Planning faculty

Alan Bell, MD, CCFP, FCFP
Family Physician
Toronto, ON

Brian Berenbaum, MC, CCFP
Family Physician
Toronto, ON

Jim Douketis, MD, FRCPC
Internal Medicine
Hamilton, ON

Jeff Habert, MD, CCFP
Family Physician
Thornhill, ON

Eddy Lang, MDCM, CFPC (MU), CSPQ
Emergency Medicine
Calgary, AB

Sudeep Shivakumar, MD, FRCPC
Hematologist
Halifax, NS

Deepa Suryanarayan, MD, MSc, FRCPC
Hematologist
Calgary, AB

Eric Tseng, MD, MScCH, FRCPC
Hematologist
Toronto, ON
**Presenter disclosures**

**Alan Bell, MD, CCFP, FCFP**

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

**Jim Douketis, MD, FRCPC**

Relationships with commercial interests:
- **Grants/Research Support:** N/A
- **Speakers Bureau/Honoraria:** Janssen, Pfizer, Bayer, BMS, Sanofi, Servier, Portola
- **Consulting Fees:** N/A
- **Other:** N/A

**Eddy Lang, MD, FRCPC**

Relationships with commercial interests:
- **Grants/Research Support:** N/A
- **Speakers Bureau/Honoraria:** BMS/Pfizer Boeringher
- **Other:** All speaking and ad board fees direct to Calgary Health Trust Emergency Med Research Fund

**Deepa Suryanarayan, MD, MSc, FRCPC**

Relationships with commercial interests:
- **Grants/Research Support:** N/A
- **Speakers Bureau/Honoraria:** Pfizer
- **Consulting Fees:** N/A
- **Other:** N/A

**Sudeep Shivakumar, MD, FRCPC**

Relationships with commercial interests:
- **Grants/Research Support:** Daiichi-Sanyko, Bayer Inc
- **Speakers Bureau/Honoraria:** Bayer Inc, Pfizer Inc
- **Consulting Fees:** N/A
- **Other:** N/A

**Eric Tseng, MD, MScCH, FRCPC**

Relationships with commercial interests:
- **Grants/Research Support:** N/A
- **Speakers Bureau/Honoraria:** Fresenius Pharmaceuticals
- **Consulting Fees:** N/A
- **Other:** N/A
Disclosure of commercial support

This program has received financial support from the following companies in the form of unrestricted educational grants:

- Bayer Canada
- BMS-Pfizer Alliance
- Leo Pharma
- 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

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<th>Speaker</th>
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<td>Impacts of COVID-19 on primary care</td>
<td>Alan Bell, MD</td>
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<td>Current state of COVID-19</td>
<td>Jim Douketis, MD</td>
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<td><strong>Hematologist perspectives</strong></td>
<td>Hematologic and coagulopathic issues in COVID-19</td>
<td>Eric Tseng, MD</td>
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<td>Managing your thrombosis patient remotely</td>
<td>Deepa Suryanarayan, MD</td>
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<td>Managing anticoagulants, especially VKAs, remotely</td>
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<td>Impact of COVID-19 in the ER</td>
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<td><strong>Question period</strong></td>
<td></td>
<td>Alan Bell, MD, moderator</td>
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</table>
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 complications

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

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

www.thrombosiscanada.ca

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

View Guides!
Click to view or download!
Solutions: COVID-19

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

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
• 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)
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**
Diagnosis
- Detection of genetic material from virus using PCR from lower respiratory tract (intubated patients), uninduced sputum, NP swabs, NP aspirates

Clinical and radiological features
- Fever, dry cough, malaise, myalgia, headache, dyspnea (not dehydrated or septic)
- Unexpected symptoms: anosmia, dysgeusia, diarrhea, nausea
- CXR: bilateral pneumonia features; CT: bilateral, peripheral, inferior lobes, ground-glass opacification (week 2), pleural thickening and effusion, lymphadenopathy

Differential Diagnosis
- Influenza, other viral respiratory infections
- Atypical pneumonia
- Pneumocystosis
Where we’re at with COVID-19

Testing, testing
Promising drugs to treat covid-19

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

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

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

The Economist
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

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<th>Parameter</th>
<th>Trend in COVID-19</th>
<th>Clinical Significance</th>
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<tr>
<td>Platelets</td>
<td>20-30% have platelets 100-150</td>
<td>Not clearly associated with mortality</td>
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<td>Lymphocytes</td>
<td>Often moderate to severe lymphopenia; 75-83% have ALC &lt; 1.5</td>
<td>Severe lymphopenia (ALC &lt; 0.5) and LDH elevation often seen in critical illness</td>
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<td>PT (prothrombin time)</td>
<td>Mild prolongations (15-16 sec)</td>
<td>Prognostic (some association with mortality)</td>
</tr>
<tr>
<td>D-Dimer</td>
<td>Persistent, marked elevations (4-6x ULN) often seen in severe COVID</td>
<td>Prognostic (associated with mortality)</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>Typically elevated until late in disease course</td>
<td>Reductions can be seen late (10-14 days) into admission</td>
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Bhatraju PK, et al. NEJM. 2020;0(0):null. doi:10.1056/NEJMoa2004500
Guan W, et al. NEJM. 2020;0(0):null. doi:10.1056/NEJMoa2002032
The coagulopathy of COVID has some features of DIC

Coagulation parameters on admission (Wuhan)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal</th>
<th>Survivors (n = 162)</th>
<th>Non-Survivors (n = 21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT (sec)</td>
<td>11.5-14.5</td>
<td>13.6</td>
<td>15.5</td>
</tr>
<tr>
<td>aPTT (sec)</td>
<td>29.0-42.0</td>
<td>41.2</td>
<td>44.8</td>
</tr>
<tr>
<td>D-dimer (mcg/ml)</td>
<td>&lt;0.50</td>
<td>0.61</td>
<td>2.12</td>
</tr>
<tr>
<td>Fibrinogen (g/L)</td>
<td>2.0-4.0</td>
<td>4.51</td>
<td>5.16</td>
</tr>
</tbody>
</table>

Guan et al. (Wuhan): among 1,099 COVID+ patients
- 46% had elevated D-dimer on presentation
- 70% requiring ICU/intubation had elevated D-dimer

Guan W, et al. NEJM. 2020;0(0):null. doi:10.1056/NEJMoa2002032
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

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

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 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

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*)

Zhang Y, et al. NEJM. 2020;0(0):null.doi:10.1056/NEJMc2007575
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)

ASH 2020 https://www.hematology.org/covid-19
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

1. D-dimer*
2. Prothrombin time
3. Platelet count
4. Fibrinogen**

1. D-dimer markedly raised***
2. Prothrombin time prolonged
3. Platelet count 100 x 10^9/L
4. Fibrinogen <2.0 g/L

Admit (even if no other concerns)
Monitor once or twice daily

In all patients
Worsening
Start prophylactic dose low molecular weight heparin

- Blood products as per protocol (see box on the right)
- Consider experimental therapies

1. D-dimer not markedly raised***
2. Prothrombin time normal
3. Platelet count normal
4. Fibrinogen elevated

If admitted for other clinical reasons, Monitor daily

If discharged, use as baseline for if re-presenting with symptoms

In non-bleeding patients, keep
- platelet count above 20 x 10^9/L
- fibrinogen above 2.0 g/L

In bleeding patients, keep
- platelet count above 50 x 10^9/L
- fibrinogen above 2.0 g/L
- PI ratio <1.5 (not the same as INK)

Not evidence based
Blood bank resources?
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.
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.
• 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 Calculators

As a thank you for being on the front lines, get free CMEs.

What's New This Week?
- 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
- 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 Q 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/
Support our efforts to prevent illness and death due to thrombosis.
Donate today at ThrombosisCanada.ca/DONATE.