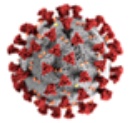
Evidence current as of 05/07/2020



Covid-19

Rapid Review for the EC

Tuesday 7th July 2020

Review 12

Compiled by Dr Luke Bush, Dr Lauren Lai King and Dr Kamlin Ekambaram

The purpose of this regular review, is to present COVID-19 related questions in Emergency Medicine

We accept that available literature on the topics covered in these reviews may be scarce or incomplete, but shared discussion of novel front line strategies may be a tool to augment our clinical practice and develop future policy

Topic:

- **Non-Respiratory Manifestations of COVID-19**
  PART TWO: Myocardial Injury
  Neurological Injury
  Venous Thromboembolism

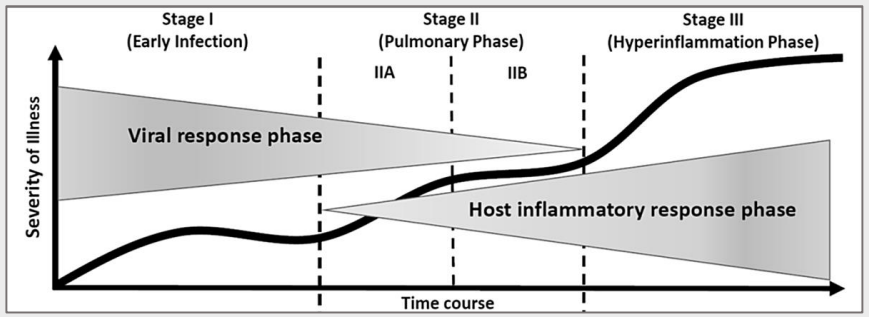
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SARS-CoV2 organ involvement

THREE STAGES - MULTIPLE CONSEQUENCES

Siddiqi et al proposed a three-stage progression in patients with severe and critical disease. Whilst the stages aren't discrete, progression from a viral response to a predominant host inflammatory response, corresponds with clinical decline and an increasing incidence of the non-respiratory consequences of the disease process.(1)



NON-RESPIRATORY COMPLICATIONS

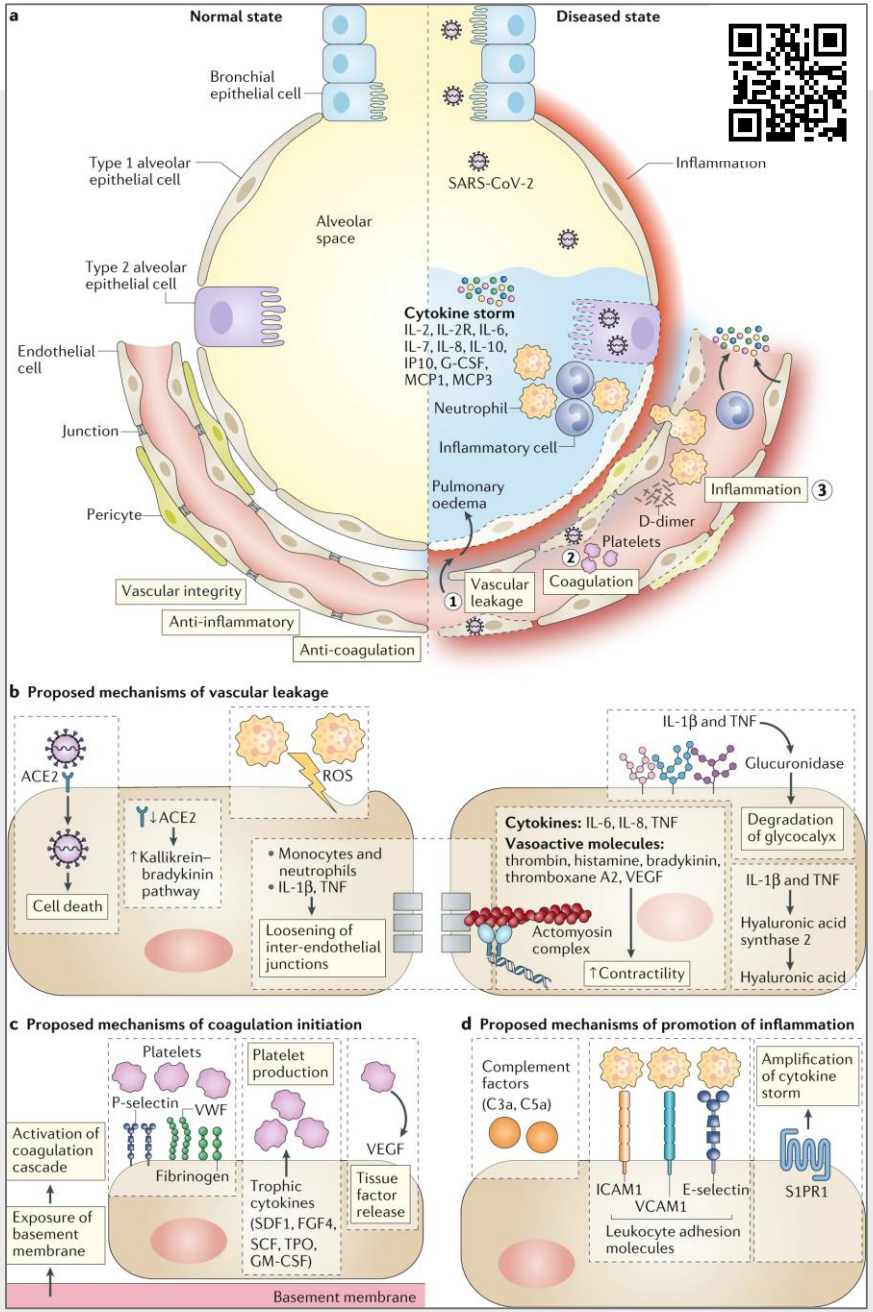
- Acute kidney injury
- Dysregulated glucose metabolism
- Myocardial injury
- Neurologic insults
- Venous thromboembolism

COVID-19 Associated Coagulopathy

The cytokine response to infection increases vascular permeability, facilitates oedema and widespread inflammation, as well as triggering hypercoagulation, causing small and large vessel thrombosis that affects multiple organs.(2)

This proposed mechanism explains a proportion of the cardiac, neurologic and thromboembolic complications.

The role of therapy directed at modulating coagulation, beyond thromboprophylaxis and anticoagulation, and potentially improving outcomes remains to be proven. Even the effective dose of both prophylactic and anticoagulant heparin therapy is still to be clearly defined.



Proposed vessel–lung tissue interface in normal state and in COVID-19 disease. a | On the left, the normal interface between the alveolar space and endothelial cells is depicted; the right side highlights pathophysiological features of coronavirus disease 2019 (COVID-19) in the lung, including loss of vascular integrity (1), activation of the coagulation pathway (2) and inflammation (3). **b–d** | Proposed contributing endothelial cell-specific mechanisms are detailed. ROS, reactive oxygen species; S1PR1, sphingosine 1 phosphate receptor 1; VWF, von Willebrand factor.

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References, resources & comments via QR code

Acute Cardiac Injury

STEMI may represent the first clinical manifestation of COVID-19

Elevated troponin is a strong predictor of mortality(5)

Patients with CV comorbidities are at increased risk of severe disease and complications of COVID-19

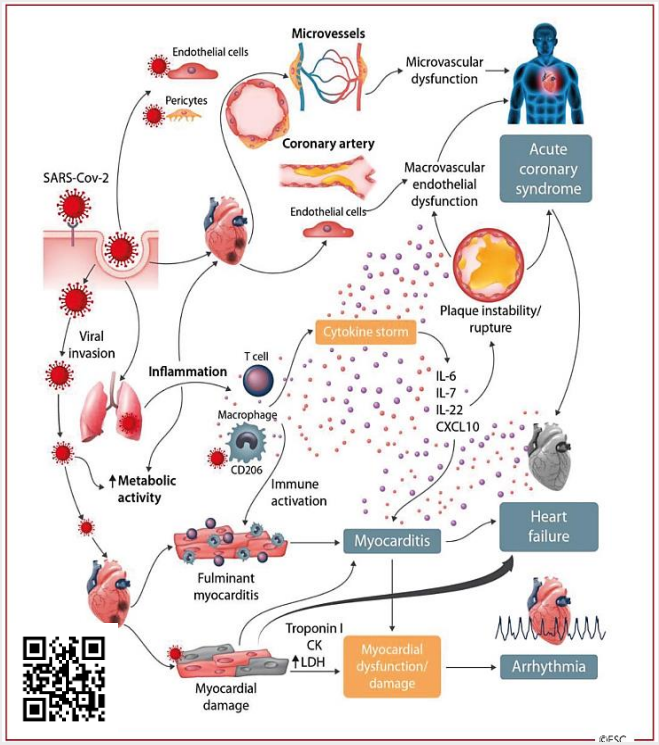
COVID 19 infection appears to have a comparable spectrum of cardiac manifestations to preceding coronavirus outbreaks such as SARS and MERS(3)

The incidence of cardiac injury due to SARS-CoV2 infection has ranged from 7.2% to 27.8%(6)

The spectrum of cardiovascular complications are varied requiring careful clinical evaluation. They include:

- Arrythmia
- Myocarditis
- ACS
- VTE
- Cardiogenic shock
- Heart failure

Cardiovascular Involvement in COVID-19 – key manifestations and hypothetical mechanisms (7)



CVD associated with COVID-19, likely involves dysregulation of the RAS/ACE2 system due to SARS-CoV-2 infection and due to comorbidities, such as hypertension;

CVD may be a primary phenomenon in COVID-19, but may be secondary to acute lung injury, which leads to increased cardiac workload, potentially problematic in patients with pre existing HF

Cardiomyopathy and heart failure

Zhou et al reported that heart failure was observed in 23.0% of patients with COVID-19(5) and it is unclear whether this is an exacerbation of pre-existing ventricular dysfunction or new cardiomyopathy.

Underlying mechanisms of acute heart failure in COVID-19 may include acute myocardial ischaemia, infarction or inflammation (myocarditis), ARDS, acute kidney injury and hypervolaemia, stress-induced cardiomyopathy and tachyarrhythmia.

Fulminant cardiomyopathy can occur and may be a late feature, occurring after patients are recovering from respiratory failure.(7)

Myocarditis

Myocardial injury and increased levels of biomarkers are likely associated with infection-induced myocarditis and ischaemia.

As a quantitative marker of cardiomyocyte injury, the concentrations of cardiac troponin I/T in a patient with COVID-19 should be seen as the combination of the presence/extent of pre-existing cardiac disease AND the acute injury related to COVID-19.(3)

Myocarditis appears in COVID-19 patients several days after the onset of fever and should be considered as the precipitating cause in a patient presenting with undifferentiated cardiogenic shock.(4)

Incidence, underlying mechanisms and risk factors of SARS-CoV-2-associated myocarditis are currently unclear.(3)

Acute coronary syndrome

Potential causes of troponin elevation in COVID-19 patients may include(7)

- Myocardial injury i.e. troponin elevation without symptoms/ ECG/echo findings of myocardial ischemia
- Type-I MI due to plaque rupture – this is among the least common causes.
- Type-II MI (stress MI)
- Stress cardiomyopathy a.k.a. Takotsubo cardiomyopathy
- Viral cardiomyopathy

Among non-survivors, troponin tends to increase steadily from day 4 of illness through day 22.(5)

STEMI was the **first** clinical manifestation of COVID-19 in 86% of patients with confirmed COVID-19 undergoing coronary angiography for STEMI in Lombardy, Italy. Notably, 17 of 28 patients (61%) had a culprit lesion requiring stenting and 11 (39%) had non-obstructive coronary disease.(8)

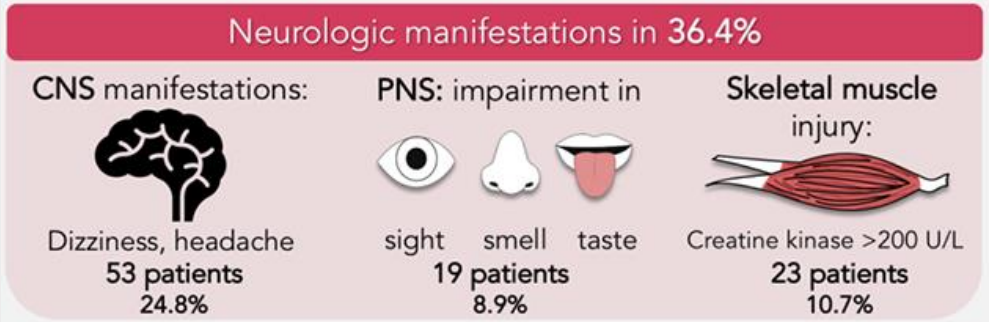
The same ECG diagnostic criteria for cardiac conditions apply in patients affected by the SARS-CoV-2 infection and in the general population

References, resources & comments via QR code

Neurologic Injury

THE LANCET Psychiatry
The Neurology and Neuropsychiatry of COVID-19
Covid-19 Rapid Review for the EC

Anosmia, stroke, paralysis, cranial nerve deficits, encephalopathy, delirium, meningitis, and seizures are some of the neurological complications in patients with COVID-19.



Blog | Journal of Neurology, Neurosurgery & Psychiatry

Neurobiology of COVID-19

Once again, the proposed mechanisms causing significant neurological manifestations relate to the excessive cytokine response seen in severe disease.

BUT

There are multiple case reports of thrombotic stroke in patients with minimal other symptomatology who subsequently test SARS-CoV2 PCR positive.

GAPS IN KNOWLEDGE

The role of aspirin and heparin in preventing neurovascular events in COVID-19 is still unclear.

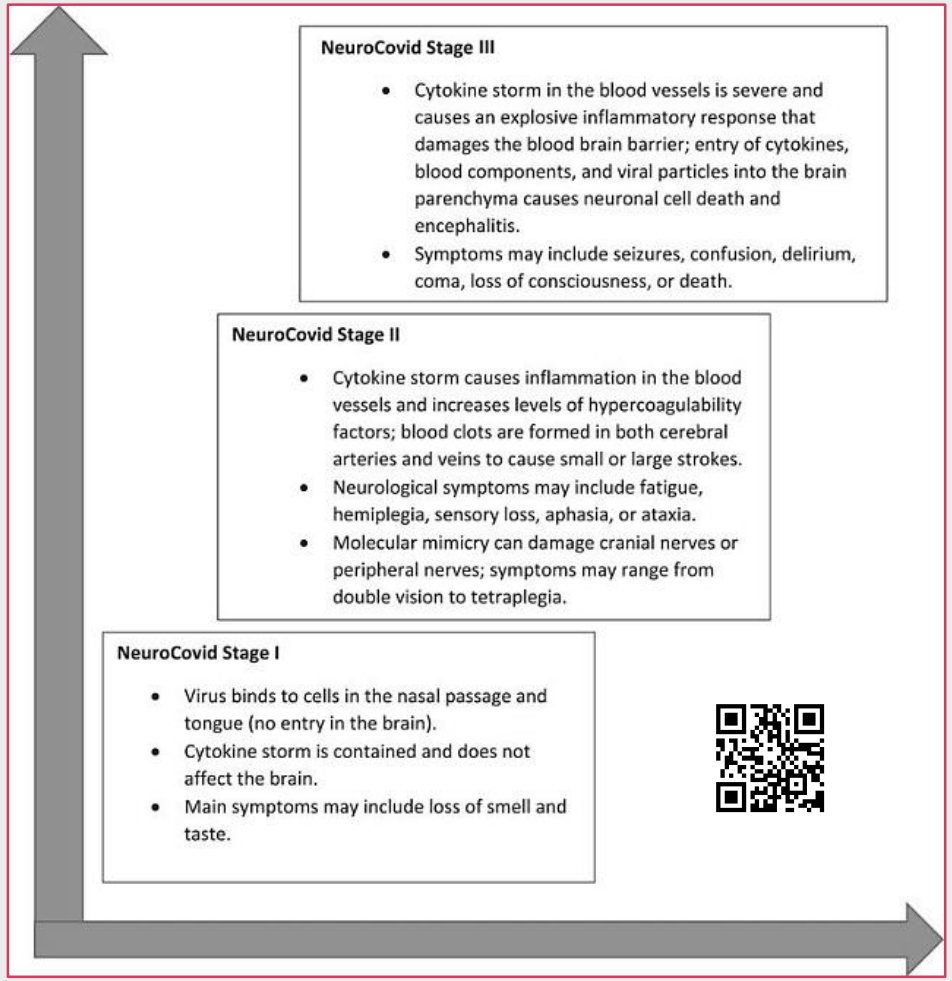
Myopathy and wasting may be due to viral effects on muscle and not just related to critical illness myopathy or the use of muscle relaxants for those who are ventilated.

There are concerns related to certain diseases being triggered by SARS-CoV2 infection including:

- Guillain-Barre Syndrome
- Parkinson's

Deficits from small punctate strokes are likely to be missed during admission and may have long-term neurocognitive consequences.

- Between 36% to 55% of patients with COVID-19 that are hospitalized have some neurological symptoms.
- Patients may present with acute neurological symptoms even without typical respiratory symptoms.



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Venous Thromboembolism

Thromboembolic complications of the disease increase morbidity and mortality

Even with thromboprophylaxis, thrombosis occurs in 20-30% of critically ill covid-19 patients (12,13)

Elevated D-dimers may be of prognostic value in COVID-19 (3,4) and there is evidence of pulmonary microvascular and systemic macrovascular thrombosis (5-7). These and other findings suggest a **widespread thrombotic disease**, an endothelitis combined with immune mediated **hypercoagulability** and venous stasis are part of the proposed mechanisms (19-21).

Our usual practice for hospitalised medical patients is to use **prophylactic LMWH** to decrease their risk of DVT and thromboembolic complications. In COVID-19, this practice does not appear to decrease the risk to the same extent(22). There have been suggestions, that in moderate to severely ill COVID-19 patients, not at risk of bleeding, we should be adjusting prophylactic dosages, or at least ensuring the correct weight-based prophylactic dosage.



Understanding pathophysiology of hemostasis disorders in critically ill patients with COVID-19

thebmj **Covid-19 and thrombosis: what do we know about the risks and treatment?**

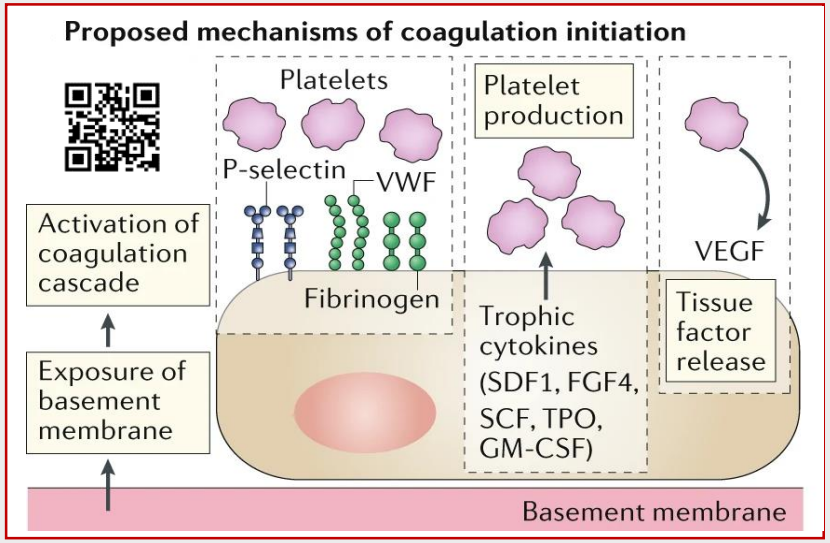
nature reviews immunology
COVID-19: the vasculature unleashed

The **optimal preventative strategy, including risk assessment, dosage and duration of prophylaxis** are under investigation and in the interim some international and local centres are adjusting their prophylactic and therapeutic strategies (23).

See RR7 – VTE and CAC for more details

GAPS IN KNOWLEDGE

- The effective dose of both prophylactic and anticoagulant heparin therapy
- Monitoring of anticoagulant adequacy particularly in a resource restricted environment
- Evaluation of the non-anticoagulant properties of heparin including its role as an anti-inflammatory, in endothelial protection and potential viral inhibition.



Venous Thromboembolism in COVID-19: Towards an Ideal Approach to Thromboprophylaxis, Screening, and Treatment

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