# COVID-19 Treatment: Focus on Immune-Based Therapies

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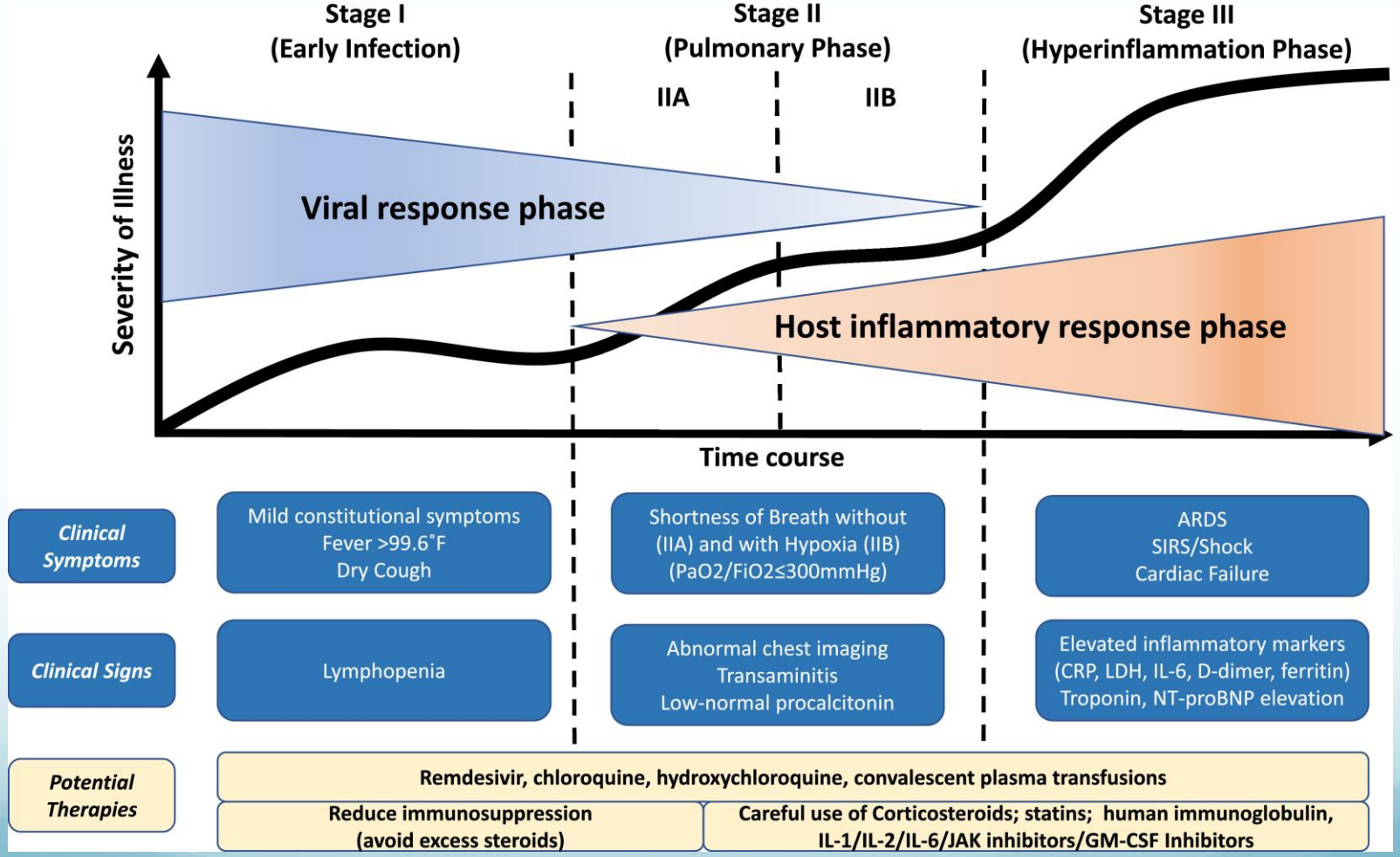
# Objectives

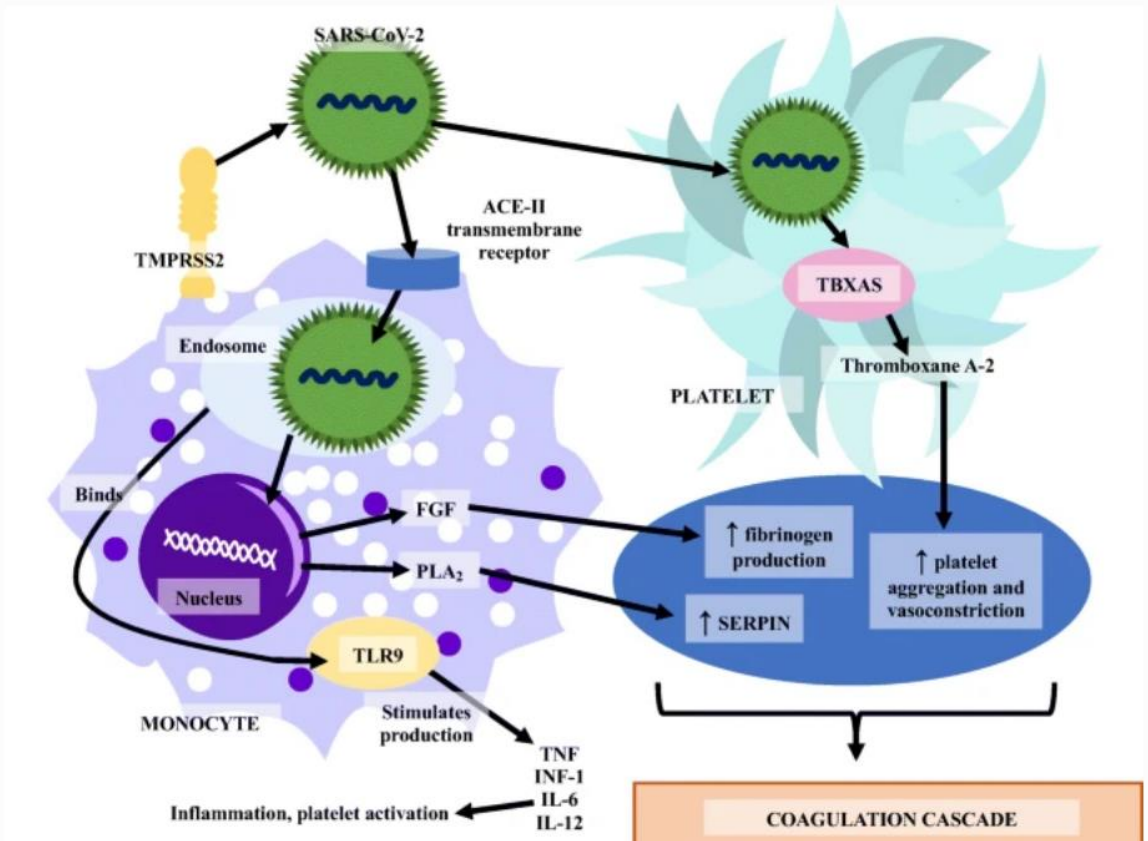
- To discuss the cytokine storm and hypercoagulable state during COVID-19
- To discuss the role of immune-based therapies for COVID-19.
- To discuss where each of the treatment options fits in the paradigm of care.

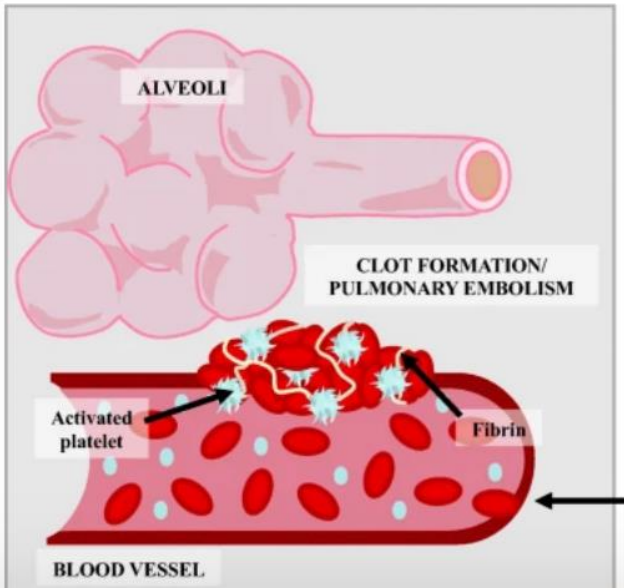
# Cytokine Storm

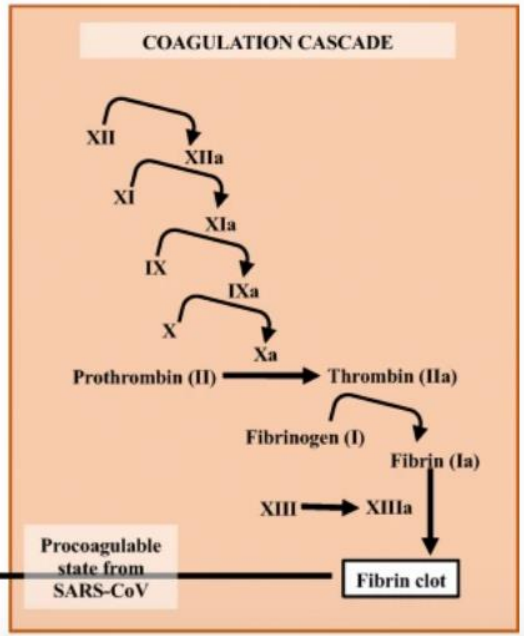
# 3 Stages of COVID-19 Infection




*The Journal of Heart and Lung Transplantation* 2020 39405-407DOI: (10.1016/j.healun.2020.03.012)




Rico-Mesa et al. *Current Cardiology Reports* 2020; 22: 53

# Corticosteroids

# Overview

- MOA: Anti-inflammatory/immunomodulatory
- Dexamethasone is the only drug found to have a mortality benefit in SARS-CoV-2 infection in a controlled trial.
- Dosing: Dexamethasone 6 mg IV or PO for 10 days (or until discharge if earlier). Equivalent total daily doses of alternative glucocorticoids to dexamethasone 6 mg daily are methylprednisolone 32 mg and prednisone 40 mg.

# RECOVERY Trial

- Hospitalized patients with clinically suspected or laboratory confirmed SARS-CoV-2
- **Study population:**
  - 6,425 patients admitted with COVID-19 disease to 176 National Health Service hospitals in the U.K., of whom 2,104 were randomly allocated to receive dexamethasone (6 mg/day for up to 10 days) + SOC and 4,321 received SOC alone.
- **Primary endpoint:**
  - All-cause mortality within 28 days of randomization.

The Recovery Collaborative Group. *NEJM* July 2020

# Results

- **Key findings:**
  - 482 patients (22.9%) in the dexamethasone arm and 1,110 patients (25.7%) in the standard of care group died within 28 days of randomization ($p < 0.001$).
  - In the dexamethasone group, the incidence of death was lower than the SOC arm in patients receiving mechanical ventilation (29.3% vs. 41.4%; rate ratio, 0.64; 95% CI, 0.51-0.81), as well as those receiving oxygen without mechanical ventilation (23.3% vs. 26.2%; rate ratio, 0.82; 95% CI, 0.72-0.94).
  - In patients who were moderately ill but did not require oxygen at baseline, use of dexamethasone was associated with a non-statistically significant finding of increased mortality (17.8% vs. 14.0%; rate ratio, 1.19; 95% CI, 0.91-1.55).

The Recovery Collaborative Group. *NEJM* July 2020

# Conclusions

- Overall, in this controlled open label trial, dexamethasone reduced mortality in those patients receiving mechanical ventilation or oxygen.
- There was no benefit for patients who did not require respiratory support; in fact, there was a non-statistically significant trend toward increased mortality.

# WHO Pooled Data

- Pooled data from 7 trials (RECOVERY, REMAP-CAP, CoDEX, CAPE COVID, and 3 additional trials).
- 1703 patients (678 randomized to corticosteroids and 1025 to usual care or placebo), of which 59% were from the RECOVERY trial.
- 28-day mortality was lower in patients randomized to corticosteroids: 32.7% corticosteroids vs. 41.5% usual care or placebo (summary odds ratio, 0.66 [95% CI, 0.53,-0.82]; $P < 0.001$).

The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group.. *JAMA*. September 2, 2020.

# CRP & Corticosteroids

- **Study population:**
  - 1,806 patients admitted with COVID-19
- **Primary endpoint:**
  - Mortality or need for mechanical ventilation.
- **Key findings:**
  - 140 patients (7.7%) were treated with corticosteroids, while 1,666 (92.3%) never received corticosteroids.
  - Corticosteroid use in patients with initial CRP levels >20 mg/dL was correlated with significantly reduced risk of mortality or mechanical ventilation (OR, 0.23; 95% CI, 0.08-0.70).
  - Corticosteroid use in patients with CRP levels <10 mg/dL was associated with significantly increased risk of mortality or mechanical ventilation (OR, 2.64; 95% CI, 1.39-5.03).

Keller et al. *Hosp. Med.* 2020 August;15(8):489-493.

# What do the Guidelines State?

- The Surviving Sepsis Campaign guidelines for COVID-19 issued a weak recommendation to use corticosteroids in patients with COVID-19 and ARDS who required mechanical ventilation, but also indicated that some expert panel members preferred not to make a recommendation until further high-quality evidence was available.
- Guidelines from IDSA recommends dexamethasone in those hospitalized critically ill patients or severe patients with COVID-19.

https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/#toc-5

# My Thoughts

- Corticosteroids should be started in patients with moderate-severe hypoxemic respiratory sufficiency
  - P/F ratio < 250 +requiring supplemental $O_2$
- Also factor in rise in inflammatory markers
  - CRP
  - Ferritin
  - D-dimer (inflammation drives coagulation)
  - IL-6
- Methylprednisolone 1 mg/kg or dexamethasone 6 mg/day for at least 7 days with a slow taper over a few weeks.

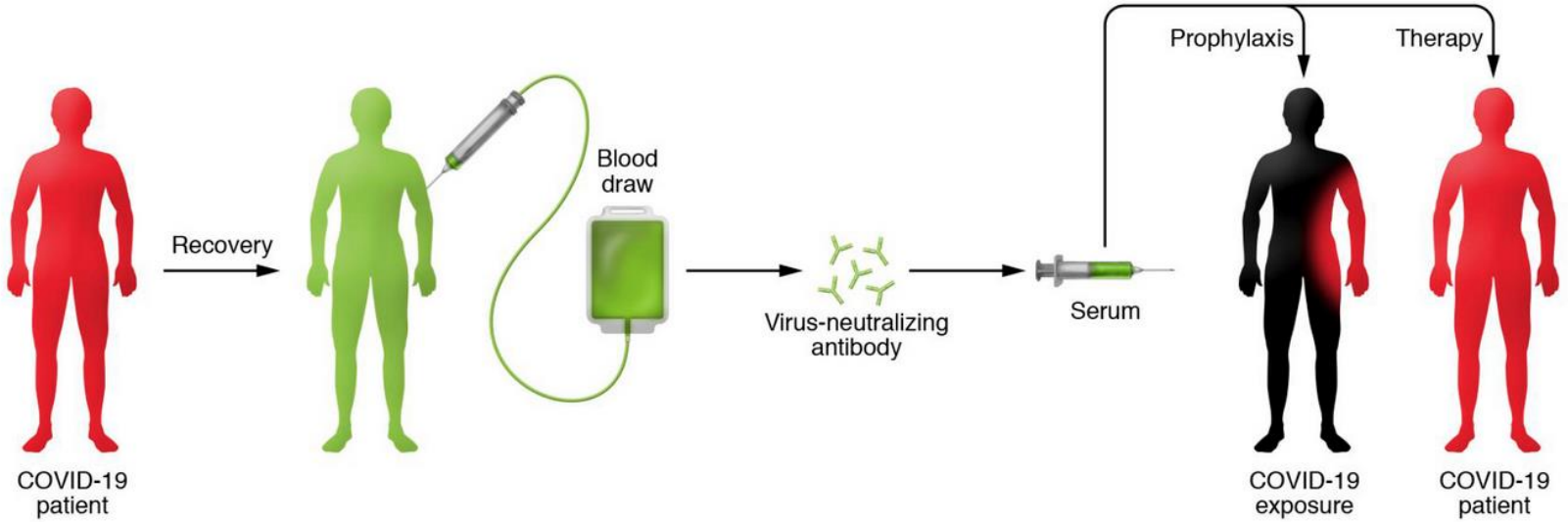
# Convalescent Plasma

# Overview

- Class: Biologic, passive antibody treatment
- Dosing: No standard recommended
  - The National Convalescent Plasma Expanded Access COVID-19 Protocol is studying a dose of 1 unit of plasma (at least 200 ML)
- August 2020: FDA announced EUA for convalescent plasma in patients with COVID-19.

https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/recommendations-investigational-covid-19-convalescent-plasma
https://www.covid19treatmentguidelines.nih.gov/statement-on-convalescent-plasma-eua/
https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/#toc-7

# Concept of Using Convalescent Plasma to Treat COVID-19




*J Clin Invest*. 2020. https://doi.org/10.1172/JCI138003

# Convalescent Plasma in Argentine Hemorrhagic Fever (AHF)

- Randomized, double-blind, placebo-controlled trial
- Primary Endpoint: Efficacy of convalescent plasma in patients with AHF $\leq$ 8 days from symptom onset (N=188)
- Intervention: Randomized to receive 500 mL of convalescent plasma or healthy donor plasma
- Results: Case fatality rate: 1.1% convalescent plasma vs. 16.5% healthy plasma donor

Maiztegui et al. *Lancet* 1979; 2: 1216-7.
Ruggiero et al. *Presse Med* 1986; 15: 2239-42

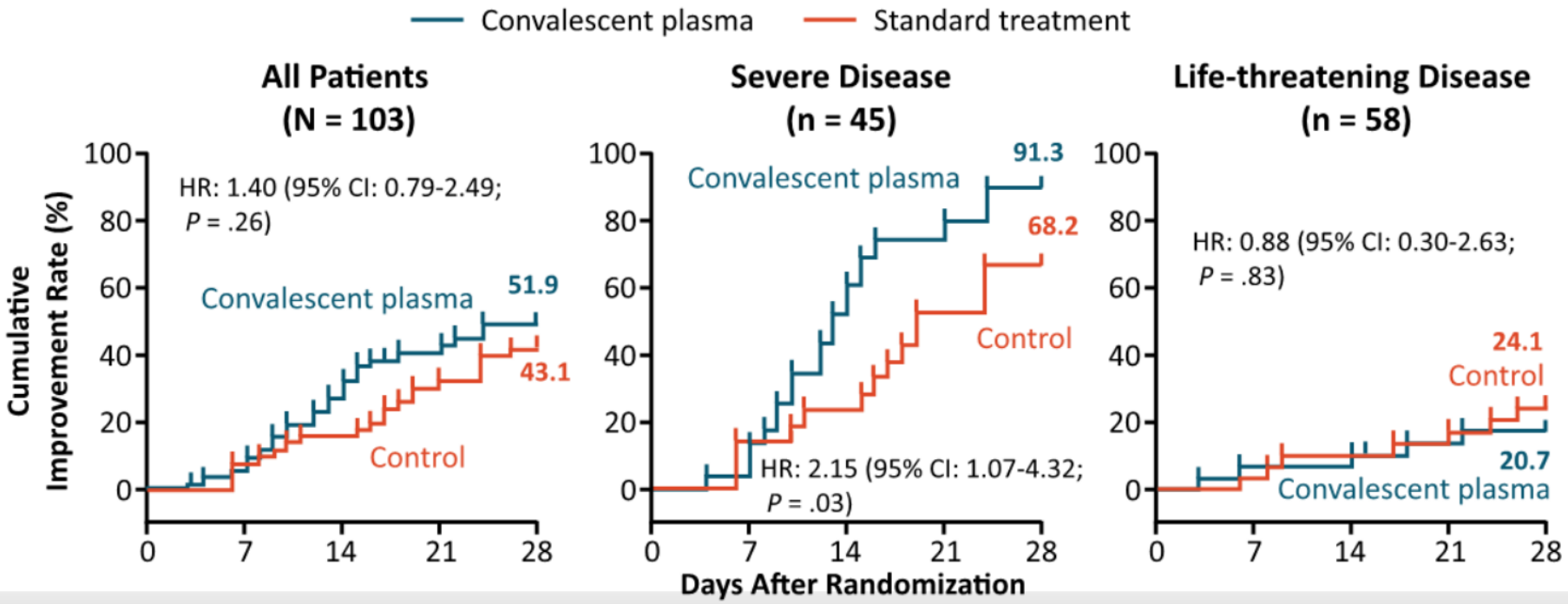
# RCT in China: Convalescent Plasma for Severe or Life-Threatening COVID-19

- Open-label study enrolling patients from 7 medical centers in Wuhan, China (February-April 2020)
- Intervention:
  - Standard treatment + convalescent plasma (N=52)
  - Standard treatment alone (N=51)
- Study terminated early due to containment of pandemic in China.
- Dose: 4-13 mL/kg, S-RBD-specific IgG titer $\geq$ 1:640
- Primary endpoint: time to clinical improvement (i.e., discharged alive or 2-point reduction on 6-point disease severity scale) within 28 days
- Secondary outcomes: 28-day mortality, time to discharge, rate of viral PCR result changing from BL positive to negative within 72 hours

Li et al. *JAMA* June 2020

# Results

## Time to Clinical Improvement




## Secondary Outcomes

- 28 day mortality: 15.7% convalescent plasma vs. 24% standard treatment
- Discharge by day 28: 51% convalescent plasma vs. 36% standard treatment

Li et al. *JAMA* June 2020

# Conclusion

- In patients with severe or life-threatening COVID-19, convalescent plasma therapy with standard of care did not significantly improve the time to clinical improvement within 28 days.
- In subgroup analysis of patients with severe, but not life-threatening disease, clinical improvement was seen in patients who received plasma, despite patients being symptomatic for a median of 33 days in this group.

# RCT in Netherlands (ConCOVID)

- Open-label RCT enrolled patients from 14 secondary and academic hospitals in the Netherlands (April-June 2020)
- Intervention:
  - Standard treatment + convalescent plasma (N=43)
  - Standard treatment alone (N=43)
- Study terminated early due to finding of substantial baseline autologous anti-SARS-CoV-2 antibodies in 79% patients, which would prevent any conclusion on efficacy of convalescent plasma
- Dose: 300 mL plasma; anti-SARS-CoV-2 neutralizing titers $\geq$ 1:80
- Primary endpoint: 60-day mortality
- Secondary outcomes: length of hospital stay, improvement by WHO 8-point severity scale on day 15, safety

Gharbharan et al. NOTE: Not peer-reviewed; July 2020; NCT04342182

# Results

- 53 of 66 patients tested had anti-SARS-CoV-2 antibodies at baseline.
- A SARS-CoV-2 plaque reduction neutralization test showed neutralizing antibodies in 44 of the 56 (79%) patients tested with median titers comparable to the 115 donors (1:160 vs 1:160, p=0.40).
- No difference in mortality (p=0.95), hospital stay (p=0.68) or day-15 disease severity (p=0.58).

# Mayo Clinic Observational Data from Expanded Treatment Protocol

- Single-arm open label study executed in 2,807 acute care hospitals in the U.S. (April-July 2020)
- N=35,322 adults hospitalized with severe or life-threatening COVID-19; 52.3% patients in the ICU; 27.5% received mechanical ventilation.
- Patients transfused with $\geq$ 1 unit of human COVID-19 convalescent plasma
- 7-day mortality rate was 8.7% in patients transfused within 3 days of COVID-19 diagnosis but 11.9% in patients transfused after 3 days ($p<0.001$).
- 30-day mortality was 21.6% vs. 26.7% ($p<0.0001$).
- The pooled relative risk of mortality among patients transfused with high antibody level plasma units was 0.65 [0.47-0.92] for 7 days and 0.77 [0.63-0.94] for 30 days versus those transfused with low antibody level plasma units.
- AEs: 15 deaths were reported within 4 hours of transfusion (0.3%), with 4 deaths (0.08%) considered possibly or probably related to convalescent plasma transfusion

Joyner et al. *May Clin Proc* 2020; 95: 1888

# My Thoughts

- May work best for patients earlier in the disease course
  - Treating patients relatively later in disease – patients may already generate their own neutralizing antibodies at baseline
- Questions remain about the antibody titer that should be used when treating patients with COVID-19, and if timing of administration is an important consideration.

# Tocilizumab/IL-6 Inhibitors

# Overview

- Class: Interleukin-6 (IL-6) receptor blocker
- Dose: Initial IV infusion of 8 mg/kg (up to a maximum dose of 800 mg). One additional dose may be given if symptoms worsen or show no improvement.
- Rationale:
  - Increased levels of inflammatory cytokines, including IL-6 has been affiliated with increased mortality from acute respiratory distress syndrome (ARDS)
  - Patients with COVID-19 have increased IL-6 levels and other inflammatory markers consistent with cytokine storm

# COVACTA Trial

- Trial did not meet its primary endpoint of improved clinical status in patients with COVID-19–associated pneumonia or the secondary endpoint of reduced patient mortality.
- The trial did show a positive trend in time to hospital discharge among patients who received tocilizumab.

https://www.gene.com/media/press-releases/14867/2020-07-28/genentech-provides-an-update-on-the-phas

# EMPACTA Trial

- Preliminary results found hospitalized patients who received tocilizumab were 44% less likely to progress to mechanical ventilation or death vs. patients who received placebo plus standard of care.
- The cumulative proportion of patients who progressed to mechanical ventilation or death by day 28 was 12.2% in the tocilizumab group vs. 19.3% in the placebo arm.
- The time to hospital discharge and mortality by Day 28 was not statistically significant

https://www.roche.com/investors/updates/inv-update-2020-09-18.htm

# Biran et al.

- **Study population:**
  - Retrospective study of 764 COVID-19 patients admitted to the ICU in 13 New Jersey hospitals; 210 (27%) received tocilizumab.
  - Propensity score-matched population included these 210 patients and 420 who did not receive tocilizumab
  - Tocilizumab was administered a median of 9 days (IQR 6–12) after the start of patient-reported symptoms.
- **Primary endpoint:**
  - Hospital-related mortality

Biran et al. *Lancet Rheumatology* 2020; 2(10): e603-e612

# Results

- 358 (57%) of 630 patients died; of these, 102 (49%) received tocilizumab and 256 (61%) did not.
- A primary multivariable Cox regression analysis with propensity matching noted an association between receiving tocilizumab and decreased hospital-related mortality (HR 0.64; p=0.0040).
- In post-hoc analysis of the 558 patients (89%) who had a CRP >15 mg/dL at baseline, tocilizumab exposure was associated with decreased hospital-related mortality (HR 0.48; p=0.0025). This was not seen in patients with a CRP <15 mg/dL.
- The frequency of secondary bacterial infections was 17% in patients who received tocilizumab and 13% in those who did not.

# My Thoughts

- Can see a benefit in patients with cytokine storm
- Use inflammatory markers to guide you:
  - CRP
  - Ferritin
  - D-dimer (inflammation drives coagulation)
  - IL-6

# Anticoagulation

# Anticoagulant in Patients With Severe COVID-19 and Coagulopathy

- Single-center, retrospective study in Wuhan, China
- Primary Endpoint: 28-day mortality
- Intervention: prophylactic heparin vs. low-molecular-weight heparin for ≥ 7 days vs no heparin or heparin for < 7 days in patients with severe COVID-19 (N = 449)
  - Severe COVID-19: RR ≥ 30 breaths/min, $SaO_2$ ≤ 93% at rest, or $PaO_2/FiO_2$ ratio ≤ 300 mm Hg
- No difference in 28-day mortality between those administered heparin vs. nonheparin in overall population (30.3% vs 29.7%; $p = 0.910$)

Tang. *J Thromb Haemost*. 2020;18:1094.

# Prophylactic Dose vs Therapeutic Dose Anticoagulation in COVID-19

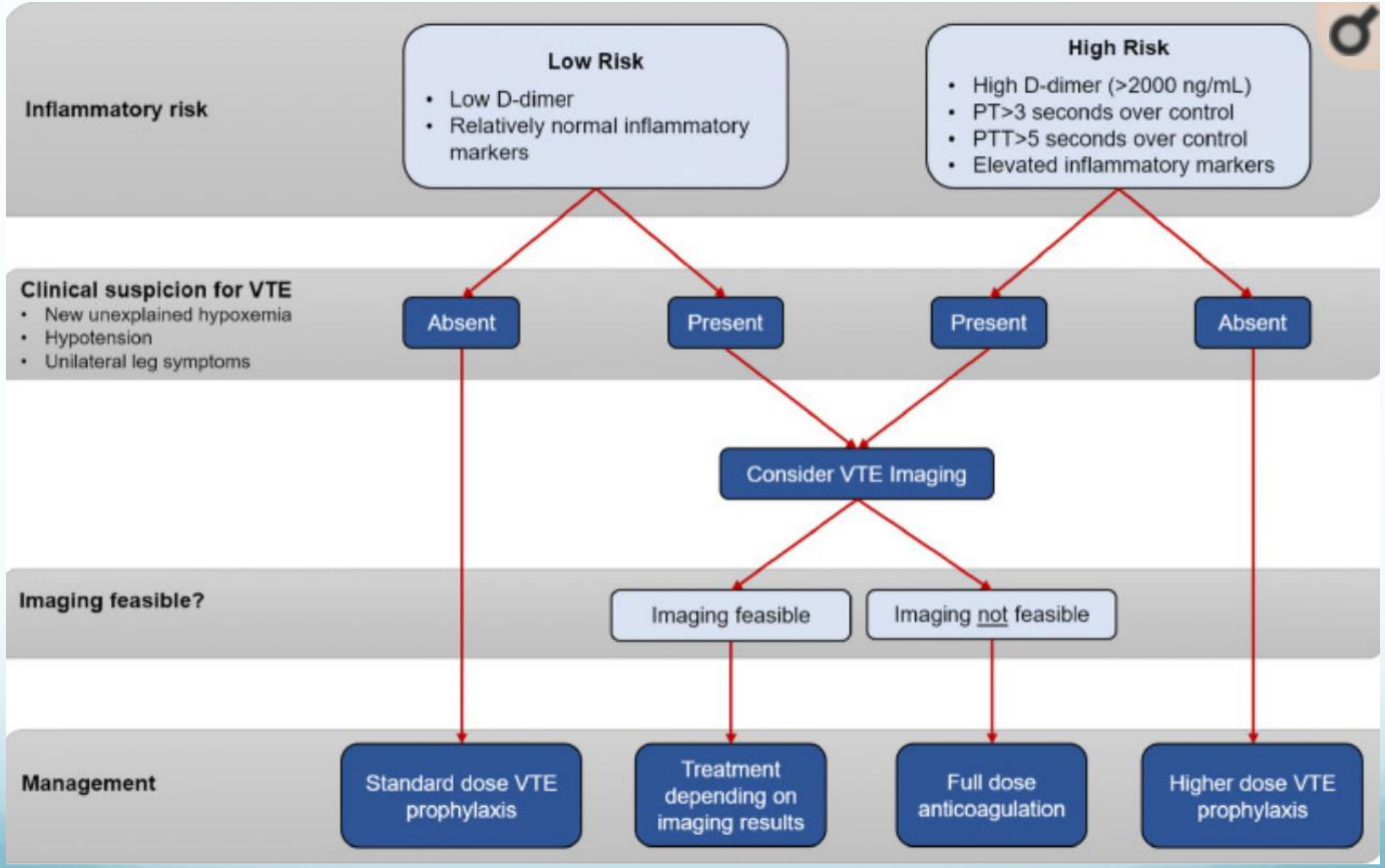
- Retrospective, cohort study compared in-hospital mortality with prophylactic dose (N=299) vs therapeutic dose anticoagulation with heparin or low-molecular-weight heparin (N=75) upon admission in patients with COVID-19.
  - Excluded patients receiving therapeutic anticoagulation for thrombotic indication; prophylactic anticoagulation group received only prophylactic dosing for whole inpatient duration
- Results:
  - In-hospital mortality: 14.4% prophylactic vs. 38.7% treatment
  - Adjusted risk ratio: 2.3 (1.0-4.9; p=0.04)

Motta. *medRxiv*. 2020;[Preprint]. Note: This study has not been peer reviewed.

# ASH Guidance

- All hospitalized adults with COVID-19 should receive thromboprophylaxis with low-molecular-weight heparin over unfractionated heparin, unless bleeding risk outweighs thrombosis risk
- Fondaparinux is recommended in the setting of heparin-induced thrombocytopenia
- In patients in whom anticoagulants are contraindicated or unavailable, use mechanical thromboprophylaxis (eg, pneumatic compression devices)
- Encourage participation on clinical trials rather than empiric use of therapeutic-dose heparin in COVID-19 patients with no other indication for therapeutic dose anticoagulation

American Society of Hematology. COVID-19 and VTE/ Anticoagulation




Aryal et al. *Curr Cardiol Rep*. 2020; 22(7): 52.

# Questions??