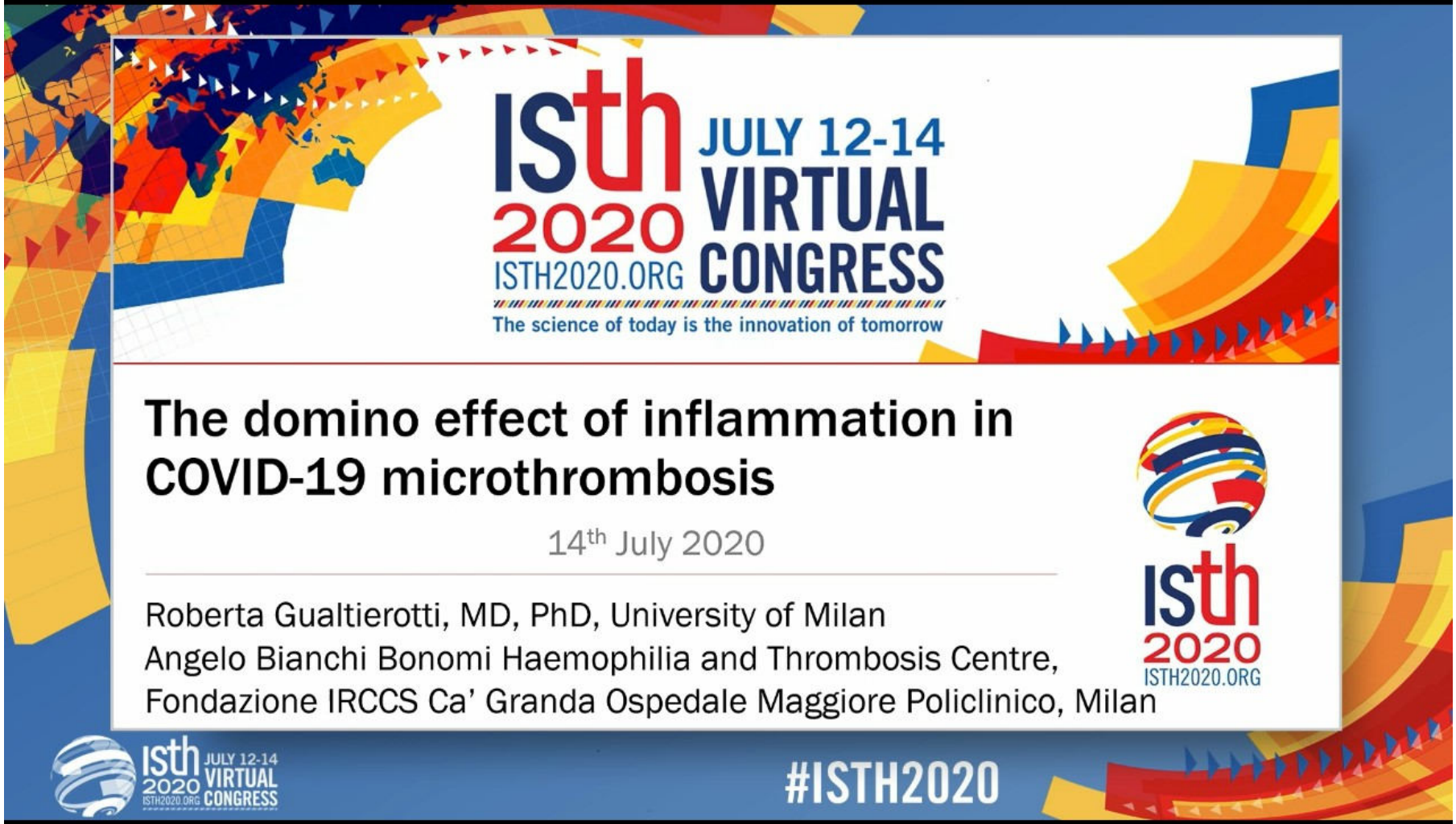

ISTH 2020
ISTH2020.ORG
JULY 12-14
VIRTUAL CONGRESS
The science of today is the innovation of tomorrow
The domino effect of inflammation in COVID-19 microthrombosis
14th July 2020
Roberta Gualtierotti, MD, PhD, University of Milan
Angelo Bianchi Bonomi Haemophilia and Thrombosis Centre,
Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan
ISTH 2020
ISTH2020.ORG
#ISTH2020

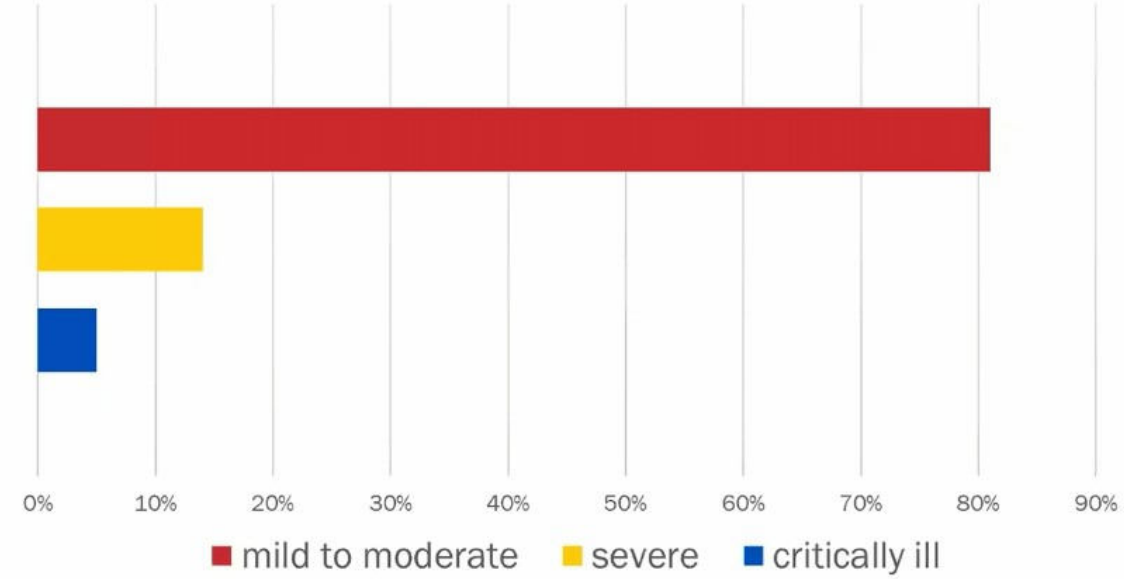
Summary

- Physiopathogenesis of COVID-19
- What is severe COVID-19
- Immune dysregulation in severe COVID-19
- The effects of hyper-acute inflammation in severe COVID-19
- Microthrombosis in severe COVID-19
- Conclusions

Physiopathogenesis of COVID-19

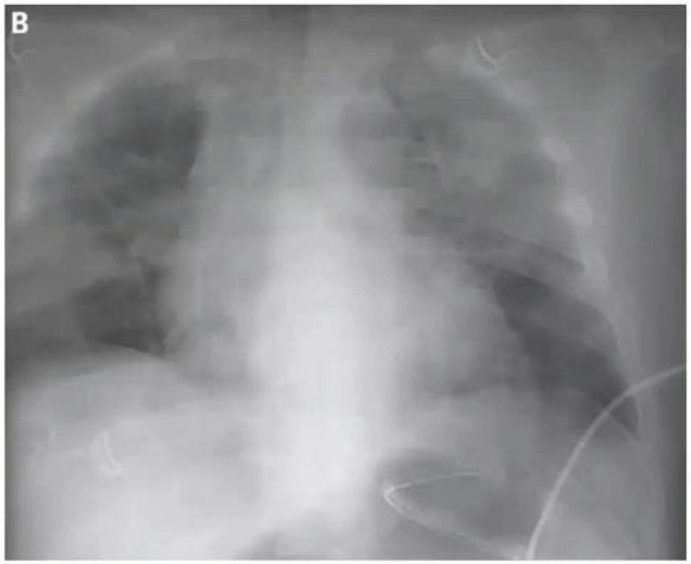
- Transmission via direct contact or respiratory droplets
- Viral entry via binding of receptor-binding domain to the ACE2 receptor
- Replication in bronchial and alveolar epithelial cells, endothelial cells and monocytes in lungs
- NK cell activation cytotoxicity and production of IFN- γ
- Antigen presentation to cytotoxic T lymphocytes and production of IFN-γ
- Humoral and cellular immune response

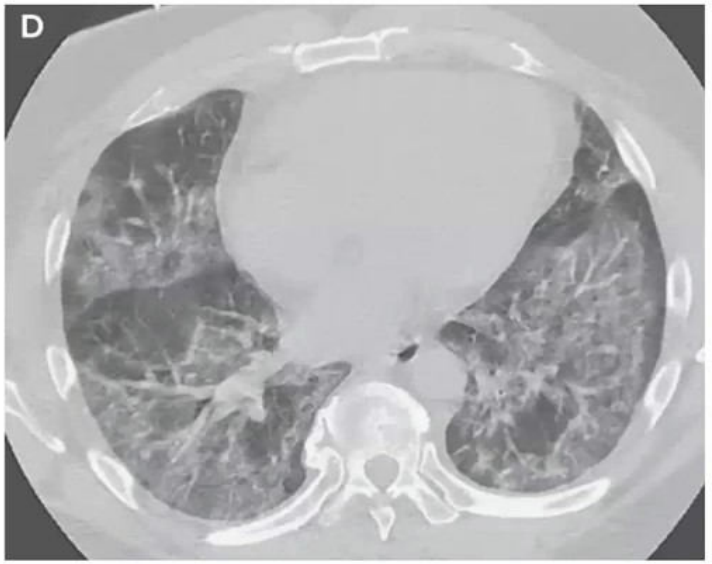
COVID-19 clinical manifestations



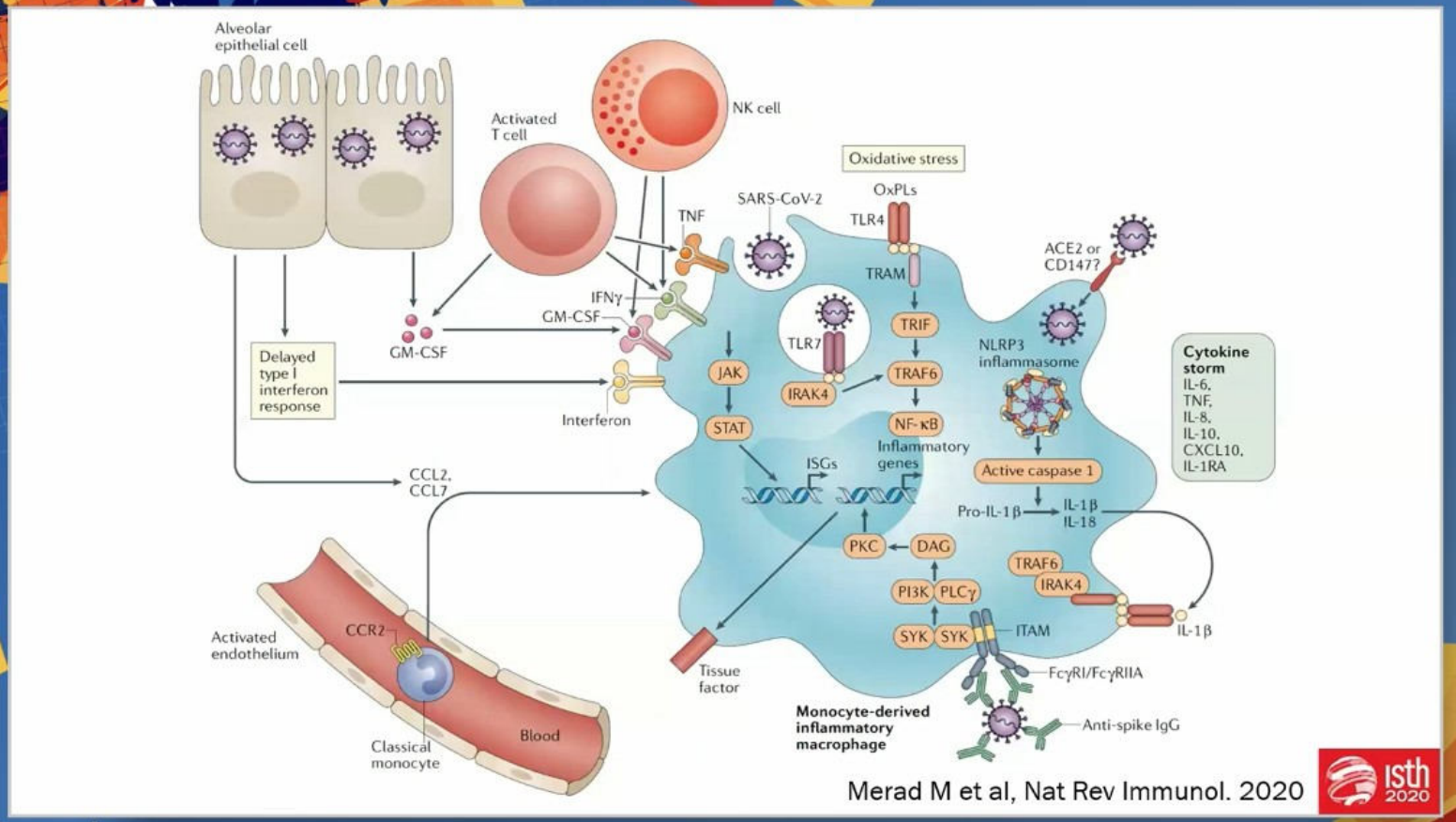
Adapted from Wu Z et al. JAMA. 2020;323(13):1239–1242

Severe COVID-19





Bhatraju PK et al NEJM 2020



Merad M et al, Nat Rev Immunol. 2020

Inflammation is caused by immune dysregulation in severe COVID-19

- Lymphocytopenia is characterised by low CD4+ with predominance of Th2 lymphocytes, low CD19+ lymphocytes, and low NK cells
- Monocytes display a reduced expression of both CD14 and HLA-DR
- An inverse correlation exists between HLA-DR molecules on CD14-monocytes and serum levels of IL-6

Giamarellos-Bourboulis E et al. Cell 2020
Lombardi A et al doi: https://doi.org/10.1101/2020.05.01.20087080

A bidirectional crosstalk exists between inflammation and coagulation

- In bacterial sepsis IL-6 is the main culprit for tissue factor expression on mononuclear cells and endothelial cells
- Tissue factor expressed by activated monocytes, endothelial cells and microvesicles activates the extrinsic coagulation pathway
- Fibrin deposition and blood clotting in an attempt to reduce pathogen spread

Merad M et al. Nat Rev Immunol 2020
Levi M et al. Circulation 2004; 109:2698-704

Cumulative incidence of venous thromboembolism in severe COVID-19

- Klok FA et al (ICU): 27% at 21 d
- Thomas W et al (ICU): 27% at 21 d
- Lodigiani et al (ICU): 27.6% at 24 d
- Martinelli I et al, submitted (intermediate care and ICU patients) : 31.6% at 21 d

Severe COVID-19 resembles...

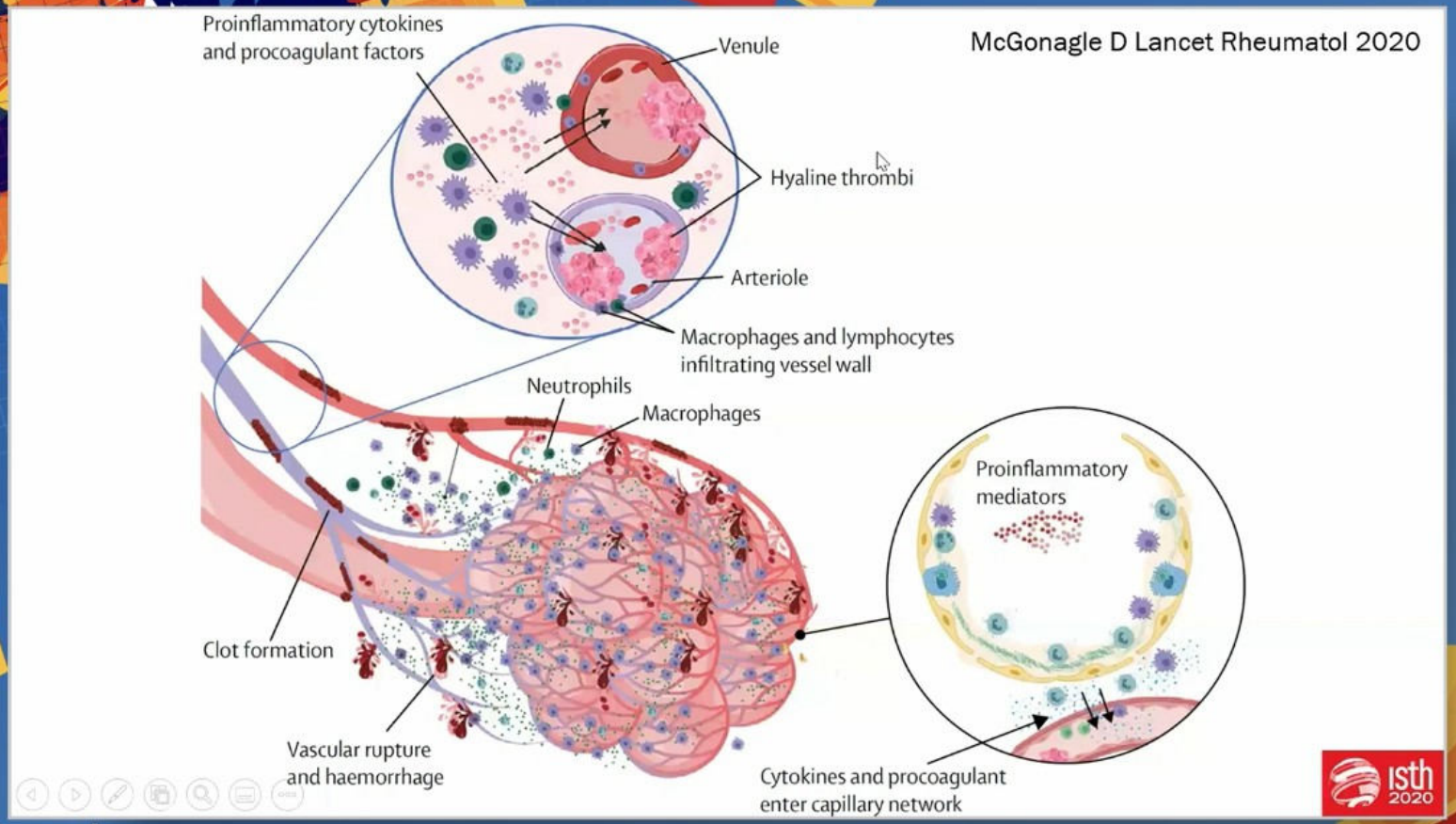
- Disseminated intravascular coagulation (DIC)
- Thrombotic mycroangiopathy (TMA)
- Secondary haemophagocytic lymphohistiocytosis (sHLH)
- Sepsis
- Cytokine storm

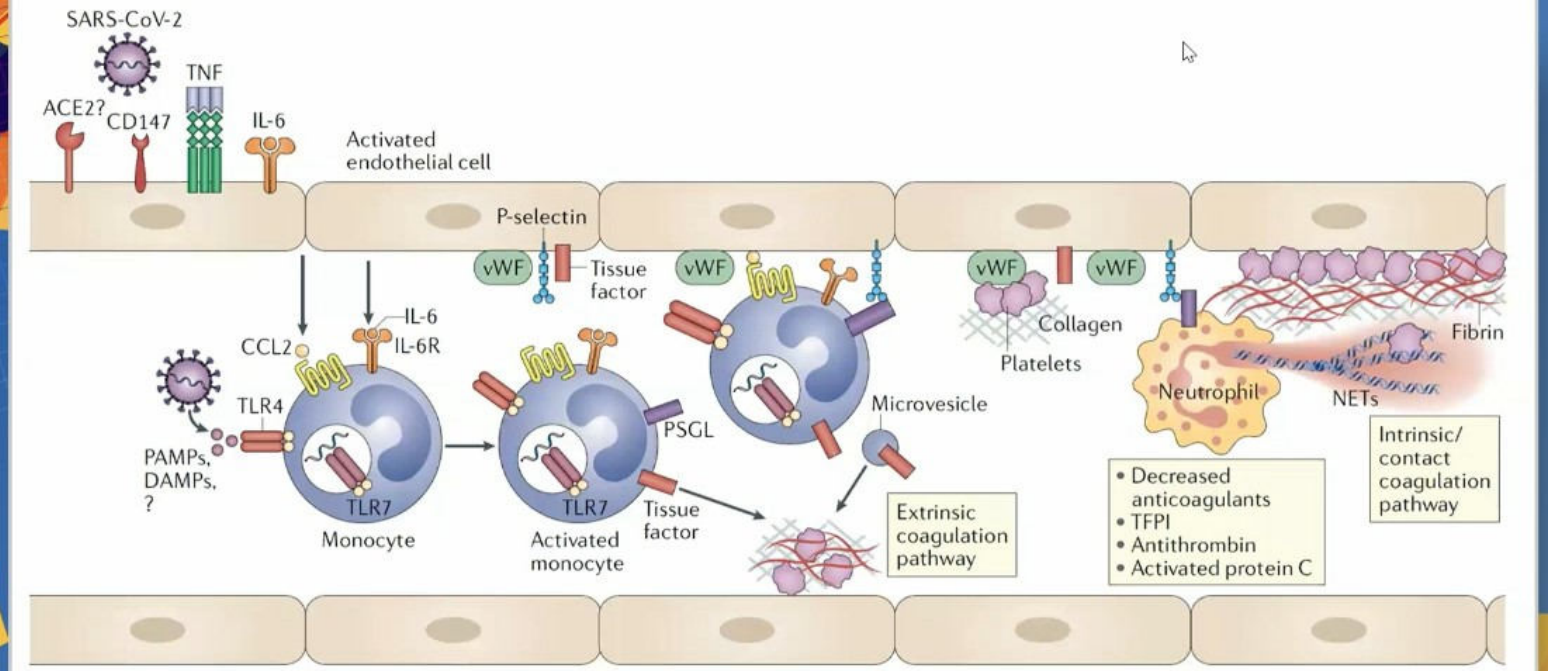
Peyvandi et al, submitted

Microthrombosis in severe COVID-19

- On CT pulmonary angiograms they are mainly segmental or subsegmental
- They are likely to be *in situ* microvascular thromboses (immunothromboses)
- Severe diffuse pulmonary immunothrombosis
- Pulmonary intravascular coagulopathy

McGonagle D Lancet Rheumatol 2020
Desborough MJR Thromb Res 2020





The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Pulmonary Vascular Endothelialitis, Thrombosis, and Angiogenesis in Covid-19

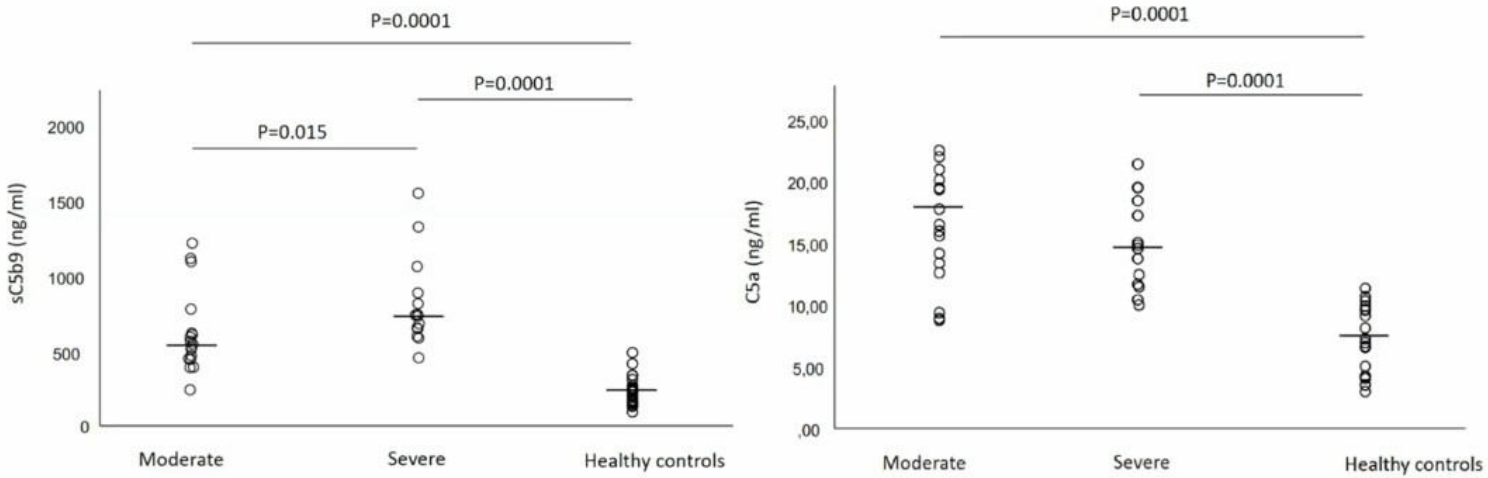
Maximilian Ackermann, M.D., Stijn E. Verleden, Ph.D., Mark Kuehnel, Ph.D., Axel Haverich, M.D., Tobias Welte, M.D., Florian Laenger, M.D., Arno Vanstapel, Ph.D., Christopher Werlein, M.D., Helge Stark, Ph.D., Alexandar Tzankov, M.D., William W. Li, M.D., Vincent W. Li, M.D., Steven J. Mentzer, M.D., and Danny Jonigk, M.D.

Endothelial activation or damage in severe COVID-19

- ACE2 is expressed on endothelial cells
- Severe endothelial injury associated with intracellular SARS-CoV-2 virus
- Widespread vascular thrombosis with microangiopathy and occlusion of alveolar capillaries

McGonagle D Lancet Rheumatol 2020
Desborough MJR Thromb Res 2020

Complement activation in severe COVID-19



Cugno M et al. JACI Insight; 2020

Neutrophil extracellular traps in severe COVID-19

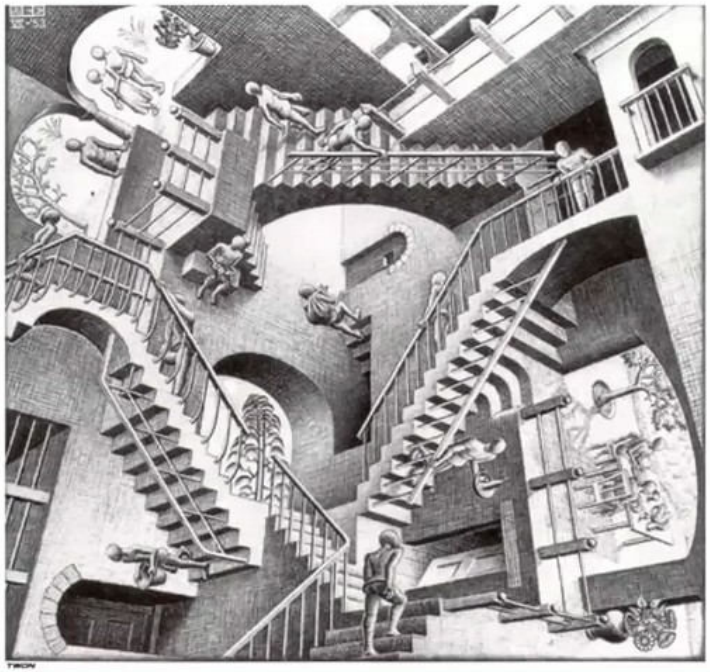
- Neutrophils are recruited by activated endothelial cells and form and release neutrophil extracellular traps (NETs)
- In the course of hyperinflammation the recruitment of neutrophils is amplified
- NETs activate the coagulation contact pathway and can bind and activate platelets
- Evidence of NETosis in COVID-19 patients exists, with higher levels of NETs in patients receiving mechanical ventilation

Zuo et al. JCI Insight; 2020

Conclusions

- Severe COVID-19 is characterised by a hyper-acute inflammatory state and a peculiar coagulopathy
- Hyperinflammation triggers a series of pathogenic mechanisms that further amplify the inflammatory state and activate coagulation and other systems
- Hypercoagulability leads to a prothrombotic state

Trying to identify and define the mechan



Relativity, 1953
Maurits Cornelius Escher

Acknowledgements

- Internal Medicine – Haemostasis and Thrombosis Unit, Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Milano
- Angelo Bianchi Bonomi Haemophilia and Thrombosis Center, Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Milano
- COVID-19 Network
- COHERENT study group

DVR

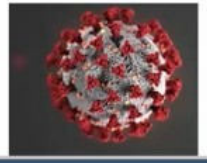
ISTH 2020 ISTH2020.ORG JULY 12-14 VIRTUAL CONGRESS

The science of today is the innovation of tomorrow

Thromboprophylaxis & COVID-19: the pandemic dilemma of managing patients without any Grade 1A evidence

Prof Beverley Hunt OBE

Recorded June 25th 2020

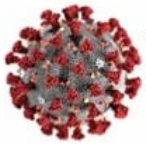


ISTH 2020 ISTH2020.ORG

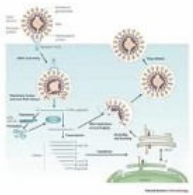
ISTH 2020 JULY 12-14 VIRTUAL CONGRESS ISTH2020.ORG

#ISTH2020

COVID-19 pathogenesis

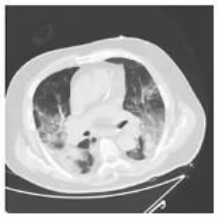


ACE2 receptor on
Pulmonary epithelium
& endothelium



Asymptomatic
Minor infection
7-10 days fever &/or flu-like symptoms
anosmia

In a minority (5%)
COVID-19 pneumonia
Massive inflammatory response
Cytokine storm/macrophage activation



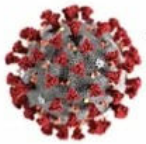
Moderate
(needs O2)

Severe
(needs mechanical
Ventilation)

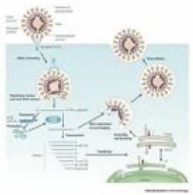
WORLD THROMBOSIS DAY
13 OCTOBER

Thrombosis UK

COVID-19 pathogenesis

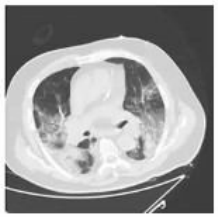


ACE2 receptor on
Pulmonary epithelium
& endothelium



Asymptomatic
Minor infection
7-10 days fever &/or flu-like symptoms
anosmia

In a minority (5%)
COVID-19 pneumonia
Massive inflammatory response
Cytokine storm/macrophage activation



Moderate
(needs O2)

Severe
(needs mechanical
Ventilation)

Prothrombotic state due to effects of IL1, IL-6

WORLD THROMBOSIS DAY
13 OCTOBER

Thrombosis UK

ISTH 2020 JULY 12-14 VIRTUAL CONGRESS
ISTH2020.ORG

#ISTH2020

When is VTE risk increased in COVID-19 inf

WORLD THROMBOSIS DAY
13 OCTOBER

Thrombosis UK

When is VTE risk increased in COVID-19 inf

Increased risk if immobile?

Hospital-associated VTE

Increased risk if immobile?

Infection

Hospitalisation

90 days post discharge

Late sequelae e.g COVID toes

.....

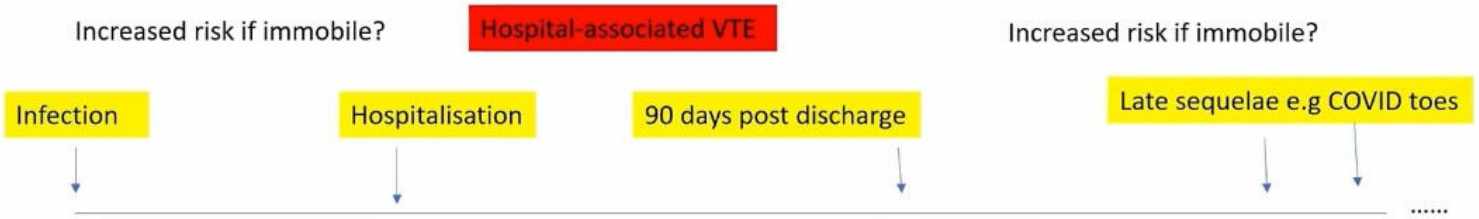
WORLD THROMBOSIS DAY
13 OCTOBER

Thrombosis UK

ISTH 2020 VIRTUAL CONGRESS
JULY 12-14
ISTH2020.ORG

#ISTH2020

When is VTE risk increased in COVID-19 inf



WORLD THROMBOSIS DAY
13 OCTOBER

Thrombosis UK

When is VTE risk increased in COVID-19 inf

Increased risk if immobile?

Hospital-associated VTE

Increased risk if immobile?

Infection

Hospitalisation

90 days post discharge

Late sequelae e.g COVID toes

.....

But also

Pneumonia at home or in care home

WORLD THROMBOSIS DAY
13 OCTOBER

Thrombosis UK

When is VTE risk increased in COVID-19 inf

Increased risk if immobile

Hospital-associated VTE

Increased risk if immobile?

Infection

Hospitalisation

90 days post discharge

Late sequelae e.g COVID toes

.....

But also

Pneumonia at home or in care home

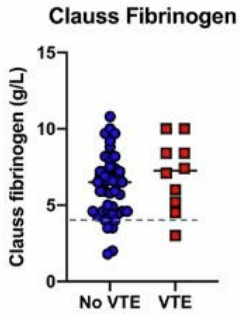
What is their risk?

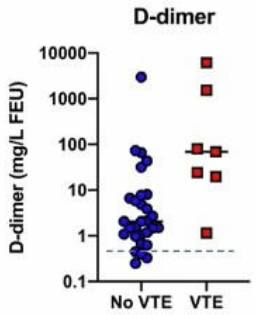
WORLD THROMBOSIS DAY
13 OCTOBER

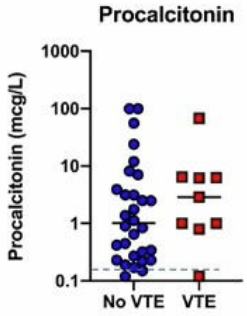
Thrombosis UK

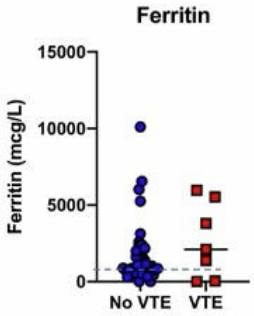
Coagulation and inflammation markers in 66 ICU patients with

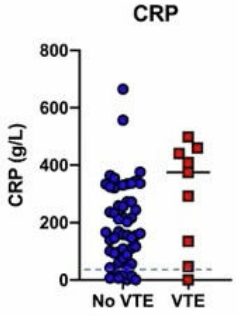
Desborough et al. Thrombosis Research preprint











Dashed line is normal range

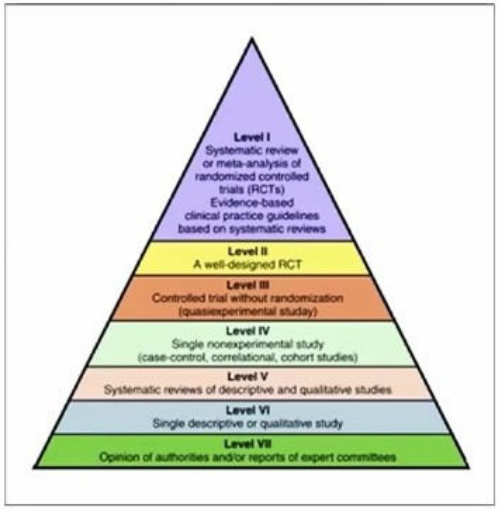
WORLD THROMBOSIS DAY
13 OCTOBER

Thrombosis UK

ISTH 2020 VIRTUAL CONGRESS
JULY 12-14
ISTH2020.ORG

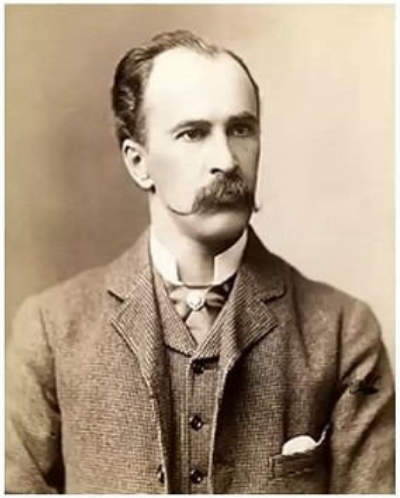
#ISTH2020

Modern medical science



versus

Old fashioned, observational me



Sir William Osler

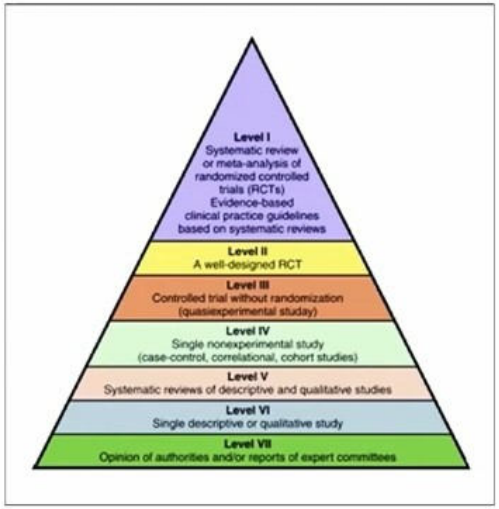
WORLD THROMBOSIS DAY
13 OCTOBER

Thrombosis UK

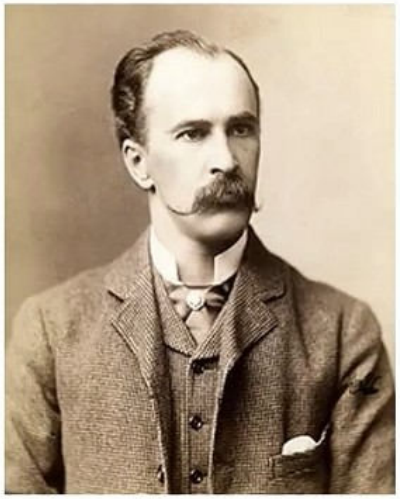
Wanting to the very best for the patients

Modern medical science

Old fashioned, observational me



versus



Sir William Osler

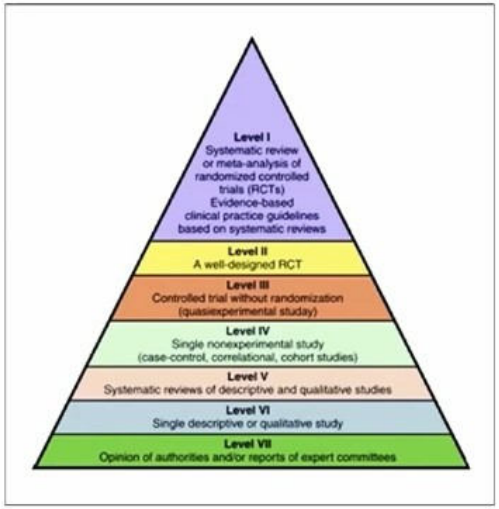
WORLD THROMBOSIS DAY
13 OCTOBER

Thrombosis UK

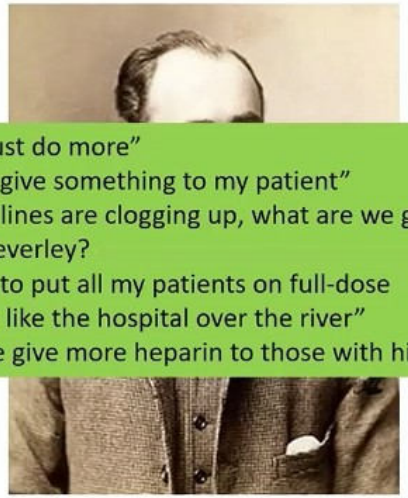
Wanting to the very best for the patients- the medical dilemma of managing patients in a new disease pandemic

Modern

tional me



versus



"We must do more"
"I must give something to my patient"
"All the lines are clogging up, what are we going to do Beverley?
"I want to put all my patients on full-dose heparin like the hospital over the river"
Shall we give more heparin to those with high D-dimers?

Sir William Osler

WORLD THROMBOSIS DAY
13 OCTOBER

Thrombosis UK

ISTH 2020 JULY 12-14 VIRTUAL CONGRESS
ISTH2020.ORG

#ISTH2020

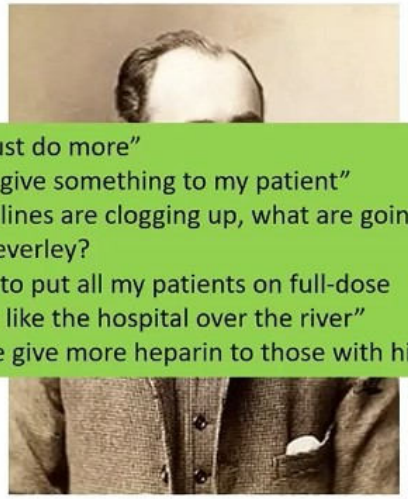
Wanting to the very best for the patients- the medical dilemma of managing patients in a new disease pandemic

Modern

tional me

We must resist all change in the absence of new evidence

versus



"We must do more"
"I must give something to my patient"
"All the lines are clogging up, what are going to do Beverley?
"I want to put all my patients on full-dose heparin like the hospital over the river"
Shall we give more heparin to those with high D-dimers?

Sir William Osler

WORLD THROMBOSIS DAY
13 OCTOBER

Thrombosis UK

DVR

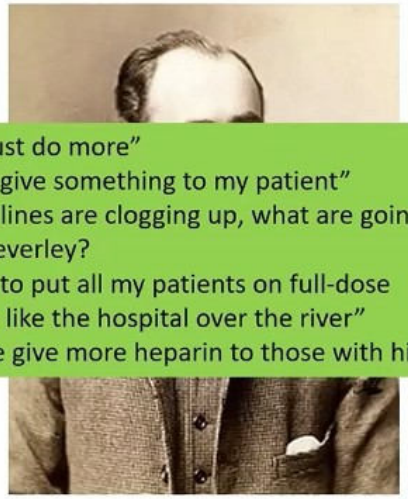
Wanting to the very best for the patients- the medical dilemma of managing patients in a new disease pandemic

Modern

tional me

We must resist all change in the absence of new evidence

versus



"We must do more"
"I must give something to my patient"
"All the lines are clogging up, what are going to do Beverley?
"I want to put all my patients on full-dose heparin like the hospital over the river"
Shall we give more heparin to those with high D-dimers?

Where do you sit?

Sir William Osler

WORLD THROMBOSIS DAY
13 OCTOBER

Thrombosis UK

ISTH 2020 VIRTUAL CONGRESS
JULY 12-14
ISTH2020.ORG

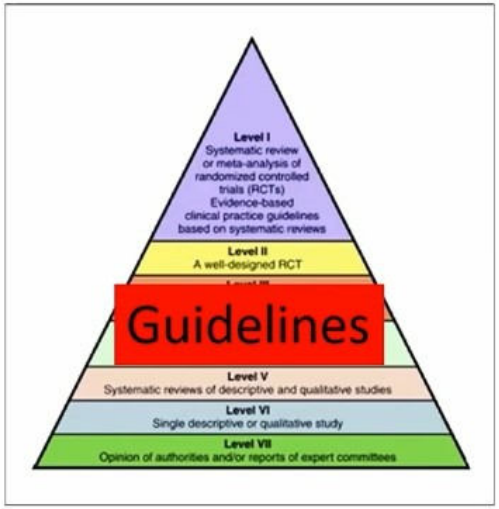
#ISTH2020

DVR

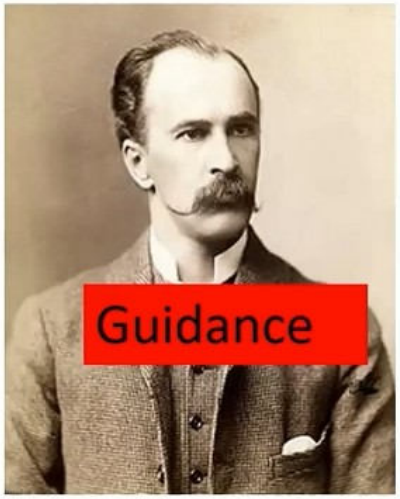
Wanting to the very best for the patients

Modern medical science

Old fashioned, observational me



versus



Sir William Osler

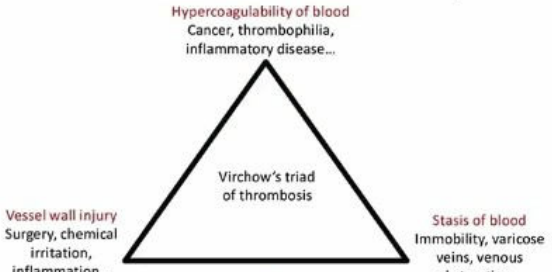
WORLD THROMBOSIS DAY
13 OCTOBER

Thrombosis UK

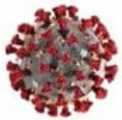
ISTH 2020 JULY 12-14 VIRTUAL CONGRESS
ISTH2020.ORG

#ISTH2020

Lung venous thromboembolism in COVID-pneumonia



Immunothrombosis



Local inflammation in pulmonary vasculature

Pulmonary thrombosis

WORLD THROMBOSIS DAY
13 OCTOBER

Thrombosis UK

ISTH 2020 JULY 12-14 VIRTUAL CONGRESS
ISTH2020.ORG

#ISTH2020

ICU and image-proven «VTE » are they counting immunothrombosis

First author	ICU patients (N)	VTE (%)	PE (%)	DVT (%)	Bleeding (%)	Standard/ther
Cui (*China*)	81	25	?	25	?	Nil
Fraissé (*France*)	92	40	27	13	24	
Klok (*The Netherlands*)	184	37	35	0.5	?	Standard
Helms (*France*)	150	16,7	16.7	2	2.7	78%/22%
Litjos (*France*)	26	?	23	69	?	31%/69%
Maatman (*USA*)	109	28	4	24	?	94%/6%
Nahum (*France*)	34	79	?	79	?	standard
Poissy (*France*)	107		20.6	4.7	?	91%/9%
Ren (*Wuhan, China*)	48	?	?	85 (88% distal)	?	Standard
Thomas (*UK*)	63	27	8	?	?	Standard
Desborough (UK)	66	5			6%	Standard

What is the evidence for managing hospital-associated VTE in medical and critical care patients pre-COVID-19?

Thromboprophylaxis for "ward" COVID-19 pneumonia

Previous evidence: benefits of heparinoid thromboprophylaxis for 6-

placebo in medical patients

Study	RRR	Thromboprophylaxis	Patients with VTE (%)
MEDENOX[1]	63%	Placebo	14.9*
$P<0.001$		Enoxaparin 40 mg	5.5
PREVENT[2]	45%	Placebo	5.0*
$P=0.0015$		Dalteparin	2.8
ARTEMIS[3]	47%	Placebo	10.5†
$p=0.029$		Fondaparinux	5.6

RRR = relative risk reduction

[1]Samama MM *et al. N Engl J Med* 1999;341:793–800
[2]Leizorovicz A *et al. J Circulation* 2004;110:874–9
[3]Cohen AT *et al. J Thromb Haemost* 2003;1 (Suppl 1):P2046

WORLD THROMBOSIS DAY
13 OCTOBER

ISTH 2020 VIRTUAL CONGRESS
JULY 12-14
ISTH2020.ORG

#ISTH2020

Thromboprophylaxis in Critical Care

Does LMWH/UFH reduce risk?

Alhazzani et al Crit Care Med 2013; 41: 2088

- Systematic review 7,226 pts in RCTs
- ↓sympt/asympt DVT RR 0.51 (95% CI 0.41-0.64); p <0.0001)
- ↓PE RR 0.52 (95% CI 0.28-0.92); p= 0.04)
- No difference in bleeding or mortality

Which is better?

Lim et al Crit Care Med 212;40: 328

- Compared LMWH vs UFH in same group
- LMWH ↓ DVT & PE> UFH
- For PE RR 0.52: 95% CI 0.28,0.97) p=0.04)
- No difference in bleeding or mortality

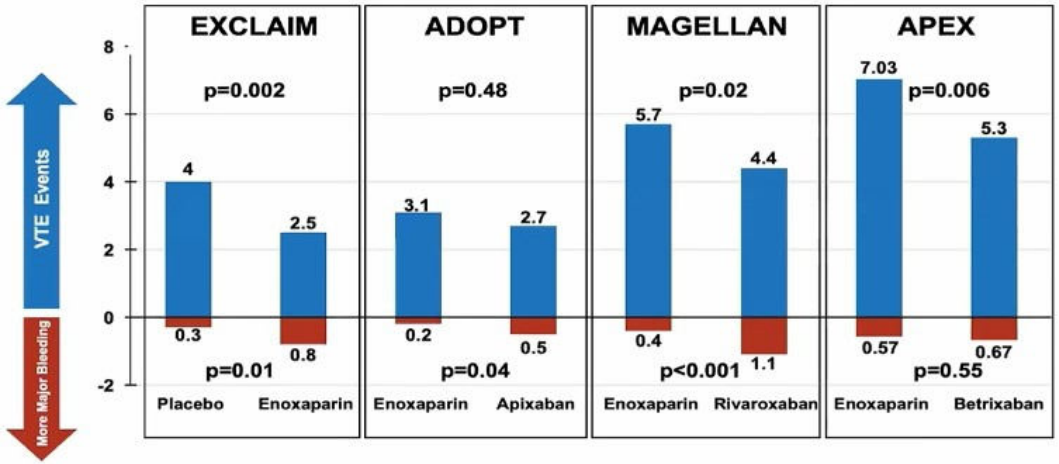
WORLD THROMBOSIS DAY
13 OCTOBER

Thrombosis UK

Extended thromboprophylaxis in medical patients (60% of hospital-associated VTE occur post discharg

Trials Of Extended Thromboprophylaxis In Acute Medically Ill Patients

VTE events (symptomatic and proximal asymptomatic)



MARINER trial (low dose rivaroxaban) excluded as only measured symptomatic & fatal VTE

WORLD THROMBOSIS DAY
13 OCTOBER

Thrombosis UK

ISTH 2020 VIRTUAL CONGRESS
JULY 12-14
ISTH2020.ORG

#ISTH2020

Criteria for extending prophylaxis?

Spyropoulos AC et al TH Open 2020: e59

- **Age ≥ 75 y or**
- **Past history of cancer or VTE or**
- **EXtra risk factors***
- *Known risk factors for VTE including: D-dimers ≥ 2 upper limit of normal range, Intensive Care Unit stay, or 2 other factors such as past history of superficial VT, obesity, varicose veins, chronic venous insufficiency, lower extremity paresis, hormone therapy, thrombophilia (congenital or acquired), concomitant use of erythropoiesis stimulating agents
- ** planned admission >2 days, but none of the admission criteria listed in the moderate risk group consider on a case by case basis

WORLD THROMBOSIS DAY
13 OCTOBER

Thrombosis UK

DVR

journal of thrombosis and haemostasis™

RECOMMENDATIONS AND GUIDELINES | Free Access

Scientific and Standardization Committee Communication: Clinical Guidance on the Diagnosis, Prevention and Treatment of Venous Thromboembolism in Hospitalized Patients with COVID-19

Alex C. Spyropoulos ✉, Jerrold H. Levy, Walter Ageno, Jean Marie Connors, Beverley J Hunt, Toshiaki Iba , Marcel Levi, Charles Marc Samama, Jecko Thachil, Dimitrios Giannis, James D. Douketis, on behalf of The Subcommittee on Perioperative, Critical Care Thrombosis, Haemostasis of the Scientific, Standardization Committee of the International Society on Thrombosis, Haemostasis+

... See fewer authors ^

First published:27 May 2020 | https://doi.org/10.1111/jth.14929

ISTH

ISTH 2020 JULY 12-14 VIRTUAL CONGRESS ISTH2020.ORG

#ISTH2020

Journal Pre-proof

Prevention, diagnosis and treatment of venous thromboembolism in patients with COVID-19: CHEST Guideline and Expert Panel Report

Lisa K. Moores, MD, Tobias Tritschler, MD, MSc, Shari Brosnahan, MD, Marc Carrier, MD, Jacob F. Collen, MD, Kevin Doerschug, MD, MS, Aaron B. Holley, MD, David Jimenez, MD, PhD, Gregoire LeGal, MD, PhD, Parth Rali, MD, Philip Wells, MD

PII: S0012-3692(20)31625-1

DOI: https://doi.org/10.1016/j.chest.2020.05.559

Reference: CHEST 3241

To appear in: *CHEST*

Received Date: 9 May 2020

Revised Date: 20 May 2020

Accepted Date: 26 May 2020

ISTH guidance: Thromboprophylaxis in hospitalised COVID-19

a)A universal strategy of routine thromboprophylaxis with standard-dose UFH or LMWH should be used after careful assessment of bleeding risk, with LMWH as the preferred agent.

Intermediate-dose LMWH may also be considered (30% of respondents)

b) VTE prophylaxis recommendations should be modified based on extremes of body weight

c) Treatment-dose heparin should not be considered for primary prevention until the results of randomized controlled trials are available.

d) **Multi-modal thromboprophylaxis with mechanical methods** (i.e., intermittent pneumonic compression devices) should be considered

DVR

CHEST guidance: Thromboprophylaxis in hospitalised COVID-19 p

In acutely ill hospitalized patients with COVID-19, we recommend current standard dose anticoagulant thromboprophylaxis over intermediate (LMWH BID or increased weight-based dosing) or full treatment dosing, per existing guidelines.

Remarks: Although there has been some concern for increased risk of VTE in hospitalized COVID-19 patients, there is insufficient data to justify increased intensity anticoagulant thromboprophylaxis in the absence of randomised controlled trials.

In critically ill patients with COVID-19, we suggest current standard dose anticoagulant thromboprophylaxis over intermediate (LMWH BID or increased weight-based dosing) or full treatment dosing, per existing guidelines.

Remarks: Although there is anecdotal and observational data that suggest an increased VTE risk in critically ill patients with COVID-19, it is not clear if the most severely ill COVID-19 patients occupy a different level of risk for VTE than other severely ill nonsurgical, medical ICU patients. There is also insufficient data regarding bleeding risk in this population, and given severity of illness, it may be just as likely that critically ill COVID-19 patients are at high risk of adverse bleeding complications. Finally, it is not clear that this population has a higher risk of VTE when treated with standard doses of anticoagulant thromboprophylaxis per existing guidelines.

CHEST guidance: Thromboprophylaxis in hospitalised COVID-19 p

In critically ill patients with COVID-19, we suggest against the addition of mechanical prophylaxis to pharmacological thromboprophylaxis.

Remarks: Although there is no evidence supporting the combination of mechanical and pharmacological thromboprophylaxis for patients with COVID-19 who are critically ill, it is not likely that adding mechanical prophylaxis in this population would cause major harm. We recommend that providers adhere to existing guidance regarding the use of mechanical thromboprophylaxis.

Duration of thromboprophylaxis in hospitalised patients with C pneumonia

ISTH

a) Either LMWH (30%) or a DOAC (i.e., rivaroxaban or betrixaban 30% of respondents) can be used for extended-duration thromboprophylaxis.

b) Extended post-discharge thromboprophylaxis should be considered for all hospitalized patients with COVID-19 that meet high VTE risk criteria.

- The duration of post-discharge thromboprophylaxis can be approximately 14 days at least (50% of respondents), and up to 30 days (20% of respondents).

CHEST

In patients with COVID-19, we recommend inpatient thromboprophylaxis only over inpatient plus extended thromboprophylaxis after hospital discharge.

Remarks: Extended thromboprophylaxis in patients with COVID-19 at low risk of bleeding should be considered, if emerging data on the post-discharge risk of VTE and bleeding indicate a net benefit of such prophylaxis.

Action Card (v1-0)

T5-8: Haematological management of patients in ICU with COVID-19

Objective: To provide basic guidance for common haematological issues in patients with confirmed or suspected COVID-19 who are being cared for in an ICU environment

Routine haematological management

ALL ITU AREAS

1. **Check haemoglobin**
   - ⊃ If <70g/l give single unit red cell transfusion and re-check
2. **Check platelet count**
   - ⊃ If <20x10⁹/l give one pool of platelets and re-check
3. **Check coagulation results**
4. **Check thromboprophylaxis**
   - ⊃ Check if special circumstances apply (see *special circumstances*)
   - ⊃ If special circumstances apply end steps on this card

— OTHERWISE —

5. **Check creatinine clearance**
   - ⊃ If >30ml/min prescribe LMHW per Thromboprophylaxis dose LMWH (see *thromboprophylaxis doses*)
   - ⊃ If ≤30ml/min prescribe unfractionated heparin 5000iu S/C TDS

General principles

Minimise phlebotomy use
- Avoid excessive blood sampling; take arterial samples not more than four hourly
- Use approved COVID order sets on EPR

Choice of Agent
- LMWH is preferred; fondaparinux if no supply of LMWH available

Special circumstances

AF or previous VTE
- If AF or previous VTE which was >90 days ago, no special circumstances apply
- If VTE ≤ 90 days ago, prescribe treatment dose LMHW

Active bleeding
- Correct abnormal results

Planned procedures
- See *Target parameters for procedures*

Thromboprophylaxis dosing

Actual weight (kg)	Dalteparin
<49	2500iu OD
50-99	5000iu OD
100-139	7500iu OD
140-180	5000iu BD

Target parameters for procedures

Central line/arterial line insertion
- Platelets transfusion required if <20x10⁹/l; experienced operator if <50x10⁹/l

Central line/arterial line removal
- Do not remove until platelets >50x10⁹/l; if urgent removal is indicated, platelet transfusion required

Chest drain or tracheostomy insertion
- INR <1.5 / APTTr <1.5
- Fibrinogen >1.5g/l
- Platelet count >80x10⁹/l

THIS DOCUMENT UNDERWENT FAST-TRACKED APPROVAL AT DIRECTORATE LEVEL FOR COVID-19 RESPONSE

Action Card (v1-0)
March 2020

thrombosis UK

WORLD THROMBOSIS DAY
13 OCTOBER

ISTH 2020 VIRTUAL CONGRESS
JULY 12-14
ISTH2020.ORG

#ISTH2020

Unanswered Qs in thrombosis & thromboprophylaxis in C infection

Rates & nature of thromboembolism

- What are the rates of VTE in all stages of COVID-19, so far we only have snapshots of rates of hospitalized patients
- What are the current rates of VTE in critically ill patients?
- Are the rates of thrombosis higher than other patients on critical care especially can we compare with non-COVID-19 viral pneumonia?
- What are the rates of immunothrombosis?
- Will rates of immunothrombosis be reduced by the universal use of dexamethasone?
- Can we differentiate immunothrombosis from PE?
- What is the role of the platelet in COVID-19 thromboembolism

Thromboprophylaxis

- Is weight adjusted thromboprophylaxis better than empirical dosing? (Many trial excluded high weight individual AND obesity rates have ⇧ since trials)
- Would a higher dose of thromboprophylaxis be beneficial without significantly increasing bleeding risk?
- Should we add in intermittent pneumatic compression?
- Should we give extended thromboprophylaxis?
- Will anticoagulation help immunothrombosis?
- When will the international trials produce results?

WORLD THROMBOSIS DAY
13 OCTOBER

Thrombosis UK

What is the role of clinicians with thrombosis expertise?

Ongoing / planned trials

Study	Patients	Intervention	Control	Follow-up	Outcome
RAPID COVID COAG (Canada)	N=462	Therapeutic heparin	Low-dose heparin	28 days	ICU/mortality
CORIMUNO19-COAG (France)	N=808	Therapeutic heparin	Low-dose heparin	28 days	Survival without ventilation
COVID-HEP (Switzerland)	N=200	Therapeutic heparin	Low-dose heparin	30 days	Thrombosis
ATTACC (Canada)	N=3,000	Therapeutic heparin	Low-dose heparin	30 days	Intubation or mortality
COVI-DOSE (France)	N=602	Therapeutic heparin	Low-dose heparin	28 days	VTE
s20-00479 (USA)	N=1,000	Therapeutic heparin	Low-dose heparin	1 year	Mortality
IMPROVE (USA)	N=100	Intermediate-dose heparin	Low-dose heparin	30 days	Thrombosis
X-Covid 19 (Italy)	N=2,712	Intermediate-dose heparin	Low-dose heparin	30 days	VTE

WORLD THROMBOSIS DAY
13 OCTOBER

Thrombosis UK

ISTH 2020 JULY 12-14 VIRTUAL CONGRESS
ISTH2020.ORG

#ISTH2020

What is the role of clinicians with thrombosis expertise?

To enter as many patients as possible into clinical trials assessing thromboprophylaxis

Ongoing / planned trials

Study	Patients	Intervention	Control	Follow-up	Outcome
RAPID COVID COAG (Canada)	N=462	Therapeutic heparin	Low-dose heparin	28 days	ICU/mortality
CORIMUNO19-COAG (France)	N=808	Therapeutic heparin	Low-dose heparin	28 days	Survival without ventilation
COVID-HEP (Switzerland)	N=200	Therapeutic heparin	Low-dose heparin	30 days	Thrombosis
ATTACC (Canada)	N=3,000	Therapeutic heparin	Low-dose heparin	30 days	Intubation or mortality
COVI-DOSE (France)	N=602	Therapeutic heparin	Low-dose heparin	28 days	VTE
s20-00479 (USA)	N=1,000	Therapeutic heparin	Low-dose heparin	1 year	Mortality
IMPROVE (USA)	N=100	Intermediate-dose heparin	Low-dose heparin	30 days	Thrombosis
X-Covid 19 (Italy)	N=2,712	Intermediate-dose heparin	Low-dose heparin	30 days	VTE

WORLD THROMBOSIS DAY
13 OCTOBER

Thrombosis UK

In the UK we only have access to the pandemic platform s

Traditional Trial Design

	Drug A
Population 1	

- Single treatment
- (Ideally) homogeneous population

Basket Trial Design

	Drug A
Population 1	
Population 2	
•••	
Population N	

- Single treatment
- Multiple sub-populations of interest (disease severity, biomarkers, demographic characteristics)

Platform Trial Design

	Drug A	Drug B	•••	Drug K
Population 1				

- Multiple treatments
- Can adaptively drop (or add) treatment arms

Platform (Umbrella) Trial Design

	Drug A	Drug B	•••	Drug K
Population 1				
Population 2				
•••				
Population N				

WORLD THROMBOSIS DAY
13 OCTOBER

Thrombosis UK

ISTH 2020 VIRTUAL CONGRESS
JULY 12-14
ISTH2020.ORG

#ISTH2020

DVR

Research into moderate & severe COVID19 25th June 2020

PRACTICE C: RANDOMIZED, EMBEDDED, MULTIFACTORIAL, ADAPTIVE PLATFORM TRIAL SEVERE CAP –WORKPACKAGE 5

REMAP-CAP
Randomized, Embedded, Multifactorial Adaptive Platform trial for Community-Acquired Pneumonia

Already had an anticoagulation arm (full-dose heparin Vs standard of care
Anti-platelet arm being designed

Has yielded vital information about the benefits of dexamethasone

WORLD THROMBOSIS DAY
13 OCTOBER

Thrombosis UK

ISTH 2020 JULY 12-14 VIRTUAL CONGRESS
ISTH2020.ORG

#ISTH2020

Thank you for listening

Special thanks to
-Mike Desborough, Karen Breen, Andy Retter & Andy Doyle
-the wonderful clinicians I work with on wards and critical care
-all on the committee of the SSC in Perioperative Care group

WORLD THROMBOSIS DAY
13 OCTOBER

Thrombosis UK

Thank you for listening

Special thanks to
-Mike Desborough, Karen Breen, Andy Retter & Andy Doyle
-the wonderful clinicians I work with on wards and critical care
-all on the committee of the SSC in Perioperative Care group

NOT EVERYTHING IS COVID-19
"I am 27 and just spent the last three weeks in hospital with a severe PE and DVT.
Unfortunately, I had spent weeks in pain but because I had a slight cough and severe breathlessness
and my doctor assumed it was COVID even though I had tested negative. I spent weeks in and out of pain,
I think we spoke to the doctor about six times in total and then one day I woke up very breathless with a swollen leg.
I was rushed to A&E in a critical condition and the amazing team at the Hospital worked hard to help me fight this.
I am now on crutches unable to walk very far and at home resting up.
Before all of this, I was training for a half marathon and had run 9 miles about 3 weeks before going in.
I was crazily into my fitness doing training and weight lifting as well as horse riding.
It's going to be a long recovery and I just wished that in all of those calls and even when my doctor saw me
they would of #ThinkThrombosis. It's scary to think what could of happened if I didn't make it to the hospital!"

WORLD THROMBOSIS DAY
13 OCTOBER

Thrombosis UK

ISTH 2020 JULY 12-14 VIRTUAL CONGRESS
ISTH2020.ORG

#ISTH2020