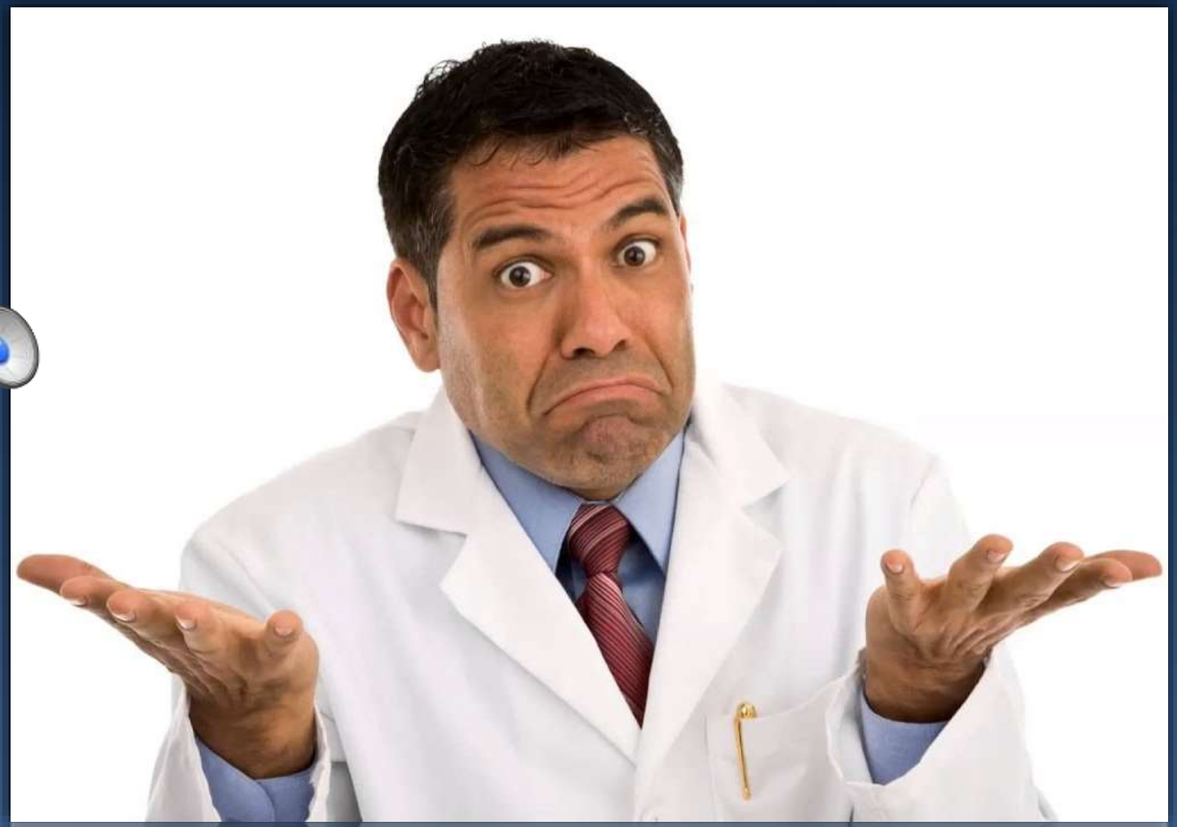
- Very common
- Total WBC count may vary
- New York City study (Goyal P, et al.; *N Engl J Med.* 2020;382(24):2372. Epub 2020 Apr 17)
  - 393 adult patients hospitalized with COVID
  - 90% had lymphocyte count <1500/µL
  - Leukocytosis (>10,000/µL) 15%
  - Leukopenia (<4000/µL) 15%

Other Lab Abnormalities in COVID

- CMP - elevated transaminases common
- Ferritin - acute phase reactant; levels 2-4 X normal commonly seen
- LDH - often 1.5-2 X normal
- CRP - over 57% of patients will have elevated levels
- Procalcitonin - marker for severity of illness; levels in hospitalized non-ICU patients may be normal to slightly elevated; progressive increases indicate worsening of illness

Management Concepts

- Hypercoagulability affects prognosis
- No high-quality studies to support interventions
- Bleeding is a concern



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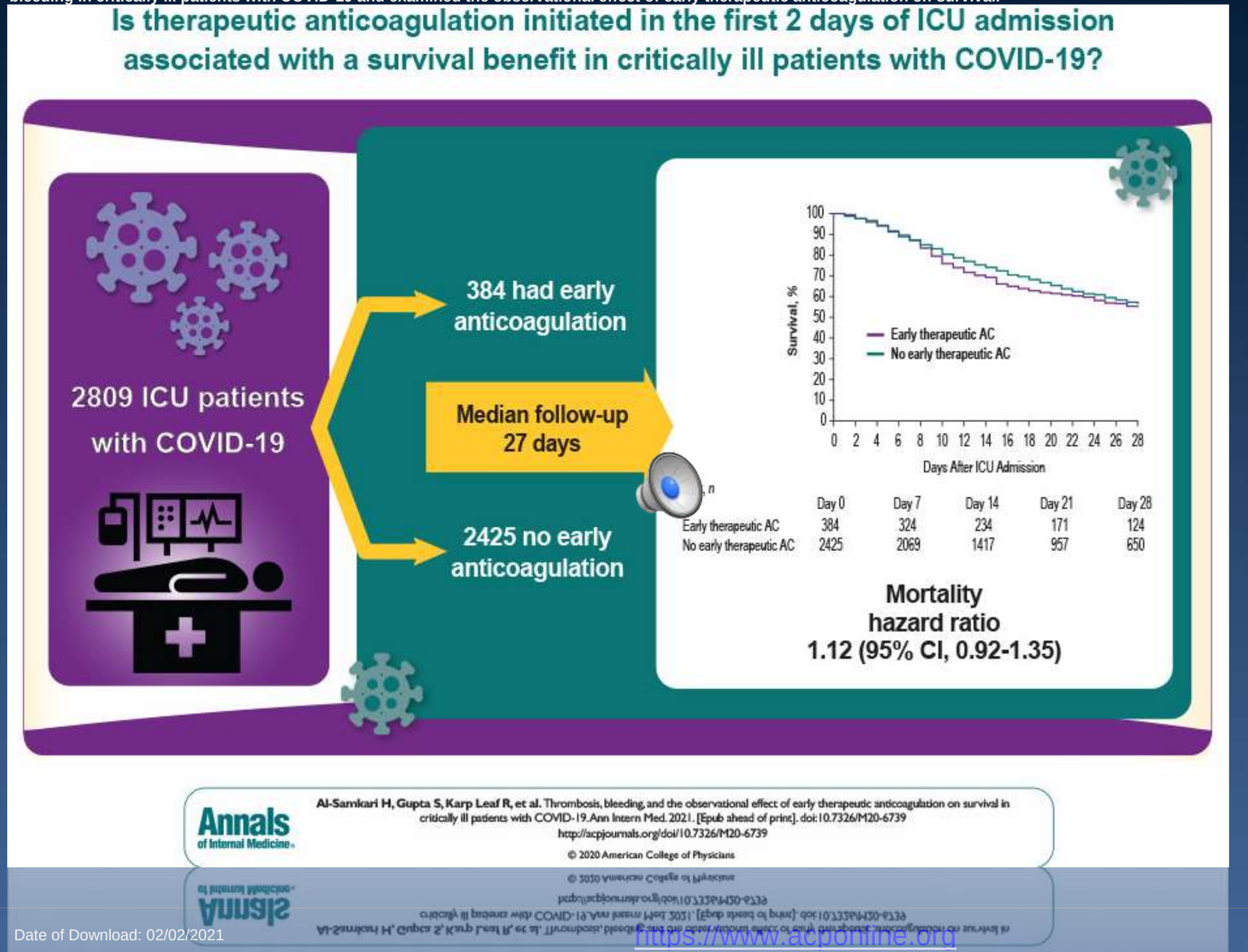
Management Concepts

- Does early anticoagulation in severely ill COVID-19 patients improve the mortality rate? (*Ann Intern Med*. Published online: 26 January 2021doi:10.7326/M20-6739)
  - Result: early anticoagulation had no beneficial effects on mortality rates in critically ill COVID patients

Figure Legend:

Hypercoagulability may be a key mechanism of death in patients with COVID-19. This cohort study evaluated the incidence of venous thromboembolism and major bleeding in critically ill patients with COVID-19 and examined the observational effect of early therapeutic anticoagulation on survival.



Annals of Internal Medicine

Al-Samkari H, Gupta S, Karp Leaf R, et al. Thrombosis, bleeding, and the observational effect of early therapeutic anticoagulation on survival in critically ill patients with COVID-19. Ann Intern Med. 2021. [Epub ahead of print]. doi:10.7326/M20-6739
http://acpjournals.org/doi/10.7326/M20-6739

Management Concepts

- Organizations with guidelines…

Organization	Website
International Society on Thrombosis and Hemostasis	https://www.isth.org/page/covid19
The Anticoagulation Forum	https://acforum.org/web/education-guidance.php
American Society of Hematology	https://www.hematology.org/education/clinicians/guidelines-and-quality-care/clinical-practice-guidelines/venous-thromboembolism-guidelines/ash-guidelines-on-use-of-anticoagulation-in-patients-with-covid-19
American College of Cardiology	https://www.acc.org/latest-in-cardiology/features/accs-coronavirus-disease-2019-covid-19-hub#sort=%40commonsortdate%20descending

Management Concepts

- DIC
  - If “classic” consumptive DIC present, manage along the standard guidelines for DIC in other diseases
    - No data on whether to add prophylactic DVT/PE prophylaxis, and bleeding risk must be considered
  - If “chronic” (DIC-ish) DIC present, manage along guidelines for DVT/PE prophylaxis in high risk patients

Management Concepts

- ICU
  - Thromboprophylaxis for all COVID-19+ patients
- Medical (non-ICU)
  - Prophylactic LMWH or unfractionated heparin for all COVID-19+ patients

Following pro-inflammatory markers through patient's clinical course may predict those at greater risk, and may have a role in medical decision-making

Management Concepts

- Surgical
  - Orthopedic: generally follows prophylaxis for non-COVID-19+ patients
  - Non-orthopedic: generally follows prophylaxis for non-COVID-19+ patients
  - Surgery should be urgent or emergent only while COVID positive!

Caveat: there is very little data on which to base medical decisions!

Management Concepts

- Obstetrical
  - LMWH prior to and following delivery in COVID-19+ patients if delivery is not expected within 24 hours
  - Unfractionated heparin is an option if
    - Faster discontinuation is needed
    - Neuraxial anesthesia
    - Invasive procedure anticipated

Caveat: there is very little data on which to base medical decisions!

Management Concepts

- Thrombocytopenia
  - Prophylactic transfusion not required if patient not undergoing invasive procedure or not bleeding
    - In patients with platelet count < 50,000/µl who undergo invasive procedure, base transfusion on clinical situation
  - Transfusion for bleeding with a platelet count < 30,000/µl is a consideration

FAQ

- What are the criteria for vaccine-induced immune thrombotic thrombocytopenia? (Patients must meet all five criteria!)
  - COVID vaccine 4 to 42 days prior to symptom onset.
  - Any venous or arterial thrombosis (often cerebral or abdominal).
  - Thrombocytopenia (platelet count < 150 x 10^9/L).
  - Positive PF4 “HIT” (heparin-induced thrombocytopenia) ELISA.
  - Markedly elevated D-dimer (> 4 times upper limit of normal).

FAQ

- What is the prognosis in a patient with COVID-19-associated coagulopathy/DIC?
  - Patients with a serious infection are more likely to have COVID-19 associated coagulopathy
  - Those who die from COVID-19 are more likely to have met the ISTH criteria for DIC compared to survivors
  - Elevated D-dimer at admission and markedly increasing D-dimer levels (3- to 4-fold) over time are associated with high mortality, likely reflecting coagulation activation from infection/sepsis, cytokine storm and impending organ failure

FAQ

- Does a normal D-dimer effectively rule out DVT/PE?
  - Yes, the rate of false negatives is 1-2% using highly sensitive D-dimer assays, thus a normal value has a 98% confidence rate that PE or DVT is not present
  - But, since D-dimer levels are usually higher in COVID-infected patients, the question of whether a “new normal” for affected patients should be established is not clear and no data exists

FAQ

- How should an elevated D-dimer be interpreted in a patient with COVID-19?
  - While a normal level of D-dimer excludes VTE in patients with a low clinical probability, an elevated D-dimer does not necessarily indicate that a patient has VTE
  - An elevated D-dimer in a patient with COVID-19 should not be used as a sole criterion for hospital admission or mandate imaging for DVT/PE unless other signs or symptoms of VTE are present

FAQ

- Should all COVID-19 patients be tested for antiphospholipid antibodies (aPL Ab)?
  - No, aPL Ab can arise transiently at times of acute infection, inflammation, or thrombosis 
  - The presence of aPL Ab does not necessarily indicate a hypercoagulable state; the ISTH recommends acute and convalescent testing at 12 weeks before declaring a patient as having an antiphospholipid syndrome

FAQ

- How long should COVID-19 patients receive post-discharge thromboprophylaxis?
  - Risk of thrombosis extends for up to 90 days post-discharge
  - No data from clinical trials - we should encourage enrollment in a trial if one is available
  - Suggestions: ASA for 90 days (full or mini), or if there are other risk factors (a-fib, etc.) then prophylaxis for thromboembolic events as per guidelines of that disorder
    - Early, frequent activity as tolerated - get ‘em moving!!

FAQ

- I have a patient who is hospitalized in the ICU with COVID-19. The patient has now developed heparin-induced thrombocytopenia. How should I manage thromboprophylaxis?
  - No data!
  - A few case reports of managing with argatroban infusions

FAQ

- What are the potential risks of convalescent plasma for COVID-19?
  - Comparable to non-immune plasma
  - Allergic reactions, transfusion-associated circulatory overload (TACO), and transfusion-associated acute lung injury (TRALI)
  - Joyner et al. (*J Clin Invest.* 2020;130(9):4791-4797. https://doi.org/10.1172/JCI140200) looked at 20,000 patients who were treated under expanded access, incidence of severe events was < 1%, most deemed unrelated to the convalescent plasma

TRALI vs TACO

Feature	TRALI	TACO
Fever	May be present	None
Blood Pressure	Hypotension	Hypertension
Symptoms	Acute dyspnea	Acute dyspnea
Neck veins	Unchanged	Can be distended
Auscultation	Rales	Rales; may have S3
Chest X-ray	Diffuse bilateral infiltrates	Diffuse bilateral infiltrates
PA occlusion pressure	18 mmHg or less	Greater than 18 mmHg
BNP	< 200 pg/ml	> 1200 pg/ml
Response to diuretic	Minimal	Significant

Conclusions

- Hematologic complications are common in COVID-19 infected patients
- Understanding the pathophysiology involved can be very helpful in medical decision-making 
- The yardstick for measuring disease course must be different than with other viral illnesses
- Additional clinical trials addressing important gaps in our knowledge will be very helpful

things are changing quickly…

Stay Tuned!!!

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