



Thrombosis Canada

Thrombose Canada



Thrombosis & COVID-19: Canadian Expert Perspectives

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Relationships with commercial interests:

Grants/Research Support: Amgen, Boehringer Ingelheim, AstraZeneca, BMS, Lilly, Sanofi, Akcea

Speakers Bureau/Honoraria: Amgen, BMS, Janssen, AstraZeneca, Novartis, Pfizer, Bayer, Lilly, Boehringer Ingelheim, HLS Therapeutics, Spectrum Therapeutics, Sanofi, Bausch Health

Consulting Fees: N/A

Other: Shares of most pharma companies in personal investment portfolio

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Relationships with commercial interests:

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Other: All speaking and ad board fees direct to Calgary Health Trust Emergency Med Research Fund

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- Bayer Canada
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- Novartis Pharmaceuticals Canada
- Pfizer Canada
- Servier Canada



Mitigating potential bias

The agenda and faculty for this program was developed by the scientific steering committee from Thrombosis Canada. All faculty have been directed that any recommendations involving clinical medicine are to be based on evidence that is accepted within the profession; and all scientific research referred to, reported, or used in the CME/CPD activity in support or justification of patient care recommendations conforms to the generally accepted standards.



Program learning objectives

After attending this program, participants will be able to:

- Incorporate the latest information about thrombosis and COVID-19 into clinical practice;
- Effectively manage anticoagulants and thrombosis remotely;
- Discuss the hematologic coagulopathic issues around COVID-19.

Agenda

Primary care perspective	Impacts of COVID-19 on primary care	Alan Bell, MD
Internist perspective	Current state of COVID-19	Jim Douketis, MD
Hematologist perspectives	Hematologic and coagulopathic issues in COVID-19	Eric Tseng, MD
	Managing your thrombosis patient remotely	Deepa Suryanarayan, MD
	Managing anticoagulants, especially VKAs, remotely	Sudeep Shivakumar, MD
Emergency medicine perspective	Impact of COVID-19 in the ER	Eddy Lang, MD
Question period		Alan Bell, MD, moderator



Introduction and primary care perspective



Alan Bell, MD, CFPC, FCFP

The Challenge

- COVID-19 has re-defined provision of primary care
- Diagnosis and management of thrombotic diseases and other conditions requiring anticoagulant management presents specific challenges
 - Virtual visits often preclude detailed examination helpful for diagnosis of VTE
 - Emergency rooms are under increased burden and potential sources of exposure
 - INR monitoring potentially exposes patients to COVID-19 exposure
 - COVID-19 infection is associated with thrombotic and bleeding complications¹

DIC, disseminated intravascular coagulation; INR, international normalization ration; VTE, venous thromboembolism

1. Thachil J et al. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. ISTH Academy 03/25/20; 290506 <https://doi.org/10.1111/jth.14810>



Thrombosis Canada has been the voice of Thrombosis Medicine in Canada since 1991

Our vision

- We believe that providing point-of-care clinical guidance, founded on national and international guidelines, is the most effective and cost-efficient way to improve patient safety and outcomes, within a framework of patient-centred values and preferences.
- We continue with this mandate to assist health care professionals through this pandemic



Solutions



Thrombosis Canada

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DEDICATED TO FURTHERING EDUCATION & RESEARCH IN THROMBOTIC DISEASE

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CLINICAL GUIDES

Thrombosis Canada has developed practical and actionable guides related to the treatment and management of thrombosis.

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Solutions

TOOLS

Algorithms
Anticoagulant Dosing In Atrial Fibrillation
Perioperative Anticoagulant Management Algorithm
Acute Management Algorithms
Atrial Fibrillation
Bleed Management
Deep Vein Thrombosis
Pulmonary Embolism
Checklists
DOAC Follow-up
Calculators
CHADS2 Score for Atrial Fibrillation Stroke Risk
CHA2DS2-VASc Score for Atrial Fibrillation Stroke Risk
Creatinine Clearance

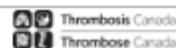
Deep Vein Thrombosis

Does the patient have massive iliofemoral DVT (eg phlegmasia)?

- Yes
- No

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Reset

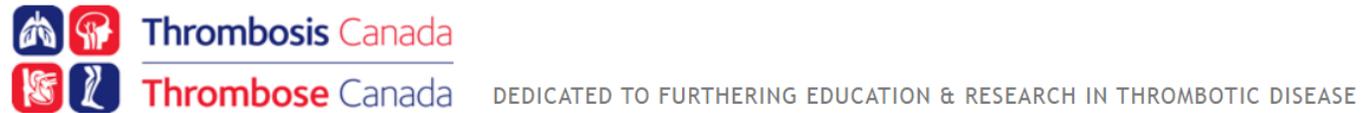


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Solutions: COVID-19

<https://thrombosiscanada.ca/covid-19/>



About Us	Clinical Guides	Clinical Tools	Resources	Patient & Family	News	Events	Search...	Q
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CLINICAL RESOURCE LINKS

New! COVID-19 Pandemic Support

Links to Relevant Resources to Support Office-based and Remote (Virtual)
Thrombosis Assessment and Management

[Register for our webinar on Thrombosis & COVID-19: Canadian Expert Perspectives: Click Here](#)

Frequently Asked Questions Document

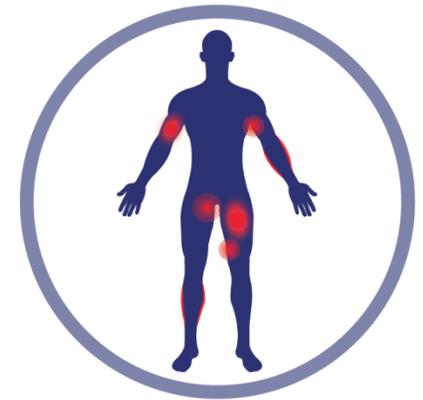
- [Download here](#)

Anticoagulant Management

- [NOACs: Management of Bleeding](#)

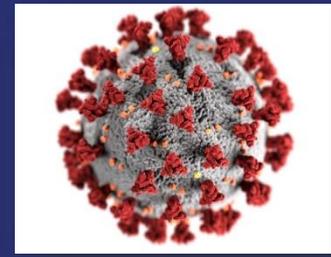


Where we're at with COVID-19: internist perspective



Jim Douketis, MD, FRCPC

Where we're at with COVID-19



Epidemiology

- Epidemiologic data available at: www.who.int, www.cdc.gov, www.ecdc.europa.eu
- April 10, 2020:
 - ~1,650,000 cases and >100,000 deaths worldwide
 - >21,000 cases and >500 deaths in Canada



Etiology

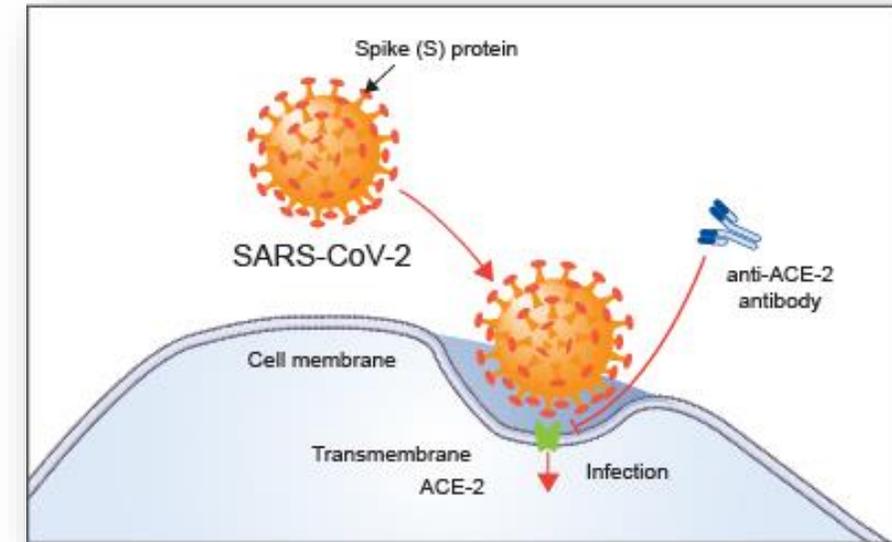
- Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), RNA virus that belongs to the *betacoronavirus* (betaCoV) genus
- Genus also includes SARS-CoV (responsible for epidemic in 2002-3)



Where we're at with COVID-19

Pathogenesis

- Virus uses ACE-2 as receptor, binding to spike glycoprotein on viral envelope
- In response to viral antigens, immune cells release pro-inflammatory cytokines and chemokines, results in uncontrolled systemic inflammatory response

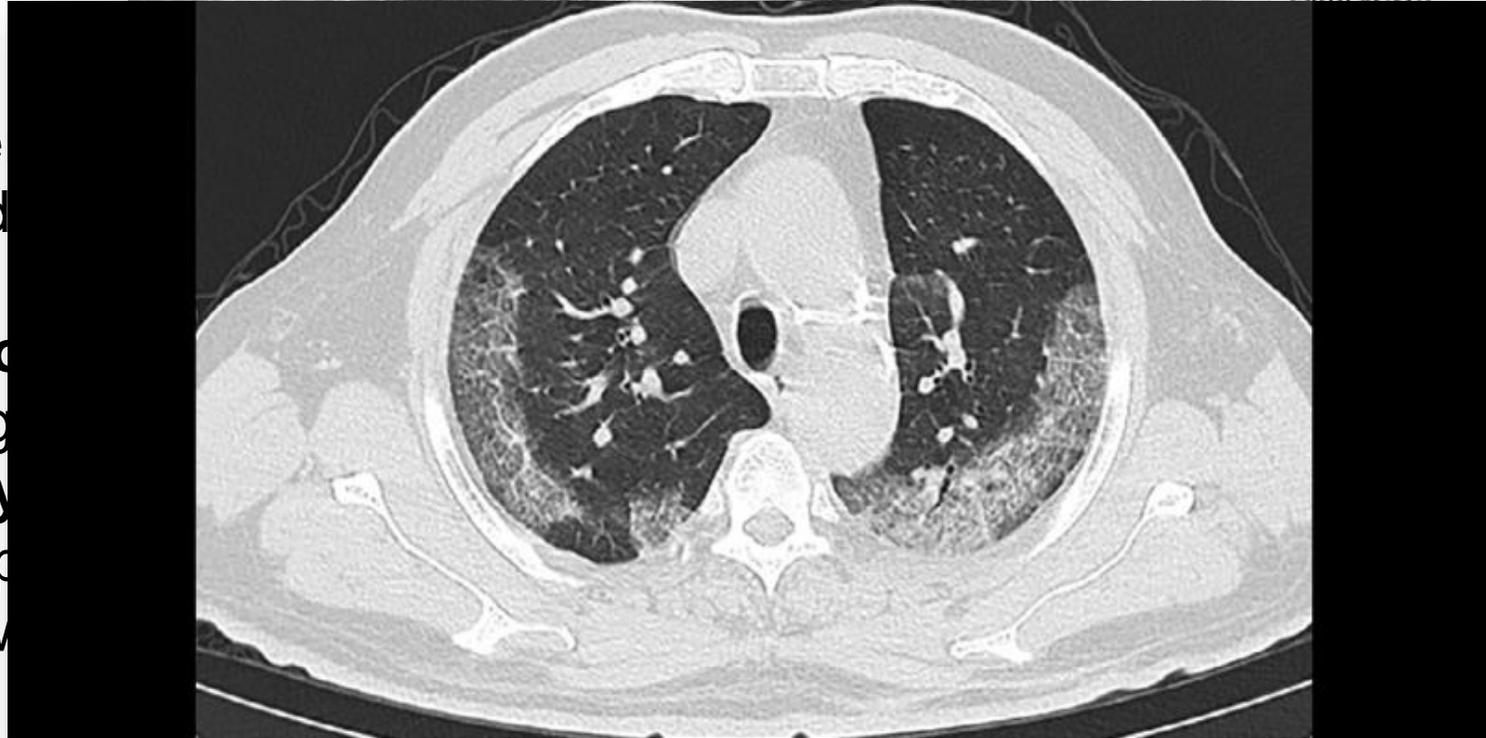


Incubation and contagious period

- Incubation period = **2-14 days** (mean = **5 days**)
- Viral shedding highest **~10 days** from time of infection (longer if severe infection)
- Mild infection recovery within **1 week** (up to 2 weeks)
- Severe infection recovery after **3-6 weeks**



Where we're at with COVID-19



Diagnosis

- Detection of genetic material (in nasopharyngeal swabs, sputum, urine, blood, and stool)

Clinical and radiologic findings

- Fever, dry cough
- **Unexpected symptoms**
- **CXR:** bilateral perihilar opacification (w/ consolidation)

Differential Diagnosis

- Influenza, other viral respiratory infections
- Atypical pneumonia
- Pneumocystosis

tract (intubated)

or septic)

s, ground-glass



Where we're at with COVID-19



Testing, testing

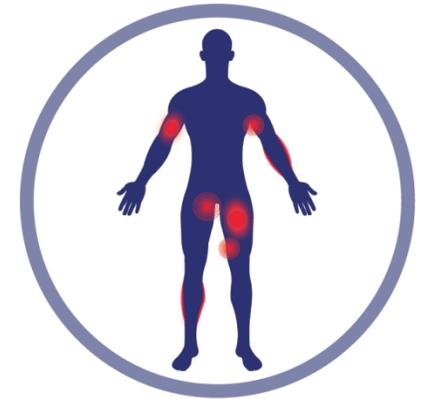
Promising drugs to treat covid-19

Drug	Current use	Original mode of action	Being tested?
Chloroquine	Antimalarial	Heme polymerase inhibitor	Yes
Kaletra (ritonavir + lopinavir)	HIV	Protease inhibitor	Yes
Interferon alfa-2b	Hepatitis-C	Immune modulator	Yes
Remdesivir	Experimental	Nucleotide analogue	Yes
Favipiravir	Influenza	RNA polymerase inhibitor	Yes
Actemra (tocilizumab)	Rheumatoid arthritis; covid-19	Anti-inflammatory	Approved*
Kevzara (sarilumab)	Rheumatoid arthritis	Anti-inflammatory	Trials expected

Source: WHO, adapted from landscape analysis, 17th February 2020

*For use on covid-19 in China, March 2020

Hematologic/coagulopathic issues in COVID-19: hematologist perspective



Eric Tseng, MD, MScCH, FRCPC

COVID coagulopathy: main messages

1. **Severe COVID infection** is likely a hypercoagulable state, although the prevalence of acute VTE remains uncertain
2. **Elevations in D-dimer are frequently seen**, are associated with mortality, and may reflect either a proinflammatory or hypercoagulable state
3. All admitted COVID+ patients should receive standard weight-adjusted VTE prophylaxis; there are **insufficient data at this juncture to recommend intensified empiric prophylaxis regimens** (for high D-dimer, ICU patients) outside of clinical trials



Common hematology lab abnormalities in COVID-19

Parameter	Trend in COVID-19	Clinical Significance
Platelets	20-30% have platelets 100-150	Not clearly associated with mortality
Lymphocytes	Often moderate to severe lymphopenia 75-83% have ALC < 1.5	Severe lymphopenia (ALC < 0.5) and LDH elevation often seen in critical illness
PT (prothrombin time)	Mild prolongations (15-16 sec)	Prognostic (some association with mortality)
D-Dimer	Persistent, marked elevations (4-6x ULN) often seen in severe COVID	Prognostic (associated with mortality)
Fibrinogen	Typically elevated until late in disease course	Reductions can be seen late (10-14 days) into admission

Bhatraju PK, et al. *NEJM*. 2020;0(0):null. doi:[10.1056/NEJMoa2004500](https://doi.org/10.1056/NEJMoa2004500)

Guan W, et al. *NEJM*. 2020;0(0):null. doi:[10.1056/NEJMoa2002032](https://doi.org/10.1056/NEJMoa2002032)

Tang Y-W, et al. *J Clin Microbiol*. April 2020. doi:[10.1128/JCM.00512-20](https://doi.org/10.1128/JCM.00512-20)

Fan BE, et al. *Amer J Hematol*. n/a(n/a). doi:[10.1002/ajh.25774](https://doi.org/10.1002/ajh.25774)



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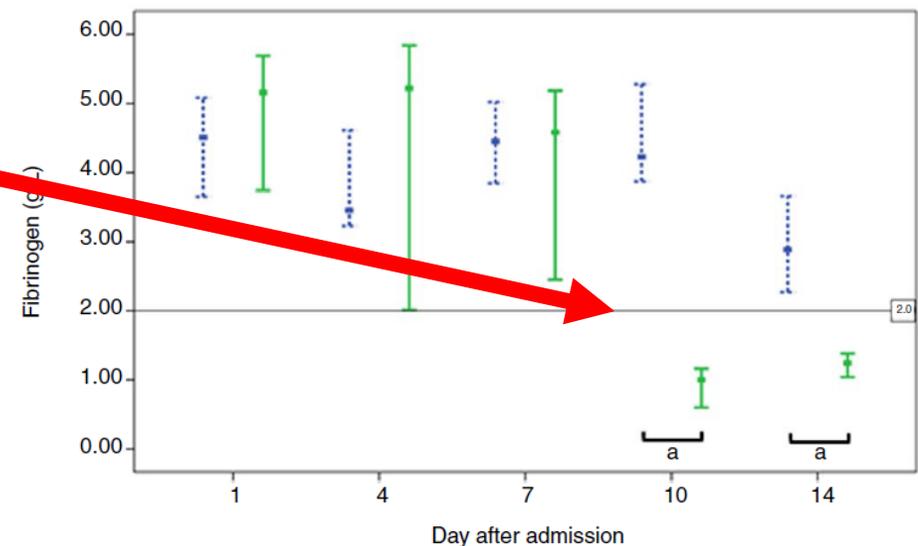
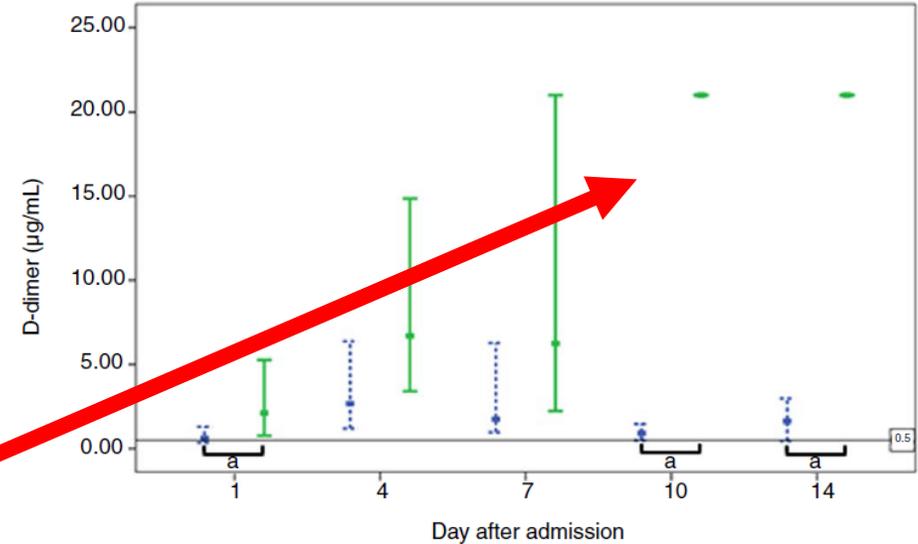
The coagulopathy of COVID has some features of DIC

Coagulation parameters on admission (Wuhan)

Parameter	Normal	Survivors (n = 162)	Non-Survivors (n = 21)
PT (sec)	11.5-14.5	13.6	15.5
aPTT (sec)	29.0-42.0	41.2	44.8
D-dimer (mcg/ml)	<0.50	0.61	2.12
Fibrinogen (g/L)	2.0-4.0	4.51	5.16

Guan et al. (Wuhan): among 1,099 COVID+ patients

- 46% had elevated D-dimer on presentation
- 70% requiring ICU/intubation had elevated D-dimer



It is unclear whether high D-dimers in COVID19 reflect hypercoagulable state or underlying inflammatory state

- D-dimer is a non-specific acute phase reactant
- Elevated in non-COVID pneumonia and other causes of SIRS/sepsis

Parameters	Normal range	COVID (n=449)	Non-COVID (n= 104)	<i>P</i> values
Coagulation parameters				
PT (sec)	11.5–14.5	15.2 ± 5.0	16.2 ± 5.2	0.068
Platelet count (× 10 ⁹ /L)	125–350	215 ± 100	188 ± 98	0.015
D-dimer (µg/mL)	< 0.5	1.94 (0.90–9.44)	2.52 (1.40–5.81)	0.140



Severe COVID is likely a hypercoagulable state marked by high D-dimers and fibrinogen

- Limited pathologic studies suggest that pulmonary microvascular thrombosis may play a role in progressive respiratory failure
- Early data suggests high rates of VTE in the absence of pharmacological prophylaxis

Luo et al. Lung biopsy COVID+ (2020)

- Pulmonary interstitial fibrosis
- Hemorrhagic pulmonary infarction
- Small vessel hyperplasia, luminal stenosis, **microthrombosis**

Cui et al. (Union Hospital, Wuhan)

- 81 ICU COVID patients
- Screened with CT chest, leg US, D-dimer
- None received pharmacologic prophylaxis
- **20/81 (25%) had lower extremity DVT**
- D-dimer cutoff of 1.5 mcg/mL had sens 85%, spec 89%, NPV 95%



Preliminary data suggests high VTE rates despite standard pharmacological prophylaxis

ICU COVID patients in 3 Dutch hospitals (n = 184)

38% coagulopathic, 13% RRT, 9% therapeutic anticoagulation, 3% active cancer

No screening US – imaging triggered by clinical suspicion

LMWH prophylaxis with low-dose LMWH (Nadroparin 2850 IU daily) with weight adjustment for > 100 kg (5700 IU daily)

After Mar 30/Apr 4, dose adjusted to 5700 IU daily or twice daily

Cumulative incidence of thrombosis during admission (many still in ICU)

Cumulative incidence of thrombosis was 31% (95% CI, 20-41%)

- 25 (81%) PE – 18 segmental or higher, 7 subsegmental only
- 1 leg DVT, 2 catheter-related DVT, 3 ischemic stroke

Independent predictors of thrombotic complications

- Coagulopathy aHR 4.1 (95% CI, 1.9-9.1) = PT > 3 sec, aPTT > 5 sec (no patients developed DIC)



There is no established association between COVID with antiphospholipid antibodies or stroke

CORRESPONDENCE

Coagulopathy and Antiphospholipid Antibodies in Patients with Covid-19

- Case series of three patients with multiple ischemic strokes during admission
- All three had CV risk factors
- None had high-risk APL serology or persistent positivity (*lupus anticoagulant negative; (+) ACL IgA, B2GP1 IgA and IgG; no titres*)



Presumptive diagnosis and treatment of VTE

If CT-PA or V/Q scan cannot be performed (*isolation or instability*)

- Clinical suspicion or traditional VTE risk factors
- *Alternative modalities*: bedside echo, bilateral CUS, POCUS

When to consider empiric therapeutic anticoagulation?

1. **Unexpected clinical deterioration** despite overall improvement in inflammatory markers, chest imaging (especially if high D-dimer or fibrinogen)
2. **Physical exam findings**
 - VTE (SVT, calf swelling, catheter- or dialysis line-related thrombosis)
 - Microvascular ischemia (peripheral cyanosis)



Efficacy of anticoagulant prophylaxis

Severe COVID+ inpatients (n = 449)

39% hypertension, 21% diabetes, 9% heart disease

All had supportive therapy
22% SIC score ≥ 4

Severe COVID: RR > 30,
PaO₂ 93%, P/F < 300 mm Hg

22% (n = 99) VTE proph:

- Enoxaparin 40-60 mg/day (n = 94)
- SC UFH 10,000-15,000 units/day (n = 5)

Mortality at 28 days
(retrospective)

No difference in 28-day mortality for heparin vs. non-heparin users (30.3% vs. 29.7%)

Heparin associated with reduced mortality if:

- **D-Dimer > 6x ULN** (32.8% vs. 52.4%, OR 0.44, p = 0.017)
- **SIC ≥ 4** (40.0% vs. 64.2%, OR 0.37, p = 0.029)

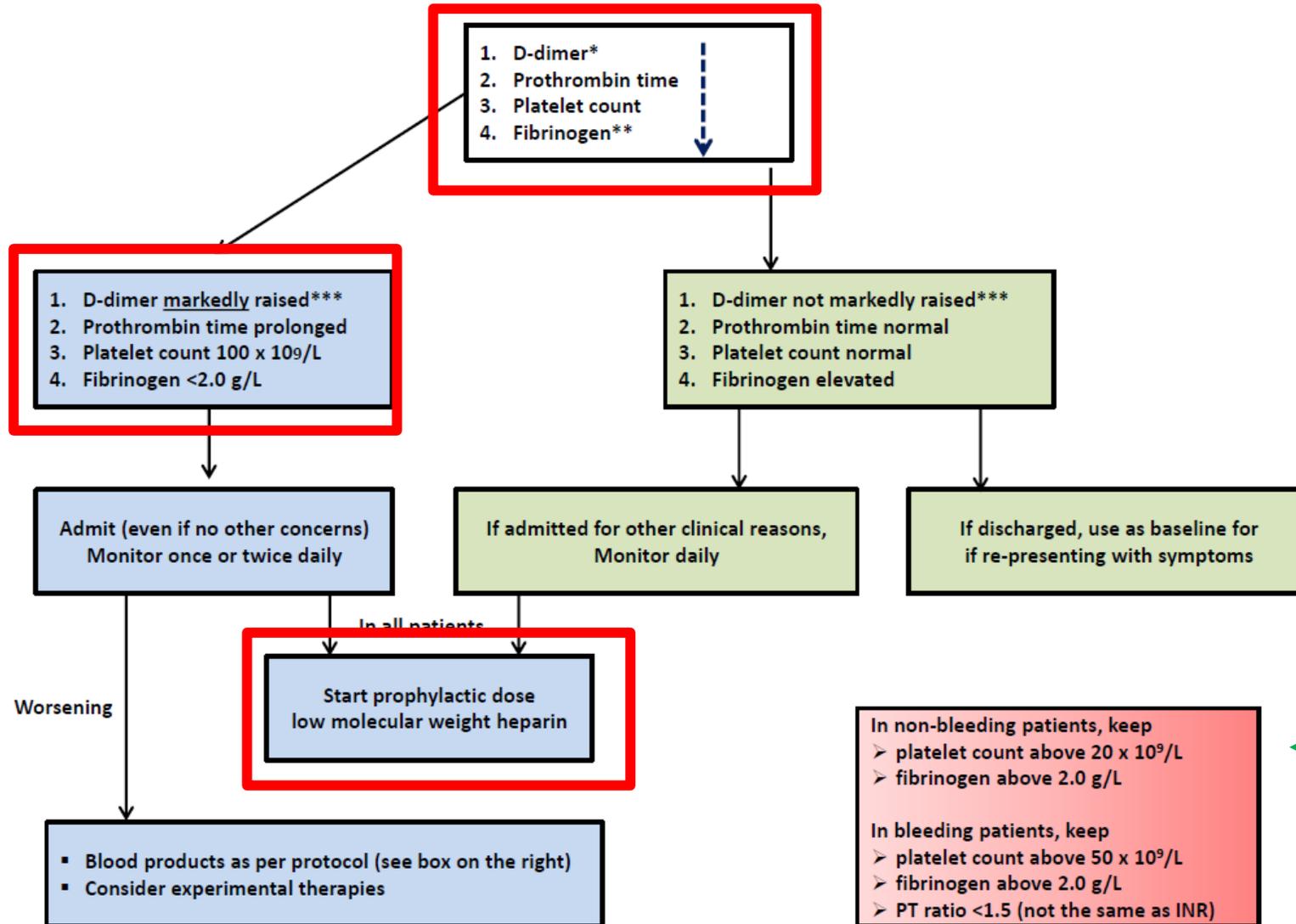


Anticoagulant prophylaxis for COVID: what to do?

- Some institutions have protocols using intermediate or therapeutic dose LMWH if elevated D-dimer – these are empiric and **currently** lack supporting clinical data
- **All patients admitted to hospital (ward or ICU) with COVID, regardless of D-dimer, should receive standard LMWH prophylaxis**
 - Consider dose adjustment in obese patients (>100-120 kg or BMI > 30)
- Efficacy of **intermediate or therapeutic dosing based on D-dimer, ICU setting, or mechanical ventilation** is unclear but generally not recommended outside of clinical trial setting



Interim guidance from the ISTH



Not evidence based
Blood bank resources?



In non-bleeding patients, keep
 > platelet count above 20 x 10⁹/L
 > fibrinogen above 2.0 g/L

 In bleeding patients, keep
 > platelet count above 50 x 10⁹/L
 > fibrinogen above 2.0 g/L
 > PT ratio <1.5 (not the same as INR)

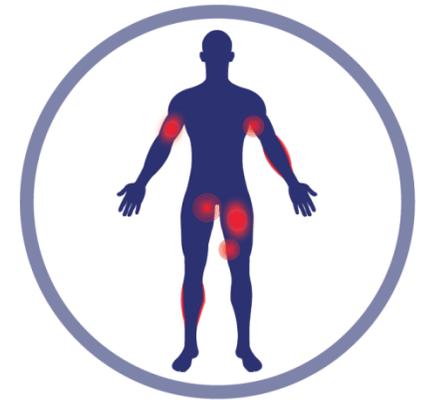


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3. All admitted COVID+ patients should receive standard weight-adjusted VTE prophylaxis; there are **insufficient data at this juncture to recommend intensified empiric prophylaxis regimens** (for high D-dimer, ICU patients) outside of clinical trials



Managing your thrombosis patient remotely in the COVID era: hematologist perspective



Deepa Suryanarayan, MD, MSc, FRCPC

The unique challenges and considerations

- We have a responsibility to ensure anticoagulant care does not contribute to the burden on hospital health system
- Continue to keep patients on anticoagulants as safe as possible
- Change the way we deliver anticoagulation therapy by optimizing local solutions while protecting resources



Categories of patients

- Patients requiring initiation of oral anticoagulation
- Patients already on anticoagulation: DOACs
- Patients already on anticoagulation: VKAs



Patients requiring initiation of oral anticoagulation

- Ideally initiated by clinicians in primary care with experience in managing anticoagulation
- Seek guidance by telehealth or phone a specialist where needed
- Where possible, move to remote consultations to initiate anticoagulation therapy with arrangement of phone follow up
- Where possible, and if there are no contraindications, consider initiating DOACs instead of warfarin to minimize monitoring
- For patients who are not candidates for DOAC, consider LMWH (will need to educate patient regarding self injections)



Patients requiring initiation of oral anticoagulation

- If warfarin is the only choice and monitoring is not possible, consider LMWH for a brief period with modifications for monitoring
- Try to provide prescriptions for 90 days where possible with electronic prescription, or provide prescription directly to community pharmacies
- Local pharmacies will need to be aware of likely increase usage of DOACs and provincial pharma care plans urged to consider covering DOACs given the exceptional health care crisis.



Patients already on anticoagulation – DOACs

- Is anticoagulation still required?
- Utilize options for remote monitoring such as telehealth visits, video or telephone visits for follow ups
- During remote follow up: enquire about bleeding symptoms, check adherence and any potential drug interactions
- Avoid repeat labs if previously stable and if it is unlikely to have significant clinical impact



Patients already on anticoagulation – DOACs

- Encourage patients to avoid presenting to the emergency room for minor bleeding issues that can be addressed at home or with phone support. These include minor cuts, bruises, and nosebleeds.
- The Michigan Anticoagulation Quality Improvement Initiative (MAQI2) has online resources for patients on how manage many common minor bleeding issues at home: <https://anticoagulationtoolkit.org/patients>
- Seek specialist support should there be any concerns

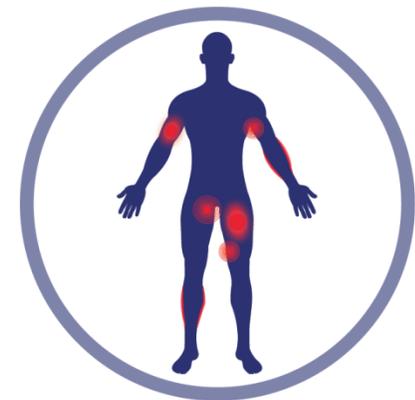


Patient on chronic anticoagulation with mild form of COVID-19

- May present with diarrhea and decreased oral intake
- May affect INR
- DOACs: likely minimal effect unless diarrhea is significant



Managing anticoagulants, especially VKAs, remotely: hematologist perspective



Sudeep Shivakumar, MD, FRCPC

Managing anticoagulants, especially VKAs, remotely

- Warfarin management requires frequent bloodwork for INR monitoring
- Many patients worried about risk of getting bloodwork
 - Requires trip outside the house
 - Concerns about waiting for tests in areas with large amounts of people
- Has to be balanced against risk of being on warfarin without monitoring
 - Bleeding and thrombosis risks
 - However, risk of thrombosis when off anticoagulation for days in atrial fibrillation is low according to perioperative studies



Ways to mitigate frequent bloodwork

- Less frequent INR draws
 - For patients that are on stable doses of warfarin with therapeutic INR, can extend INR frequency to every 8-12 weeks (instead of monthly or more frequent)
 - May be appropriate for patients with lower thrombotic risk
 - DVT/PE over 1-3 months old
 - Atrial fibrillation with low CHADS score
 - Low risk mechanical aortic valves



Ways to mitigate frequent bloodwork

- Less frequent INR draws
 - Some labs across Canada are using time-tickets to minimize patient exposures
 - Patients wait in car until time for their test
 - Quebec has CLSCs (community health centres) to expedite process



Ways to mitigate frequent bloodwork

- Use of alternate ways of monitoring INR
 - Some pharmacies have point of care machines
 - Provinces may have programs where a pharmacist can check INR and adjust dose
 - Point of care machines can be purchased by patients
 - Machines may be a few hundred dollars, but test strips can be \$\$\$
 - Not covered so may only be appropriate for select patients



Ways to mitigate frequent bloodwork

- Switching to direct oral anticoagulant (DOAC)
 - DOACs are approved for the management of DVT/PE and stroke prevention in atrial fibrillation
 - No routine lab monitoring needed
 - Rivaroxaban and apixaban do not require LMWH run-in for acute DVT/PE
 - Provincial pharmacare programs may make exceptions for coverage during this time
 - Nova Scotia is approving DOACs if COVID-19 is used as justification

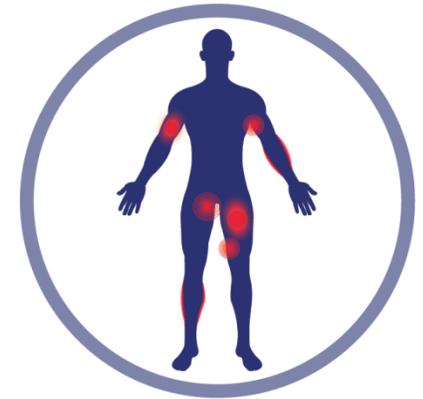


Managing warfarin and DOACs remotely

- Risk of bleeding is <2% per year
- Can check in on patients by phone
 - Ask about bleeding complications, compliance, side effects
 - Be aware of drug-drug interactions, especially with new meds
- High INRs on warfarin can often be managed by holding warfarin alone if INR<10 and no bleeding
 - ACCP guidelines can be used as guide



Impact of COVID-19 in the ER: emergency medicine perspective



Eddy Lang, MDCM, CFPC (MU), CSPQ

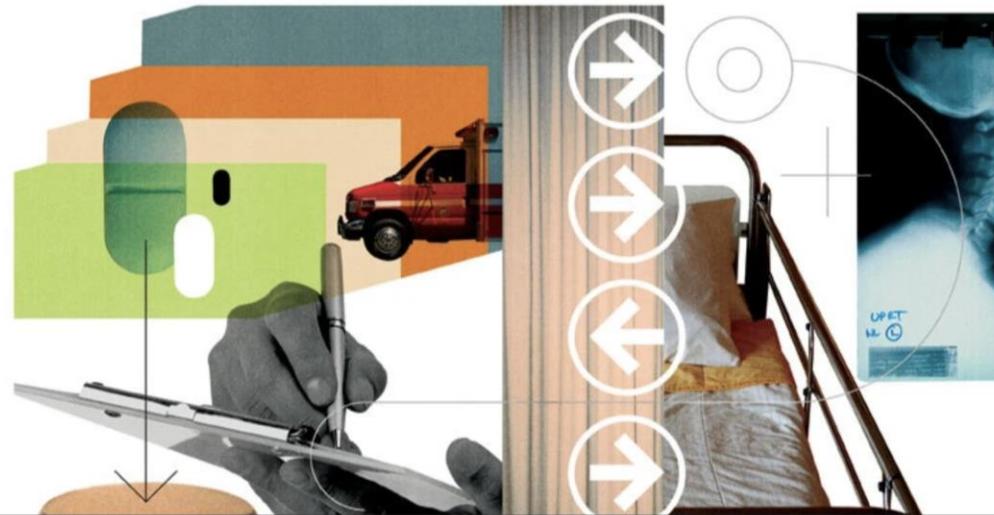
WELCOME
TO THE CLUB.



DOCTORS

Where Have All the Heart Attacks Gone?

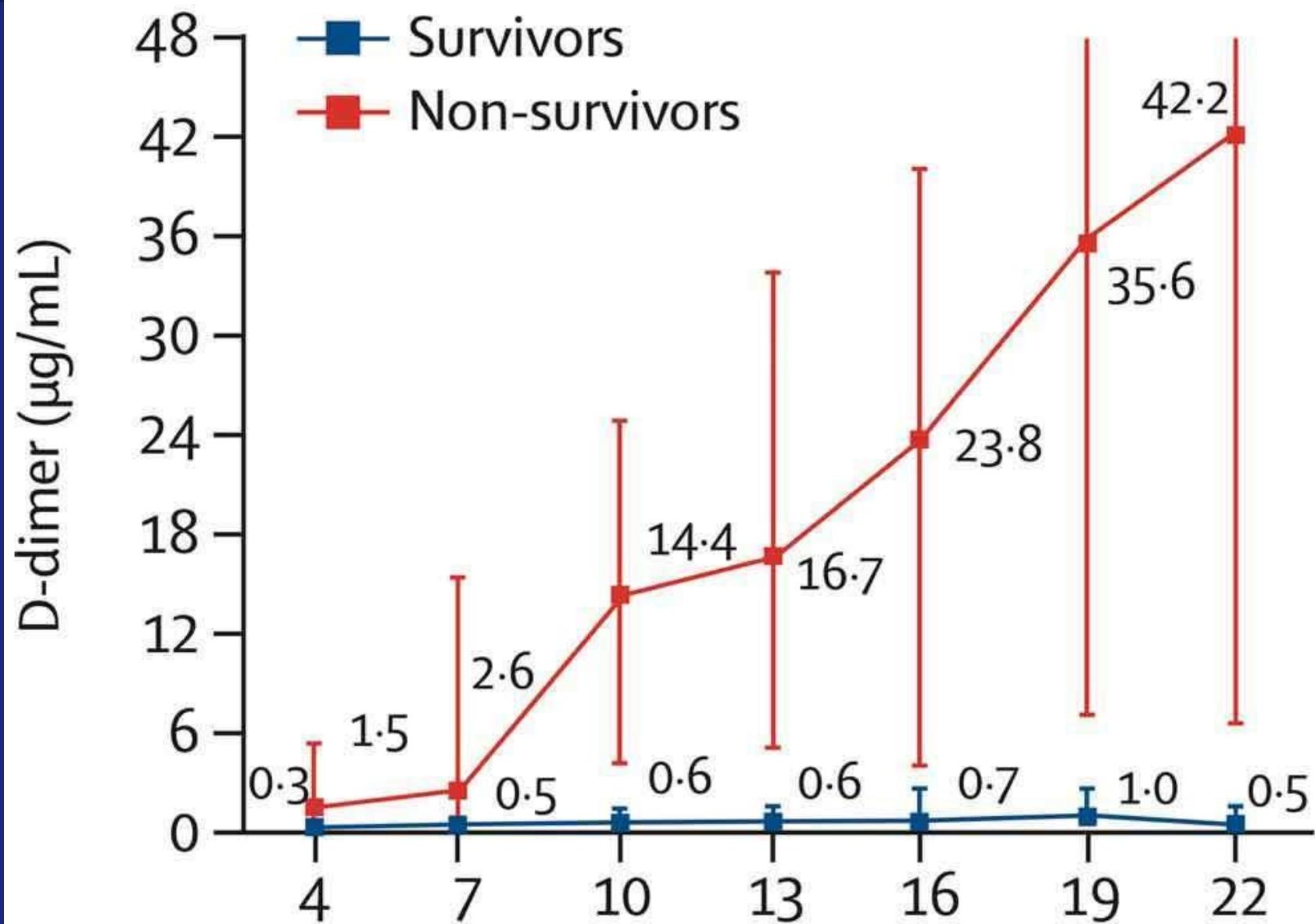
Except for treating Covid-19, many hospitals seem to be eerily quiet.



Emergency Departments and COVID

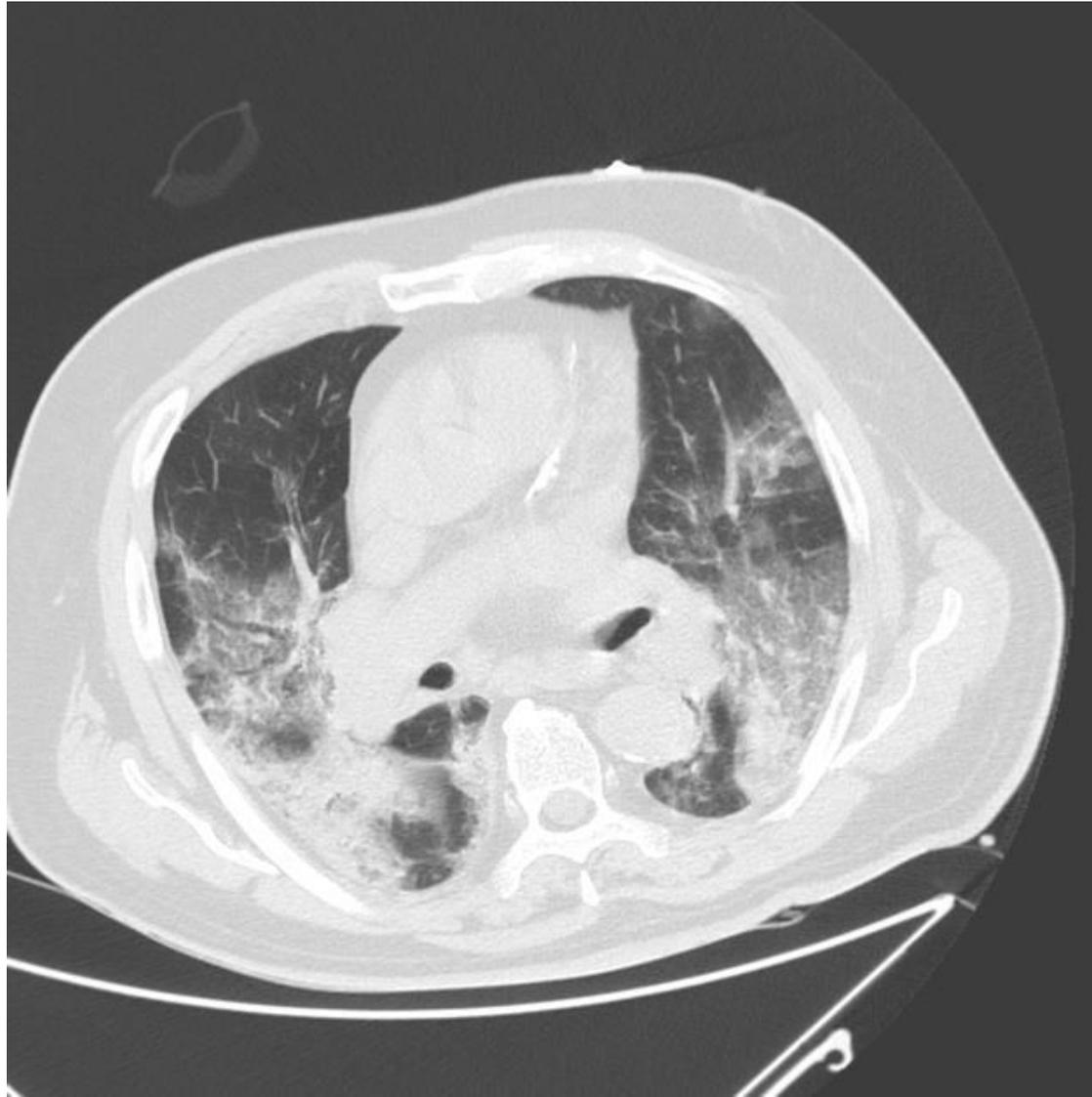
- International reduction in ED visit volumes related to COVID – 36% in Calgary
- Driven by fear of contracting infection but other factors at play
- Some delayed presentations but not many – other shoe will fall?
- More severe disease
- Reduced prevalence of provoked – less OR, less trauma





Progressive rise in D-dimer often portends death. This raises a question of whether treatment of DIC could be disease-modifying.

COVID pneumonia on CT





COVID-19 Resource Center

Core COVID-19 Calcs

Calcs for Scarce Resource Situations

Mortality and Risk Factor Odds Ratios

Expert Interview: Brescia-COVID Scale

High-Yield Clinician Resources

Want to Help? Contact Us

Core COVID-19 Calculators

As a thank you for being on the front lines, get [free CMEs](#).



What's New This Week?

- Tues 3/31/2020: [Brescia-COVID Severity Scale/Algorithm](#) - Italian step-wise approach to managing all COVID-19 inpatients.
- Tues 3/31/2020: [Cstat](#) - Calculates pressure needed to overcome elastic resistance to ventilation.
- Fri 3/27/2020: [mSOFA](#) - Broad illness severity; requires fewer labs than SOFA.
- Fri 3/27/2020: [Roth Score for Hypoxia](#) - Screens for hypoxia in dyspneic patients.



Overall Hospital Management

- [Brescia-COVID Severity Scale/Algorithm](#) - Italian step-wise approach to managing all COVID-19 inpatients.
- [MuLBSTA Score](#) - Only score specific for Viral PNA; not yet externally validated.
- [PSI/PORT Score](#) - Well-studied PNA score for all-comers.
- [Absolute Lymphocyte Count](#) - Lymphopenia appears to suggest COVID infection.



ICU - Respiratory

- [A-a O₂ Gradient](#) - Worsening A-a gradient suggests worsening respiratory severity.
- [Rapid Shallow Breathing Index \(RSBI\)](#) - Predicts successful extubation.

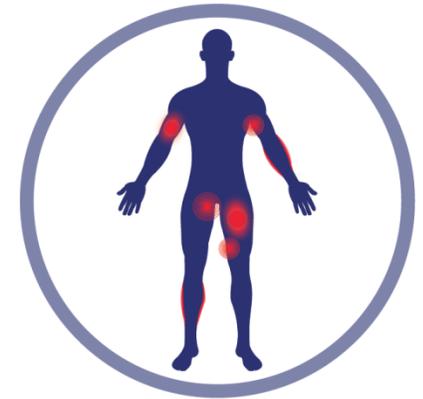


Closing thoughts ER perspective

- Dramatic changes in ED care model - sustained
- Beware of delayed presentations
- d-Dimer elevation associated with poor outcomes in COVID pneumonia
- Link to thrombosis / DIC is evolving



FAQs



Alan Bell, moderator

Next webinar

Updated information

Thursday, April 23; 2:00 pm EST

Go to Thrombosis Canada website to register

<https://thrombosiscanada.ca/thrombosiscovid19/>





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