Penn Medicine

PCCM COVID Bootcamp Lecture Series: Dimers and Cytokine Storms with Hematology

Andy Matthews

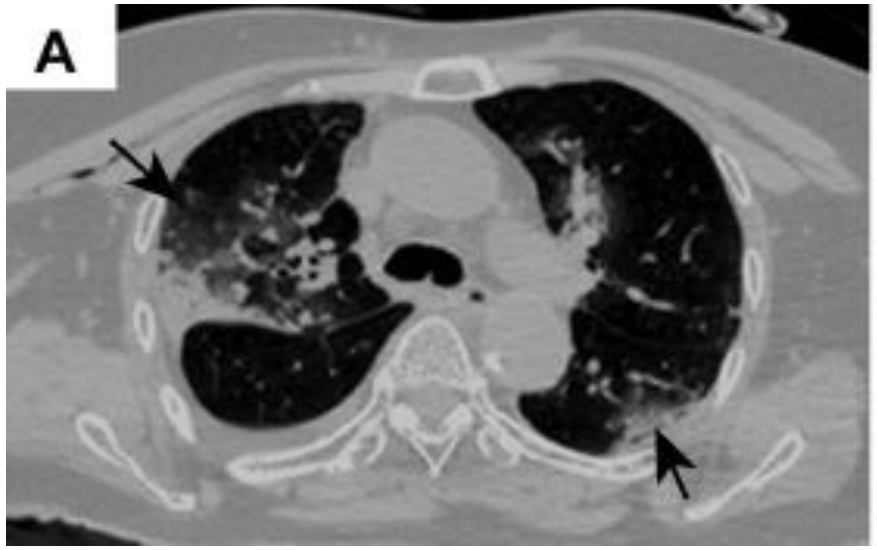
April 8th, 2020

I have no idea what's awaiting me, or what will happen when this all ends. For the moment I know this: there are sick people and they need curing.
-Camus

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

COV-2 Causes Interstitial Lymphocyte-Rich PNA



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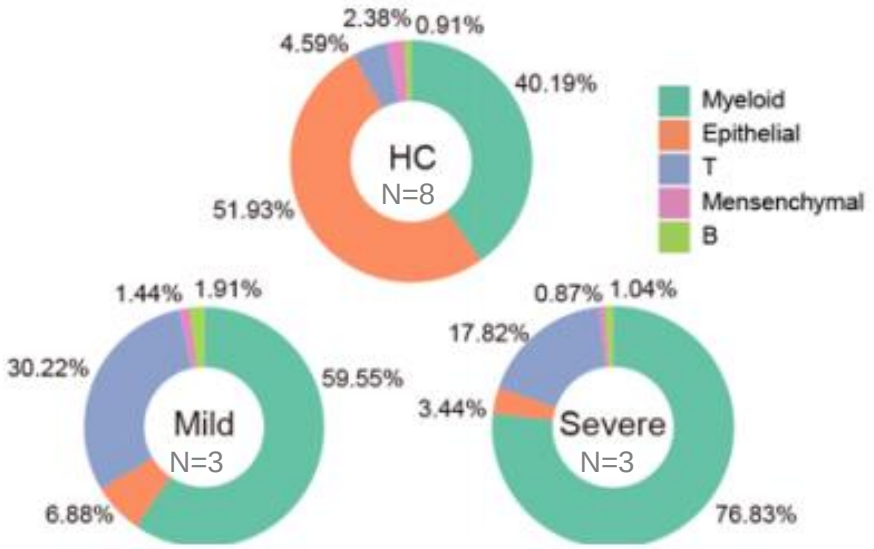


- Tissue injury precedes dry cough and fever, with peripheral GGOs near pleura
- Edema with proteinaceous exudates leading to intra-alveolar organization and fibrosis (rather than accumulation of granulocytes and fibrin)
- Increased lymphocytes in BAL of COVID-19 patients

- Tian et al. Pulmonary Pathology of Early-Phase 2019 Novel Coronavirus (COVID-19) Pneumonia in Two Patients With Lung Cancer. JTO 2020. In press. DOI: https://doi.org/10.1016/j.jtho.2020.02.010
- Liao et al. The landscape of lung bronchoalveolar immune cells in COVID-19 revealed by single-cell RNA sequencing. medRxiv preprint doi: https://doi.org/10.1101/2020.02.23.20026690.

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[9]

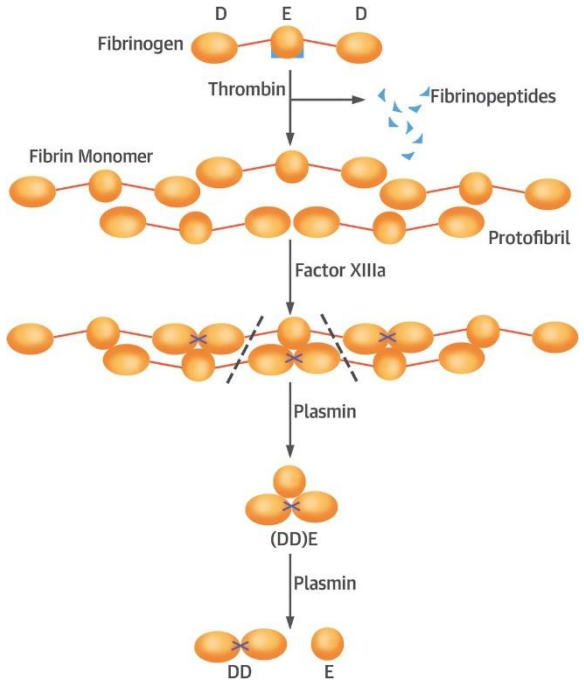
Table 1: Comparison of coagulation function between SARS-CoV-2 patients and control group ($\bar{x} \pm s$).

Parameters	SARS-CoV-2 patients (n=94)	Controls (n=40)	t-test	p-value
APTT, s	29.01±2.93	28.65±3.03	0.648	0.518
AT, %	85.46±14.43	98.82±12.91	−5.054	<0.001
D-dimer, mg/L	10.36±25.31	0.26±0.18	3.871	<0.001
FDP, mg/L	33.83±82.28	1.55±1.09	3.803	<0.001
FIB, g/L	5.02±1.53	2.90±0.53	11.88	<0.001
PT, s	12.43±1.00	12.08±5.28	0.419	0.678
PT-INR	1.07±0.09	1.05±0.49	0.244	0.809
PT-act, %	80.59±12.77	96.86±26.92	−3.651	0.001
TT, s	18.00±1.80	18.34±0.92	−1.495	0.137

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.

Zhou et al Lancet 2020, Tan et al Signal Transduction and Targeted Therapy March 2020; Guan et al NEJM Feb 2020
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

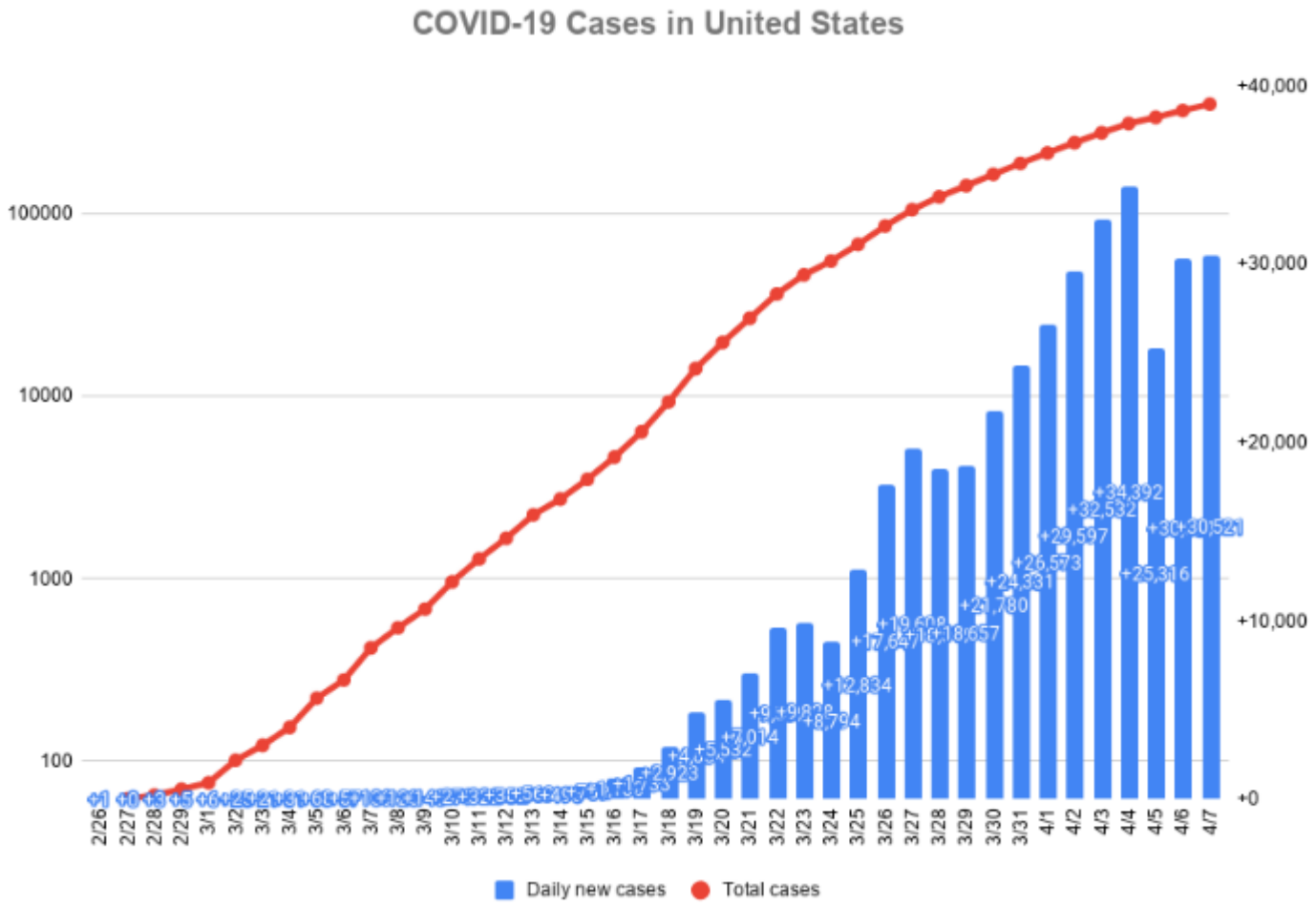
What is a D-Dimer?

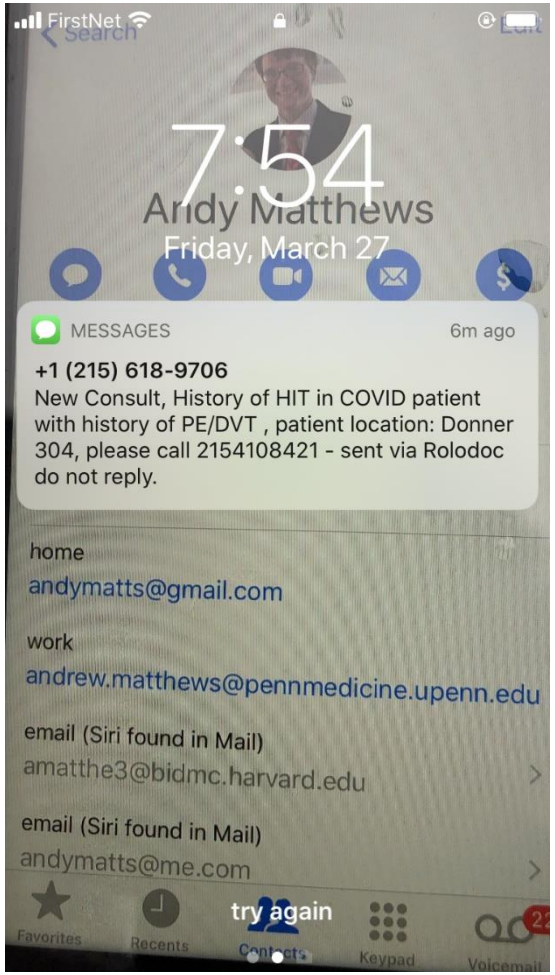


- In words “Thrombin cleaves fibrinogen into fibrin which is then cross linked by Factor XIII. Plasmin cleaves cross linked fibrin creating D-Dimers. D-dimers of cleaved fibrin can only be formed from cross linked fibrin. D-dimers are cleaved by liver. Increased dimers reflect increased micro or macrovascular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

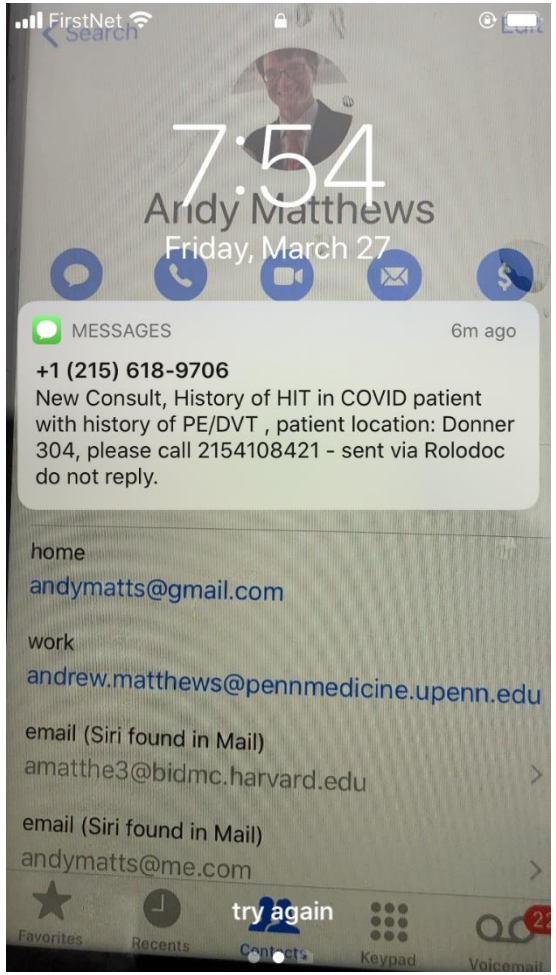
Weitz et al. Journal of the American College of Cardiology Volume 70, Issue 19, November 2017DOI: 10.1016/j.jacc.2017.09.024

As COVID continues, we're settling into high D-Dimers…



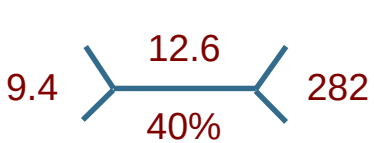


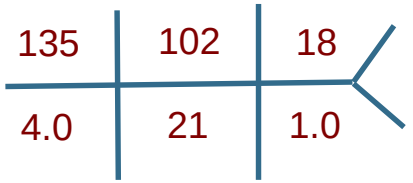
Consult question is “h/o HIT”

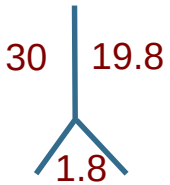


78 year-old woman with atrial fibrillation on rivaroxaban, h/o provoked saddle pulmonary embolism (2010), HIT, p/w acute hypoxic respiratory failure requiring intubation, found to have Severe ARDS 2/2 COVID 19.

- Saddle PE POD 5 s/p lap hernia repair 2010
- Seen at TJUH 2010; neg hypercoag panel, no documented HIT ELISA nor SRA

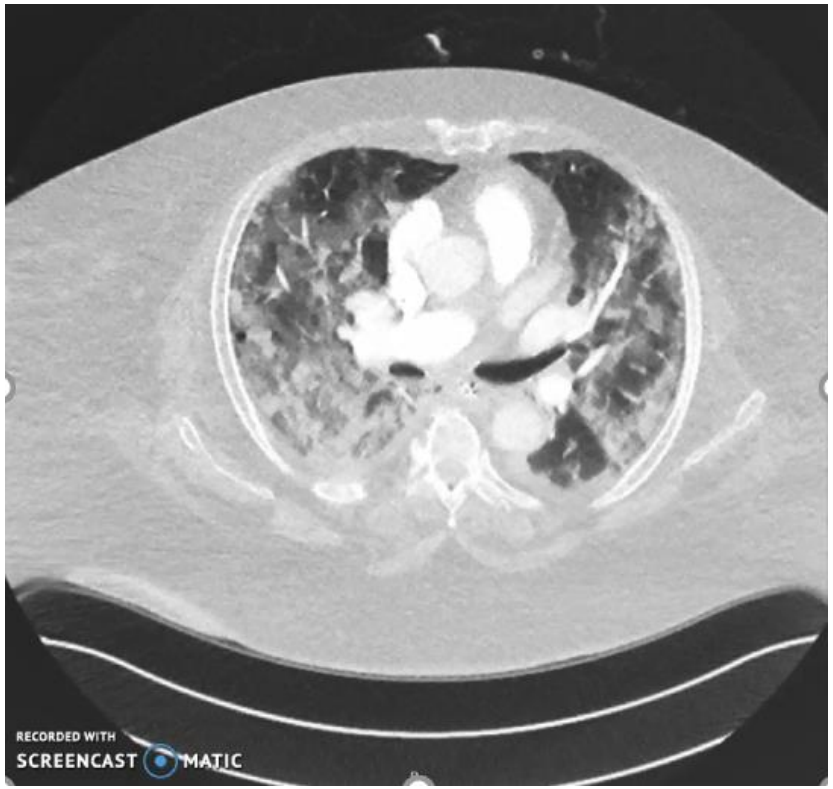




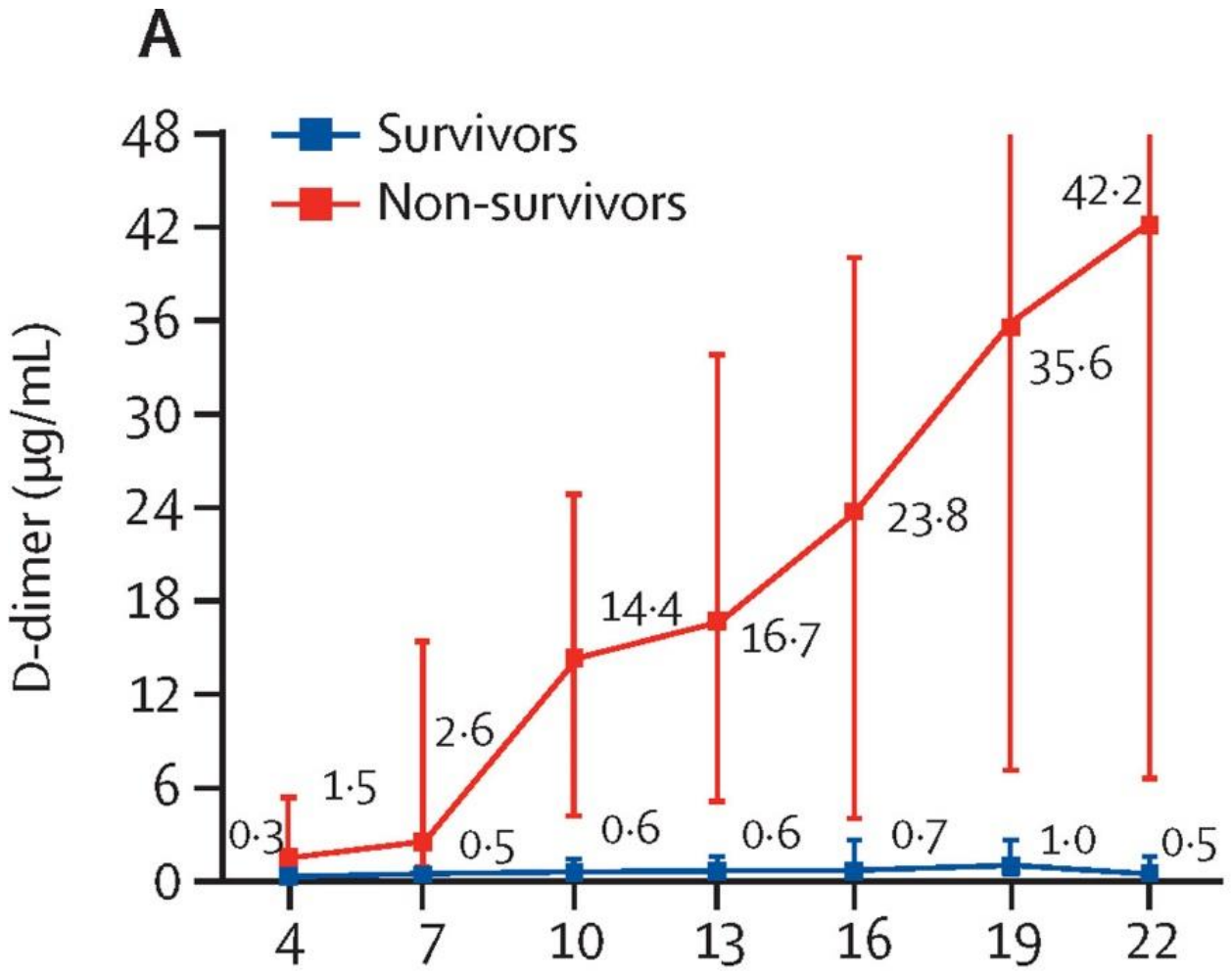


LFTs: WNL
D-dimer: 3.81 ug/mL FEU
IL-6: 21 pg/mL
Ferritin 912

CTA: no evidence of PE



D-Dimer Correlates with Mortality in COVID-19



	Univariable OR (95% CI)	p value	Multivariable OR (95% CI)	p value
Demographics and clinical characteristics				
Age, years*	1·14 (1·09–1·18)	<0·0001	1·10 (1·03–1·17)	0·0043
Female sex (vs male)	0·61 (0·31–1·20)	0·15	–	–
Current smoker (vs non-smoker)	2·73 (0·65–7·63)	0·20	–	–
Comorbidity present (vs not present)				
Chronic obstructive lung disease	5·40 (0·96–30·40)	0·056	–	–
Coronary heart disease	21·40 (4·64–98·76)	<0·0001	2·14 (0·26–17·79)	0·48
Diabetes	2·85 (1·35–6·05)	0·0062	–	–
Hypertension	3·05 (1·57–5·92)	0·0010	–	–
Respiratory rate, breaths per min				
≤24	1 (ref)	–	–	–
>24	8·89 (4·34–18·19)	<0·0001	–	–
SOFA score	6·14 (3·48–10·85)	<0·0001	5·65 (2·61–12·23)	<0·0001
qSOFA score	12·00 (5·06–28·43)	<0·0001	–	–
Laboratory findings				
White blood cell count, × 10⁹ per L				
<4	0·73 (0·26–2·10)	0·56	–	–
4–10	1 (ref)	–	–	–
>10	6·60 (3·02–14·41)	<0·0001	–	–
Lymphocyte count, × 10⁹ per L*	0·02 (0·01–0·08)	<0·0001	0·19 (0·02–1·62)	0·13
ALT, U/L				
≤40	1 (ref)	–	–	–
>40	2·87 (1·48–5·57)	0·0018	–	–

(Table 3 continues in next column)

	Univariable OR (95% CI)	p value	Multivariable OR (95% CI)	p value
(Continued from previous column)				
Creatinine, µmol/L				
≤133	1 (ref)	–	–	–
>133	4·39 (1·01–19·06)	0·048	–	–
Lactate dehydrogenase, U/L				
≤245	1 (ref)	–	–	–
>245	45·43 (6·10–338·44)	0·0002	–	–
Creatine kinase, U/L				
≤185	1 (ref)	–	–	–
>185	2·56 (1·03–6·36)	0·043	–	–
High-sensitivity cardiac troponin I, pg/mL				
≤28	1 (ref)	–	–	–
>28	80·07 (10·34–620·36)	<0·0001	–	–
D-dimer, µg/mL				
≤0·5	1 (ref)	–	1 (ref)	–
>0·5	1·96 (0·52–7·43)	0·32	2·14 (0·21–21·39)	0·52
>1	20·04 (6·52–61·56)	<0·0001	18·42 (2·64–128·55)	0·0033
Prothrombin time, s				
<16	1 (ref)	–	–	–
≥16	4·62 (1·29–16·50)	0·019	–	–
Serum ferritin, µg/L				
≤300	1 (ref)	–	–	–
>300	9·10 (2·04–40·58)	0·0038	–	–
IL-6, pg/mL*	1·12 (1·03–1·23)	0·0080	–	–
Procalcitonin, ng/mL*	13·75 (1·81–104·40)	0·011	–	–

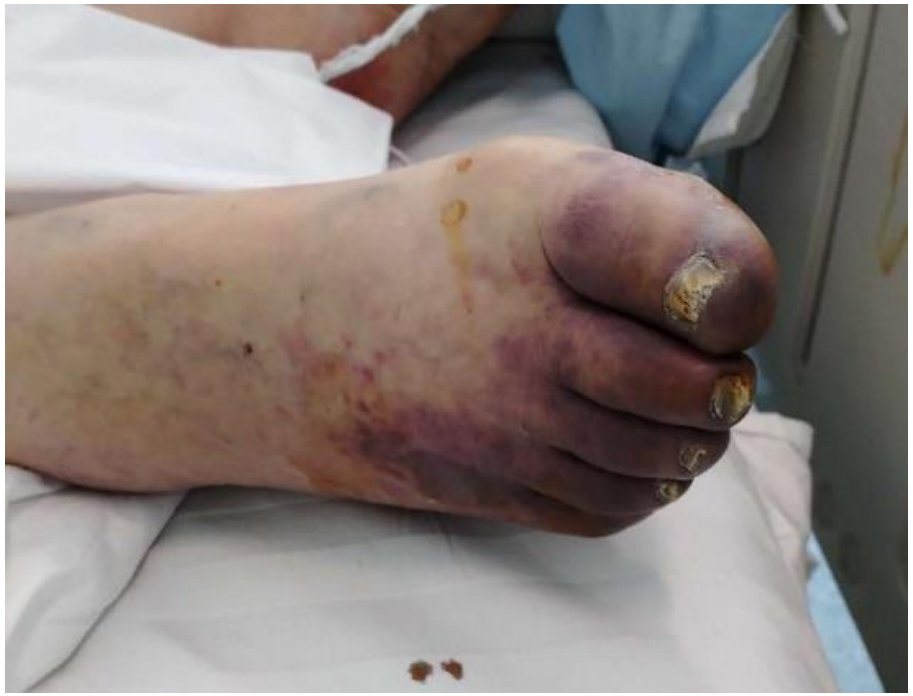
OR=odds ratio. SOFA=Sequential Organ Failure Assessment. qSOFA=Quick SOFA. ALT=alanine aminotransferase. IL-6=interleukin-6. *Per 1 unit increase.

Table 3: Risk factors associated with in-hospital death

Zhou et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020. DOI:https://doi.org/10.1016/S0140-6736(20)30566-3

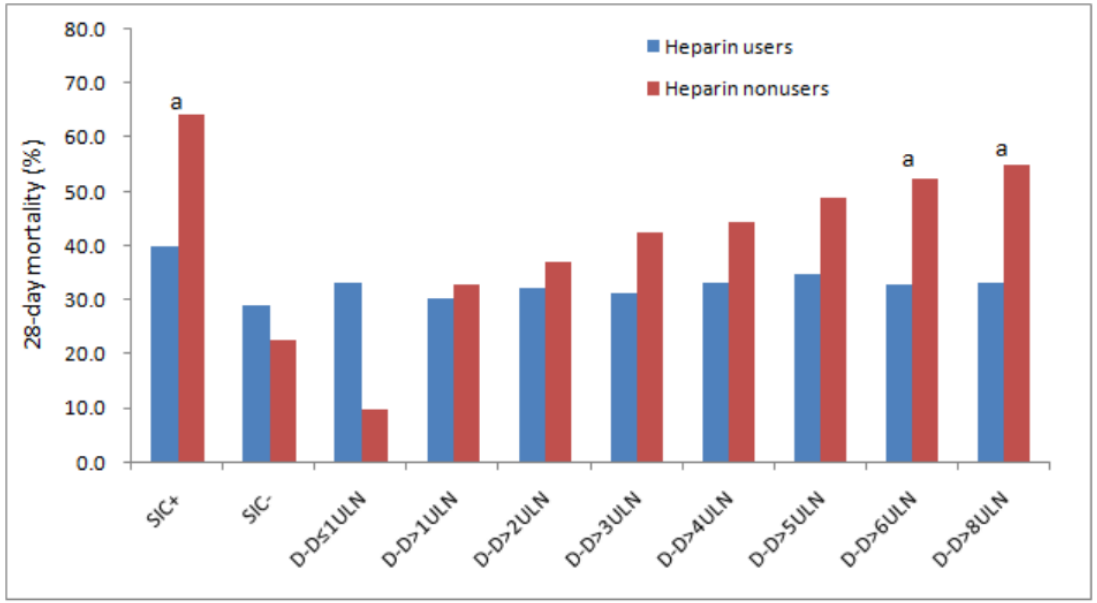
D-Dimer Correlates with Mortality in COVID-19

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)

Lin et al. Hypothesis for potential pathogenesis of SARS-CoV-2 infection-a review of immune changes in patients with viral pneumonia. Emerg Microbes Infect. 2020 Dec;9(1):727-732. doi: 10.1080/22221751.2020.1746199

Tang et al Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemost. 2020 Mar 27. doi: 10.1111/jth.1481

ASH and others have guidance… punchline is stick to the basics

Practice Guid | U@Penn | haptoglobin predictive valu | [Full text] Positive predictive | COVID-19 and VTE-Anti | Hypothesis for potential pa

https://www.hematology.org/covid-19/covid-19-and-vte-anticoagulation

EDUCATION ADVOCACY CAREERS MEETINGS PUBLICATIONS AWARDS NEWSROOM

Note: Please review ASH's disclaimer regarding the use of the following information.

What are the most common hematologic abnormalities seen in patients with COVID-19?

Elevation in d-dimer, fibrinogen and other inflammatory markers is common. Development of disseminated intravascular coagulation is associated with a worse prognosis. Thrombocytopenia occurs less frequently and is generally mild (platelet counts 100-150). Lymphopenia has been reported in ~30-50% of patients with COVID-19. Anemia has not been reported frequently.

Is COVID-19 associated with an increased risk for venous thromboembolism (VTE)?

Case reports have noted the development of venous thromboembolism in patients with COVID-19 but it is not clear currently if the risk of VTE is higher in patients with COVID-19 than other critically ill patients.

What is the recommended VTE prophylaxis in patients with COVID-19?

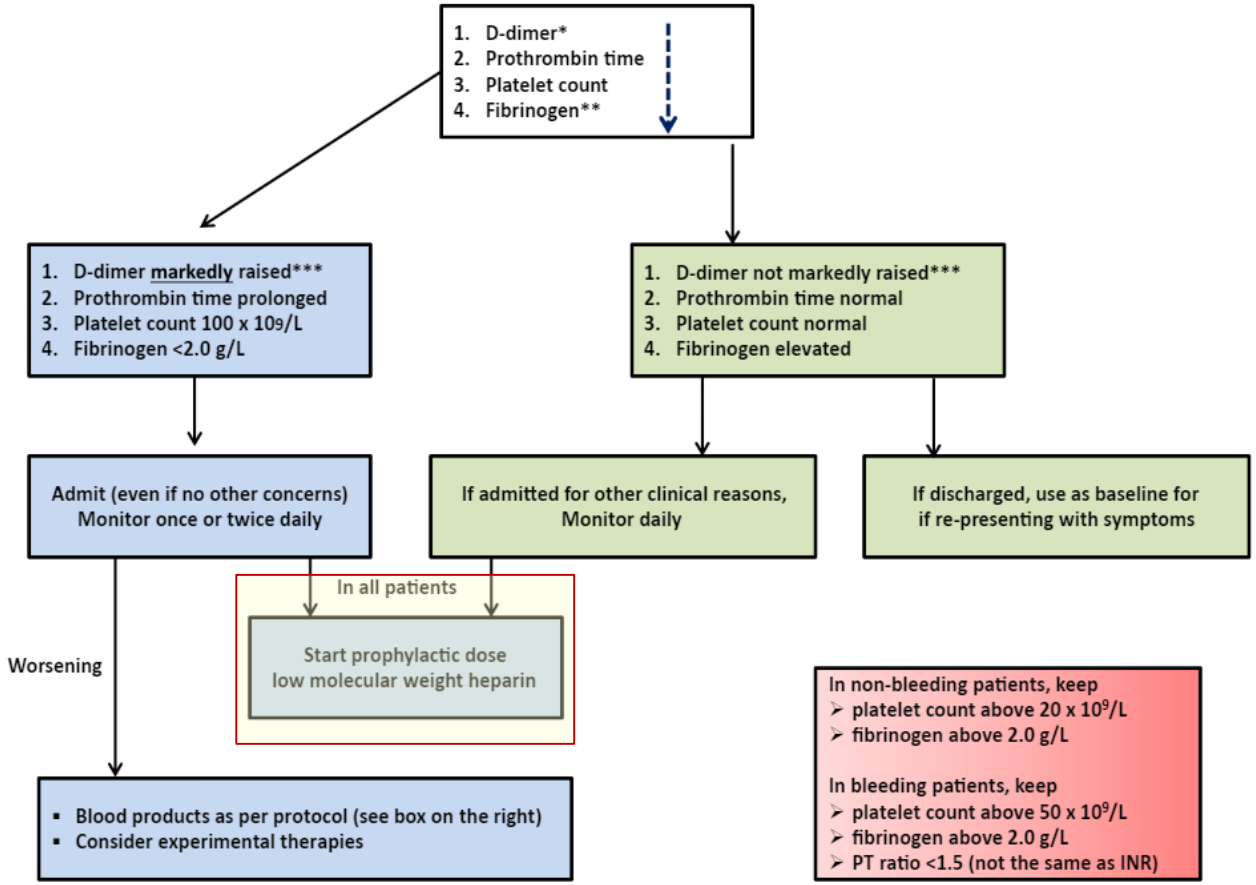
All hospitalized patients with COVID-19 should receive pharmacologic thromboprophylaxis with LMWH or fondaparinux suggested over unfractionated heparin to reduce contact) unless the patient is judged to be at increased bleeding risk. In patients with history of heparin-induced thrombocytopenia, use fondaparinux. In patients where anticoagulants are contraindicated or unavailable, use mechanical thromboprophylaxis (e.g. pneumatic compression devices).

If a patient with COVID-19 requires therapeutic anticoagulation for VTE or AFIB stroke prevention, are there any special considerations?

Multiple medications are under investigation for COVID-19. Sarilumab (KEVZARA) can increase cytochrome P450 enzyme activity. Apixaban (Eliquis®) and rivaroxaban (Xarelto®) should not be used with sarilumab and increased doses of warfarin may be required. Atazanavir and lopinavir/ritonavir will increase drug concentrations of apixaban and rivaroxaban and decrease the active metabolite of clopidogrel and prasugrel. The University of Liverpool has collated a list of drug interactions at *covid19-druginteractions.org*. Use LMWH or UFH in hospitalized critically ill patients if possible because of the shorter half life.

Should seriously ill COVID-19 patients receive therapeutic-intensity anticoagulation empirically (i.e., in the absence of confirmed VTE?

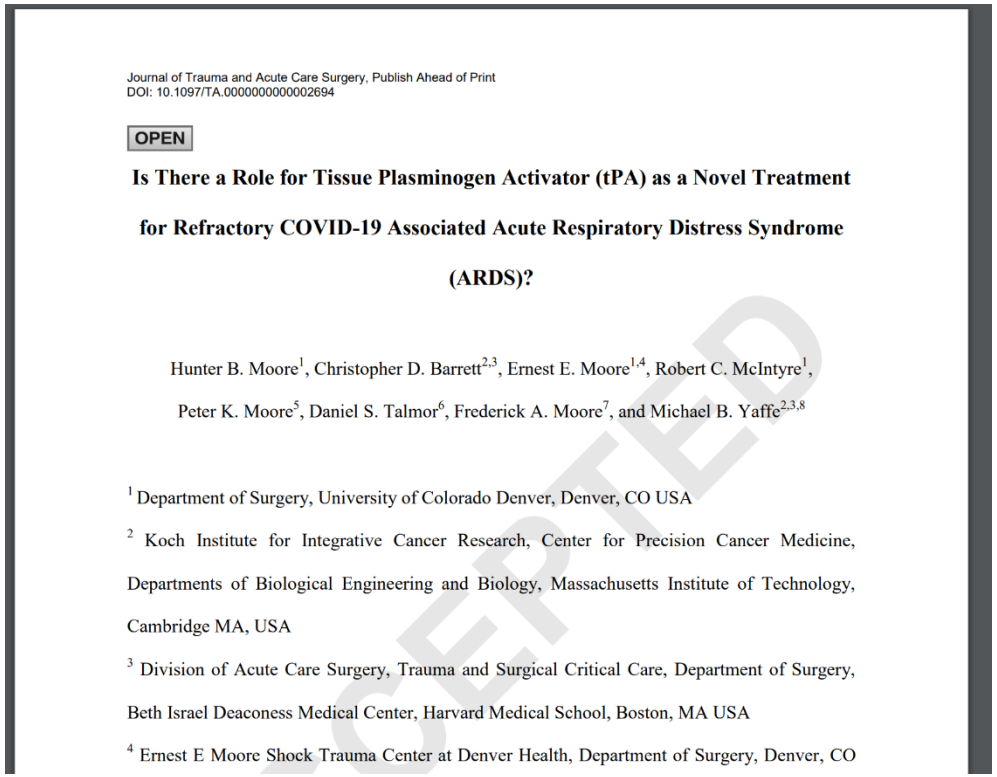
No, they should receive thromboprophylaxis only unless there is an indication for full therapeutic-intensity anticoagulation. Although therapeutic anticoagulation is recommended by some physicians in China because they have observed high rates of thrombosis in seriously ill people with COVID-19, these observations occurred in a setting where routine thromboprophylaxis may not be routinely practiced. In the U.S. or anywhere else where thromboprophylaxis is used for hospitalized patients, experts recommend using a standard approach to determine the need for pharmacologic prophylaxis and treatment, irrespective of COVID-19.



https://www.hematology.org/covid-19/covid-19-and-vte-anticoagulation

Thachil et al. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. ISHT March 2020. doi:10.1111/jth.14810

There are more aggressive approaches…



Journal of Trauma and Acute Care Surgery, Publish Ahead of Print
DOI: 10.1097/TA.0000000000002694

OPEN

Is There a Role for Tissue Plasminogen Activator (tPA) as a Novel Treatment for Refractory COVID-19 Associated Acute Respiratory Distress Syndrome (ARDS)?

Hunter B. Moore[1], Christopher D. Barrett[2,3], Ernest E. Moore[1,4], Robert C. McIntyre[1], Peter K. Moore[5], Daniel S. Talmor[6], Frederick A. Moore[7], and Michael B. Yaffe[2,3,8]

[1] Department of Surgery, University of Colorado Denver, Denver, CO USA

[2] Koch Institute for Integrative Cancer Research, Center for Precision Cancer Medicine, Departments of Biological Engineering and Biology, Massachusetts Institute of Technology, Cambridge MA, USA

[3] Division of Acute Care Surgery, Trauma and Surgical Critical Care, Department of Surgery, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA USA

[4] Ernest E Moore Shock Trauma Center at Denver Health, Department of Surgery, Denver, CO

- 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”

Moore et al. Is There a Role for Tissue Plasminogen Activator (tPA) as a Novel Treatment for Refractory COVID-19 Associated Acute Respiratory Distress Syndrome (ARDS)?. Journal of Trauma and Acute Care Surgery. March 2020. doi: 10.1097/TA.0000000000002694

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  - 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.

2.6	9.4	40
	25%	

133	104	45
3.9	17	2.9

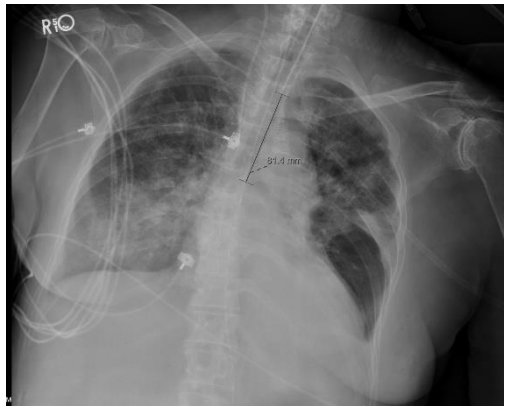
26	11
1.0	

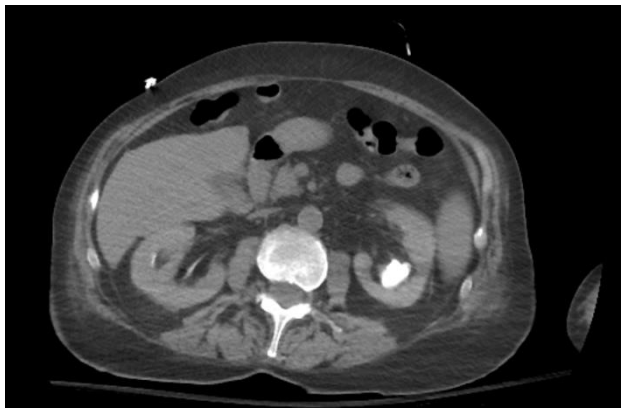
LFTs: WNL

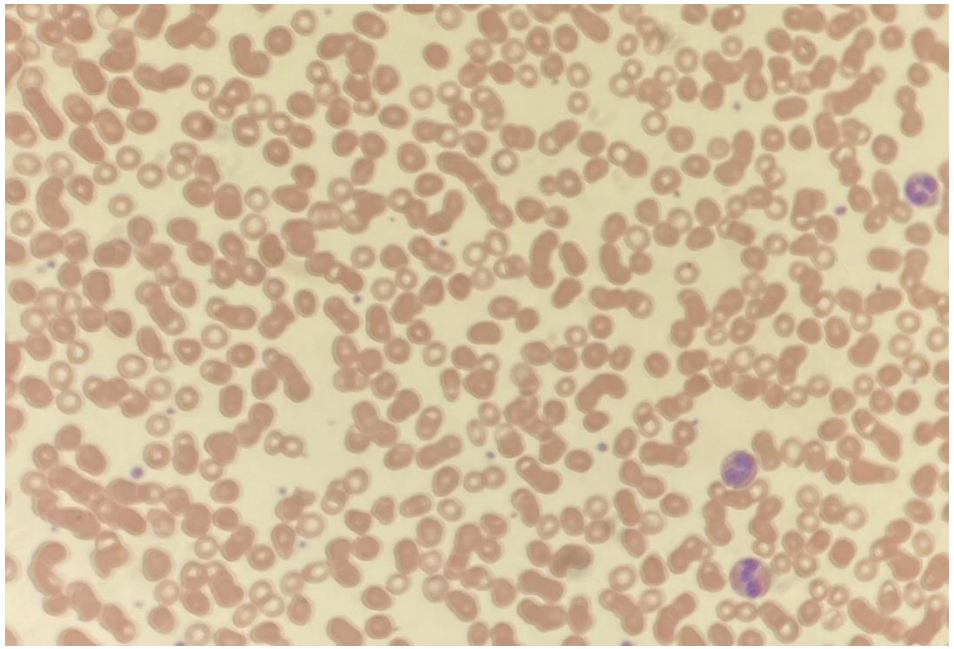
- No recent baseline
- Admission 6 days ago:
  WBC: 7, Hgb: 10.6 Plt: 110
- Diff: Abs Lymph 0.04 ANC 2.60

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

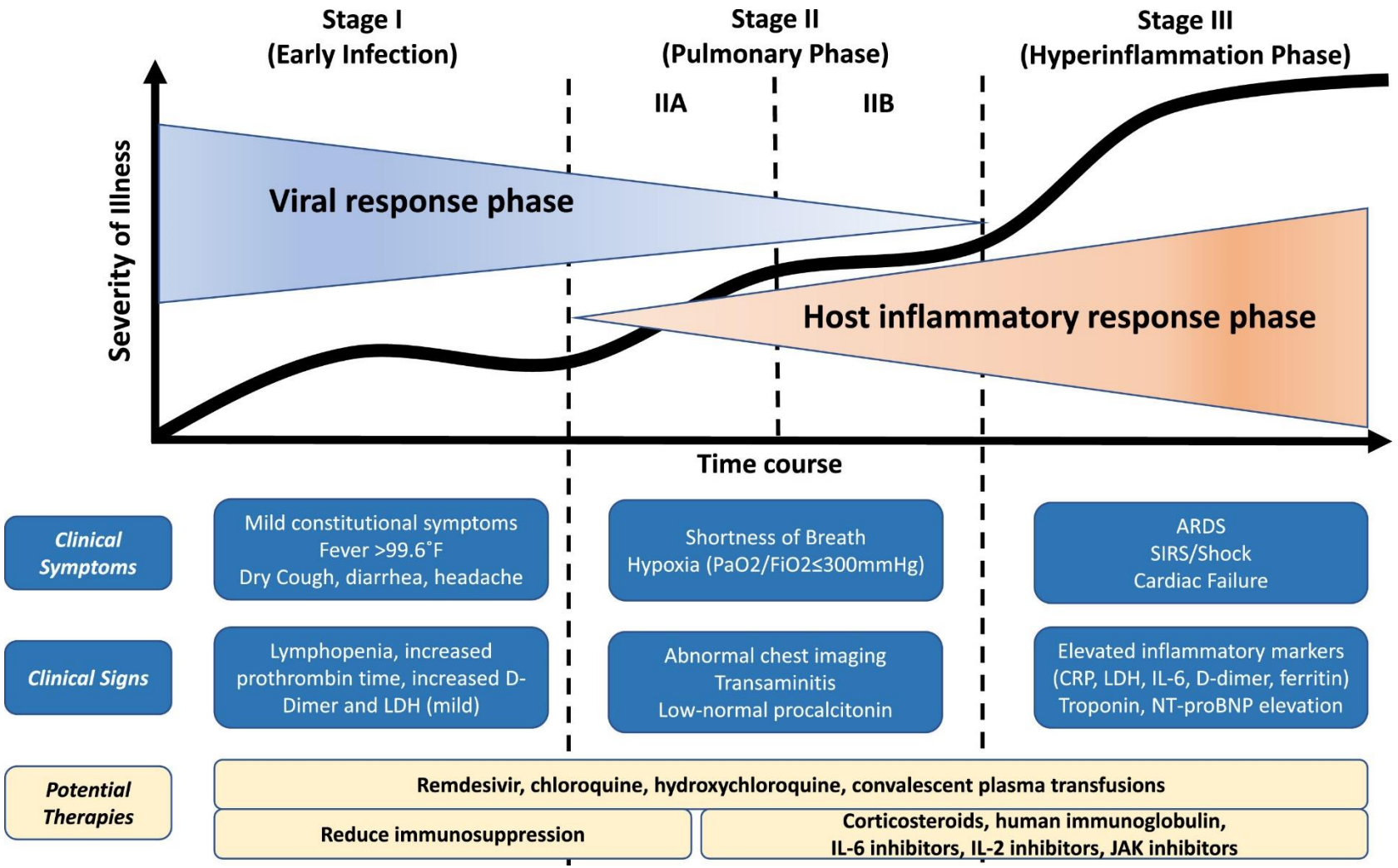
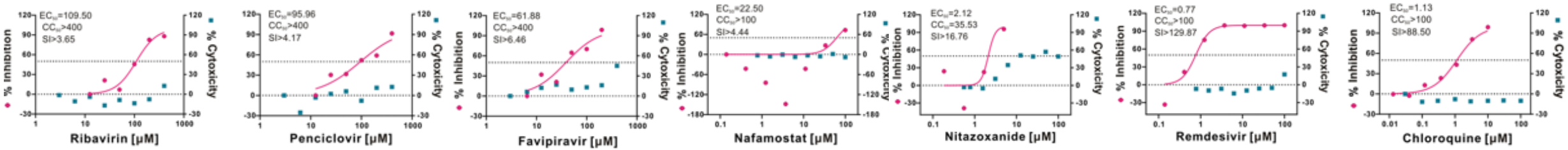


Figure from Siddiqi and Mehra. COVID-19 Illness in Native and Immunosuppressed States: A Clinical-Therapeutic Staging Proposal. Journal if Heart and Lung Transplantation. 2020. DOI: https://doi.org/10.1016/j.healun.2020.03.012

Treatment Still Supportive As We Flatten Curve



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

B. Cao, Y. Wang, D. Wen, W. Liu, Jingli Wang, G. Fan, L. Ruan, B. Song, Y. Cai, M. Wei, X. Li, J. Xia, N. Chen, J. Xiang, T. Yu, T. Bai, X. Xie, L. Zhang, C. Li, Y. Yuan, H. Chen, Huadong Li, H. Huang, S. Tu, F. Gong, Y. Liu, Y. Wei, C. Dong, F. Zhou, X. Gu, J. Xu, Z. Liu, Y. Zhang, Hui Li, L. Shang, K. Wang, K. Li, X. Zhou, X. Dong, Z. Qu, S. Lu, X. Hu, S. Ruan, S. Luo, J. Wu, L. Peng, F. Cheng, L. Pan, J. Zou, C. Jia, Juan Wang, X. Liu, S. Wang, X. Wu, Q. Ge, J. He, H. Zhan, F. Qiu, L. Guo, C. Huang, T. Jaki, F.G. Hayden, P.W. Horby, D. Zhang, and C. Wang

ABSTRACT

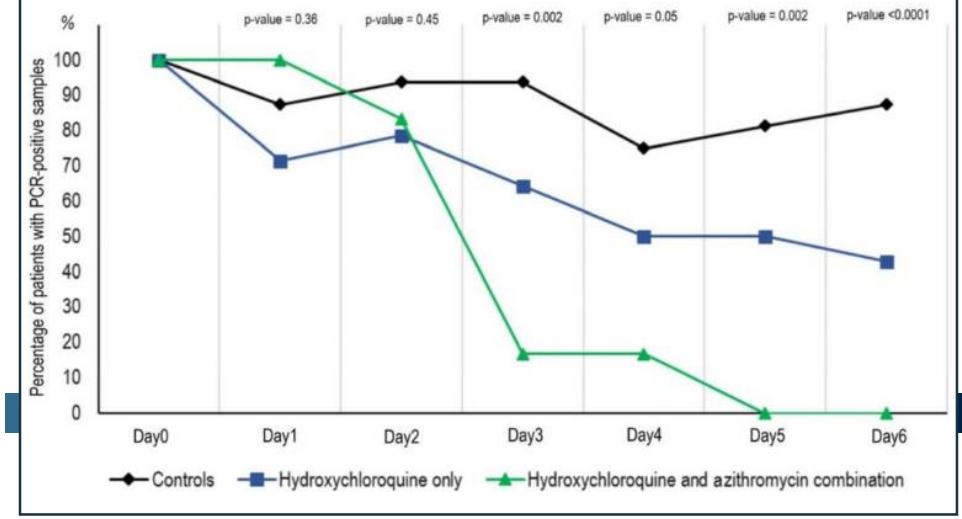
BACKGROUND

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

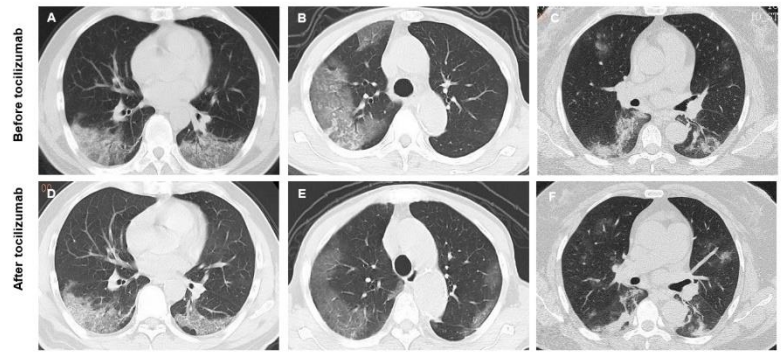
METHODS

We conducted a randomized, controlled, open-label trial involving hospitalized adult patients with confirmed SARS-CoV-2 infection, which causes the respiratory illness Covid-19, and an oxygen saturation (Sao_2) of 94% or less while they were breathing ambient air or a ratio of the partial pressure of oxygen (Pao_2) to the fraction of inspired oxygen (Fio_2) 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 ordinal scale or discharge from the hospital, whichever came first.

Hydroxychloroquine and azithromycin as a treatment of COVID-19[11]

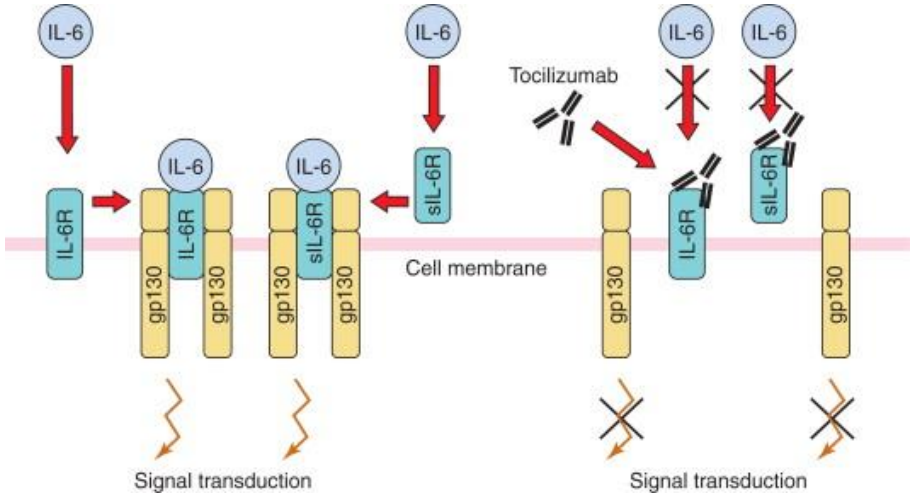


Effective Treatment of Severe COVID-19 Patients with Tocilizumab[19]

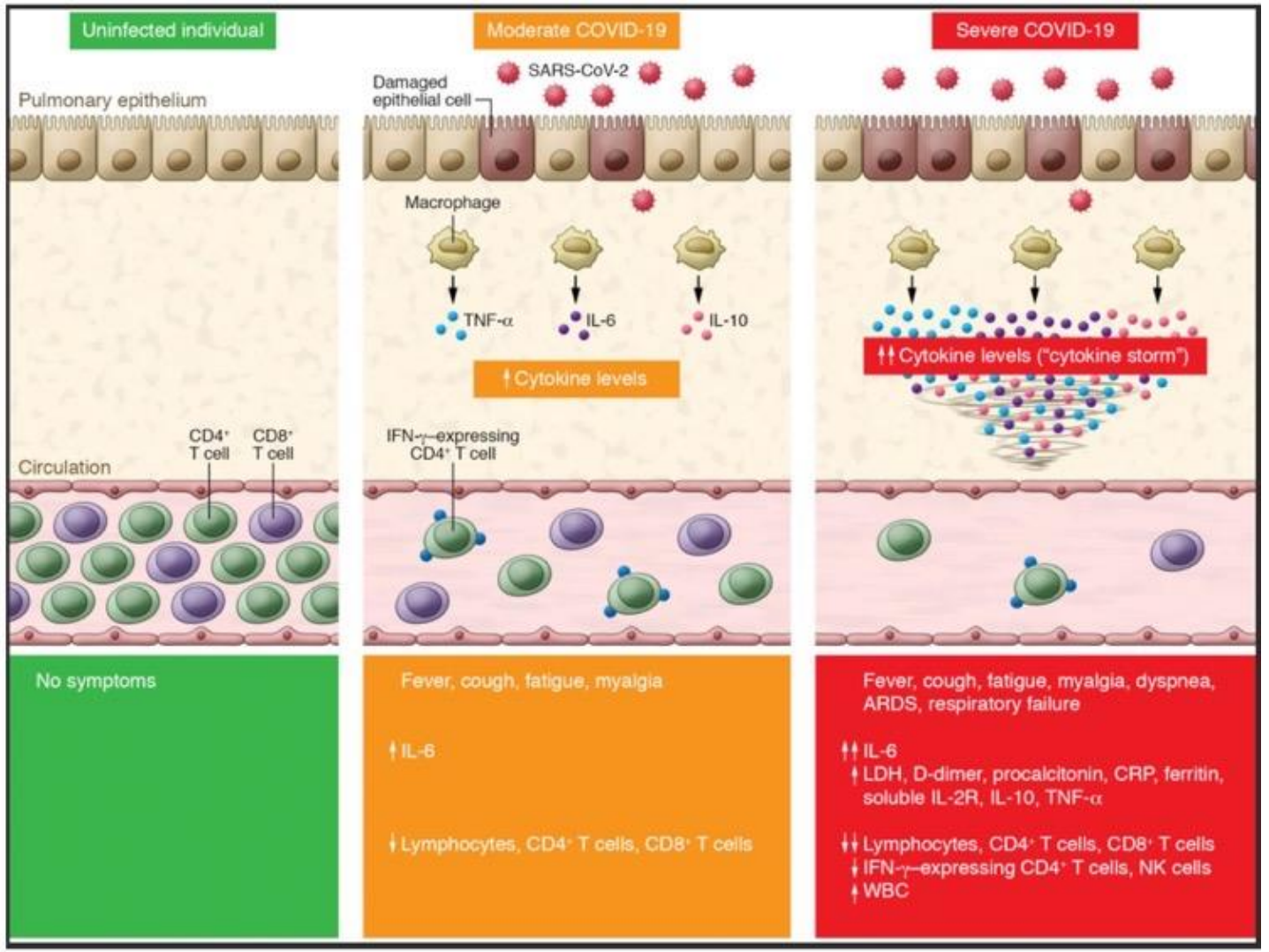


There are centers using tocilizumab or sarilumab…

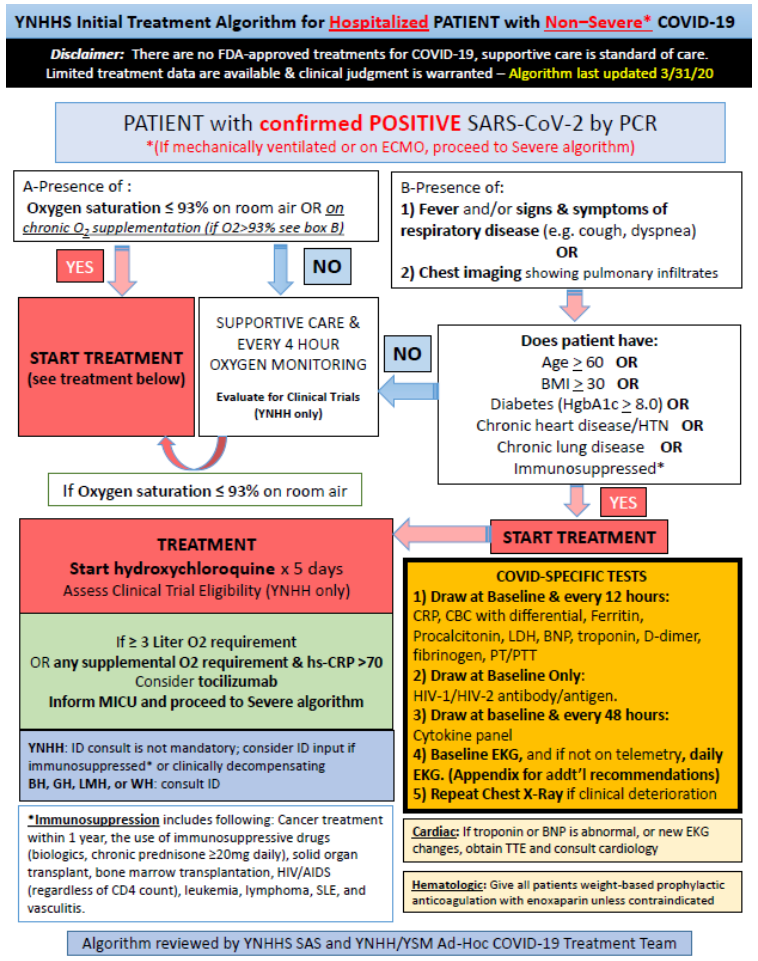
Tocilizumab

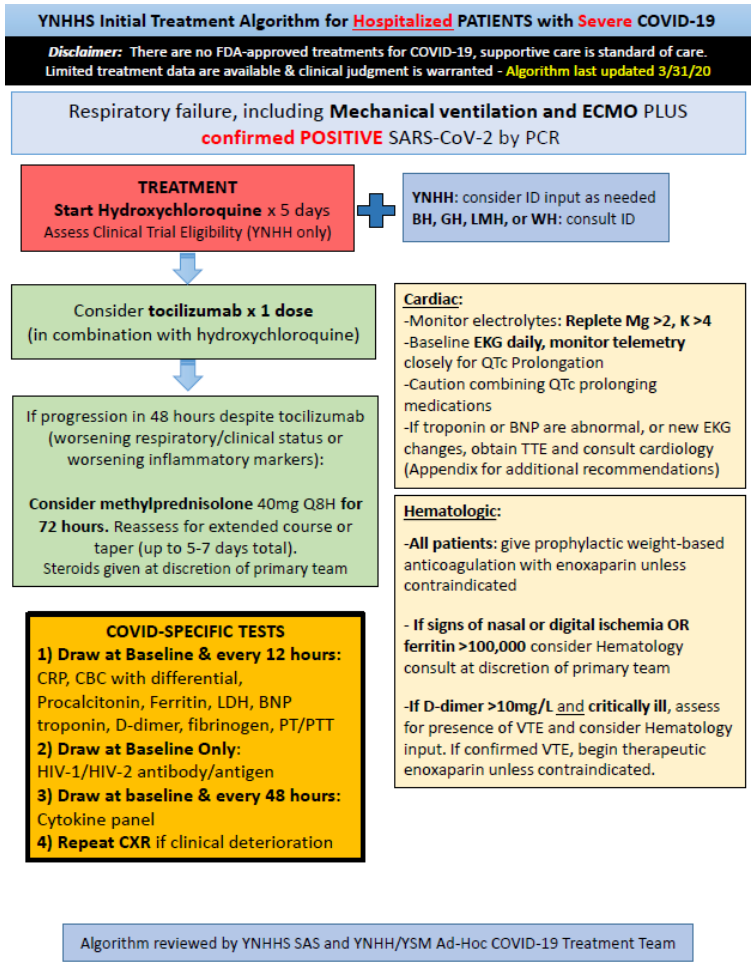


Case reports abound ("101-year-old Italian man who survived the 1918 Spanish flu pandemic and World War II, recovered from COVID-19." or 20 pt case series), the phase III is pending…

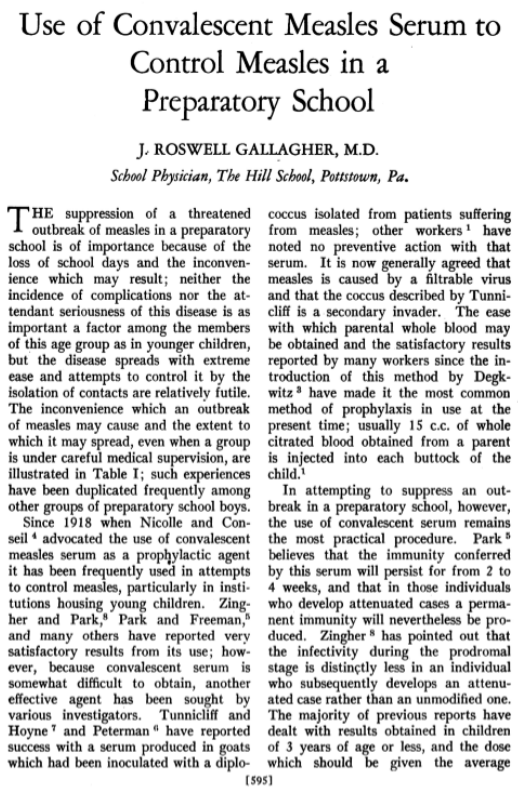


Some centers have fully incorporated tocilizumab into algorithms





Should We Go Old School? Role for IVIG?



Use of Convalescent Measles Serum to Control Measles in a Preparatory School

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THE suppression of a threatened outbreak of measles in a preparatory school is of importance because of the loss of school days and the inconvenience which may result; neither the incidence of complications nor the attendant seriousness of this disease is as important a factor among the members of this age group as in younger children, but the disease spreads with extreme ease and attempts to control it by the isolation of contacts are relatively futile. The inconvenience which an outbreak of measles may cause and the extent to which it may spread, even when a group is under careful medical supervision, are illustrated in Table I; such experiences have been duplicated frequently among other groups of preparatory school boys.

Since 1918 when Nicolle and Conseil [4] advocated the use of convalescent measles serum as a prophylactic agent it has been frequently used in attempts to control measles, particularly in institutions housing young children. Zingher and Park,[3] Park and Freeman,[5] and many others have reported very satisfactory results from its use; however, because convalescent serum is somewhat difficult to obtain, another effective agent has been sought by various investigators. Tunnicliff and Hoyne [7] and Peterman [6] have reported success with a serum produced in goats which had been inoculated with a diplococcus isolated from patients suffering from measles; other workers [1] have noted no preventive action with that serum. It is now generally agreed that measles is caused by a filtrable virus and that the coccus described by Tunnicliff is a secondary invader. The ease with which parental whole blood may be obtained and the satisfactory results reported by many workers since the introduction of this method by Degkwitz [3] have made it the most common method of prophylaxis in use at the present time; usually 15 c.c. of whole citrated blood obtained from a parent is injected into each buttock of the child.[1]

In attempting to suppress an outbreak in a preparatory school, however, the use of convalescent serum remains the most practical procedure. Park [5] believes that the immunity conferred by this serum will persist for from 2 to 4 weeks, and that in those individuals who develop attenuated cases a permanent immunity will nevertheless be produced. Zingher [8] has pointed out that the infectivity during the prodromal stage is distinctly less in an individual who subsequently develops an attenuated case rather than an unmodified one. The majority of previous reports have dealt with results obtained in children of 3 years of age or less, and the dose which should be given the average

[595]

- Major argument is for convalescent serum, see Shen et al JAMA Treatment of 5 Critically Ill Patients with Convalescent Plasma
- Beyond convalescent serum there is no convincing randomized trial data that IVIG is helpful in sepsis
  - Hypogammalgobulinemia 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?

Variable	Points
Known underlying imm	0 (no) or 18 (yes)
Temperature (°C)	(38.4–39.4), or 49 (>39.4)
Organomegaly	or splenomegaly), or
Number of cytopenias	
Ferritin (ng/ml)	0 (<2,0
Triglyceride (mmoles/l)	0 (<1.5), 44 (1.5–4),
Fibrinogen (g/l)	0 (>2.5) or 30 (≤2.5)
Serum aspartate aminotransferase (U/l)	0 (<30) or 19 (≥30)
Hemophagocytosis features on bone marrow aspirate	0 (no) or 35 (yes)

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

Σ142 (~16% chance of HLH)

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

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

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- **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


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