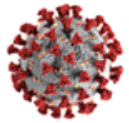
Evidence current as of 28/6/2020



Covid-19

Rapid Review for the EC

Tuesday 30th June 2020

Review 11

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 ONE: Acute Kidney Injury
  Hyperglycaemia and Diabetes

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SARS-CoV2 organ involvement

The primary infection involves multiple organs

Although SARS-CoV2 is recognised for its respiratory complications, because of its mechanism of receptor binding and those receptors being expressed in various organs, the pathology that occurs during the primary phase of infection is multisystem and accounts for the varied symptoms associated with clinical disease.

In this first part of the series we look at the effects on the kidney and glucose regulation.

Part two looks at the impact of the combined effects of the virus and the hyper-inflammatory state on the heart, brain and vasculature.

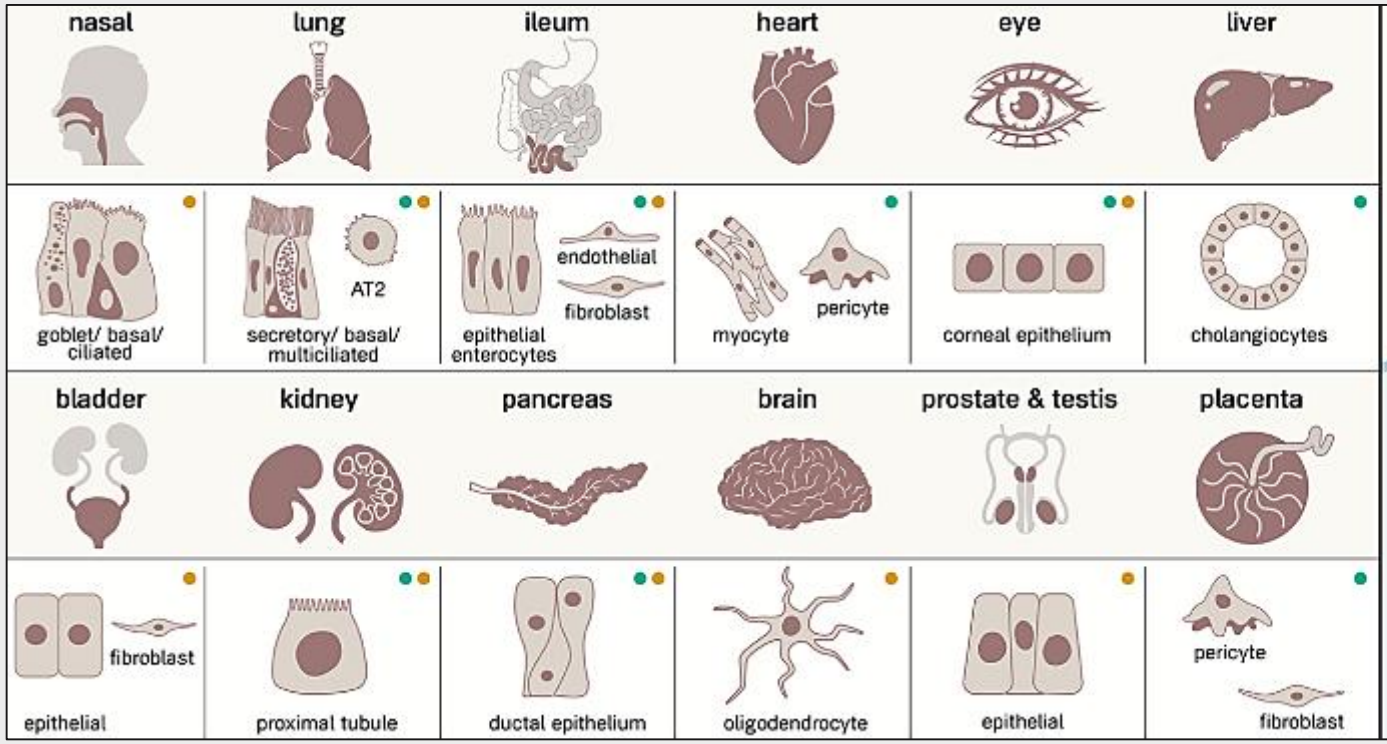
HYPERINFLAMMATORY STATE

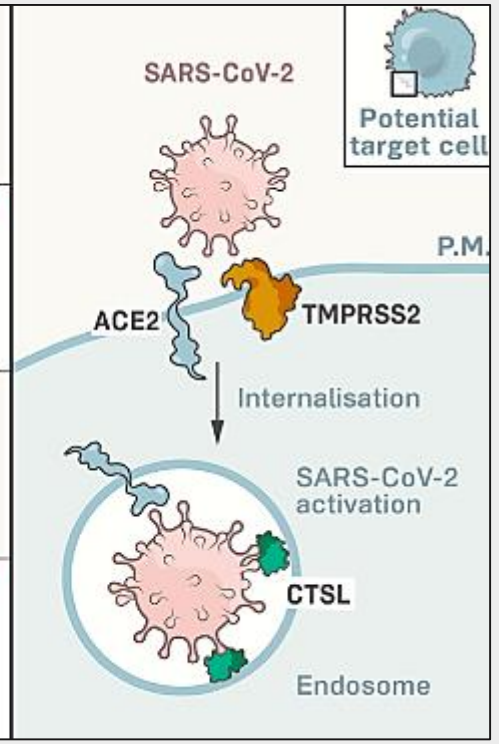
The immune response to the primary infection appears to precipitate clinical decline and is evidenced by raised inflammatory markers(1). It is difficult to delineate the viral effect from the immune response and the clinical picture is likely a combination of both. The hyperinflammatory effects tend to occur after 7-10 days - a period termed the 'cytokine storm.' The endothelial dysfunction and coagulopathy associated with disease is implicated in venous and arterial complications and associated organ dysfunction (2-4).

NON-RESPIRATORY EFFECTS

Complications may include:

- **Acute kidney injury**
- **Dysregulated glucose metabolism**
- Cardiac injury
- Neurologic insults
- Venous thromboembolism





References, resources & comments via QR code

Acute Kidney Injury in COVID-19

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AKI is an independent risk factor for in hospital mortality

Maintaining optimal fluid status is critical in reducing the incidence of AKI

The prognosis of patients with COVID-19 requiring dialysis appears poor:

- Zhou et al found a mortality of 10/10 patients in a recent study on COVID-19(5).
- During the SARS outbreak in 2003 renal failure correlated with a 92% mortality rate versus 9% for those without; and in multivariable analysis, renal failure was the strongest predictor of mortality, even more-so than ARDS(6).

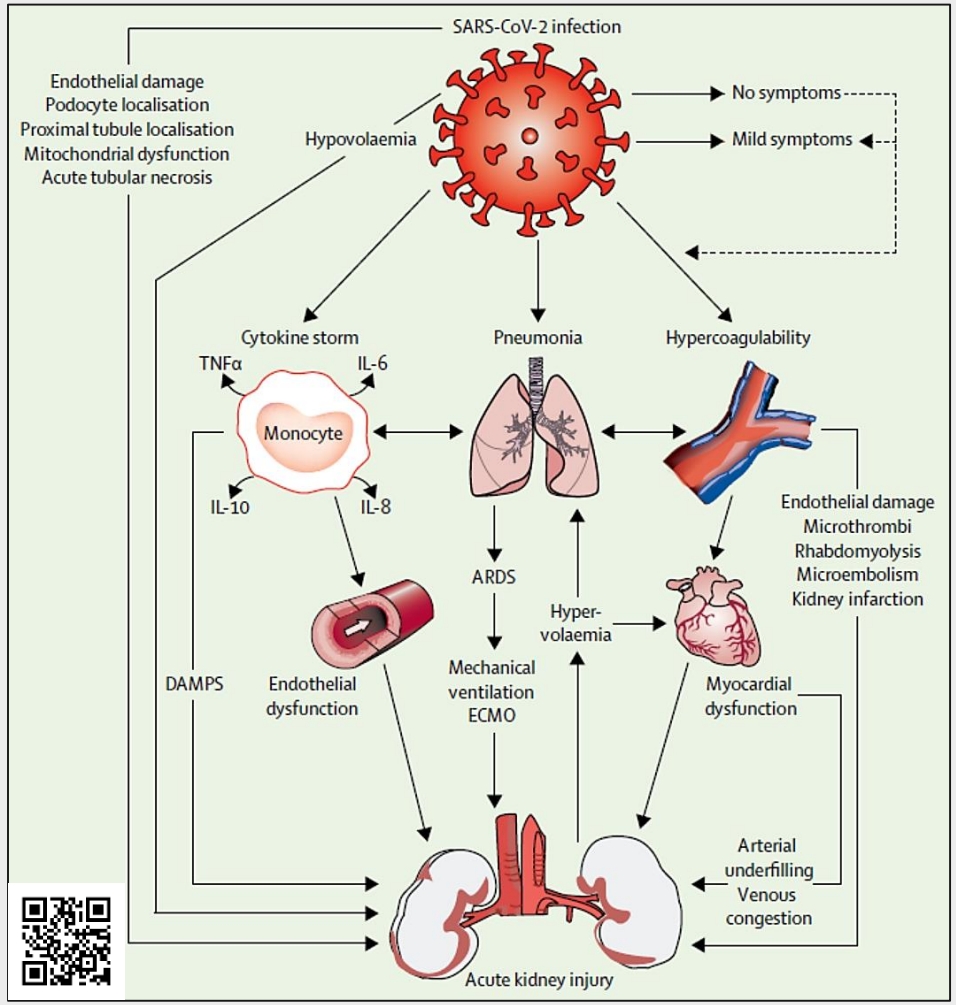
Patients who develop an Acute Kidney Injury appear to do so two weeks into the clinical course and approximately one week following admission for worsening respiratory distress(5).

There are multiple proposed pathways involved in the development of AKI in COVID-19, including(9):

- Direct viral cytopathic effects
- Acute Tubular Injury as a result of volume depletion, hypoxia, shock, rhabdomyolysis
- Cytokine storm effects on the kidney
- Myocardial dysfunction
- Hypercoagulability, micro-emboli, kidney infarction

NICE guideline recommendations for early detection of AKI:

- an increase in serum creatinine of ≥26 µmol/L in 48 hours
- an increase of ≥50% in serum creatinine, known or presumed to have occurred in the past seven days
- a fall in urine output to ≤0.5 mL/kg/hour for more than six hours.



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Project ECHO University of Cape Town South Africa

COVID-19 ECHO CLINIC: ACUTE KIDNEY INJURY

Acute Kidney Injury (AKI) Algorithm
NHS

Acute Kidney Injury in COVID-19

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Management

The goal is to prevent or decrease the severity of the initial renal injury and prevent iatrogenic worsening of renal injury secondary to therapeutic interventions.(9)

It is advised that clinicians should:

- Consider nephrotoxic effects of all pharmacological agents
- Re-dose or correctly dose renally cleared medications when AKI develops
- Be guided by a dynamic assessment of fluid responsiveness to avoid iatrogenic fluid overload

Goals of care should be explored in consultation with a multidisciplinary clinical team prior to escalation of management to continuous renal replacement therapy. Following their experience in Italy, Ronco et al note that "*Careful patient selection is necessary given the current evidence to suggest that age and comorbidities influence outcomes in critically ill COVID-19 infected patients*."(9)

NICE guidelines identify significant GAPS in knowledge(12):

"*Information regarding renal involvement in covid-19 is extremely limited in several areas, and further evidence is required. Some of the most pressing questions include:*

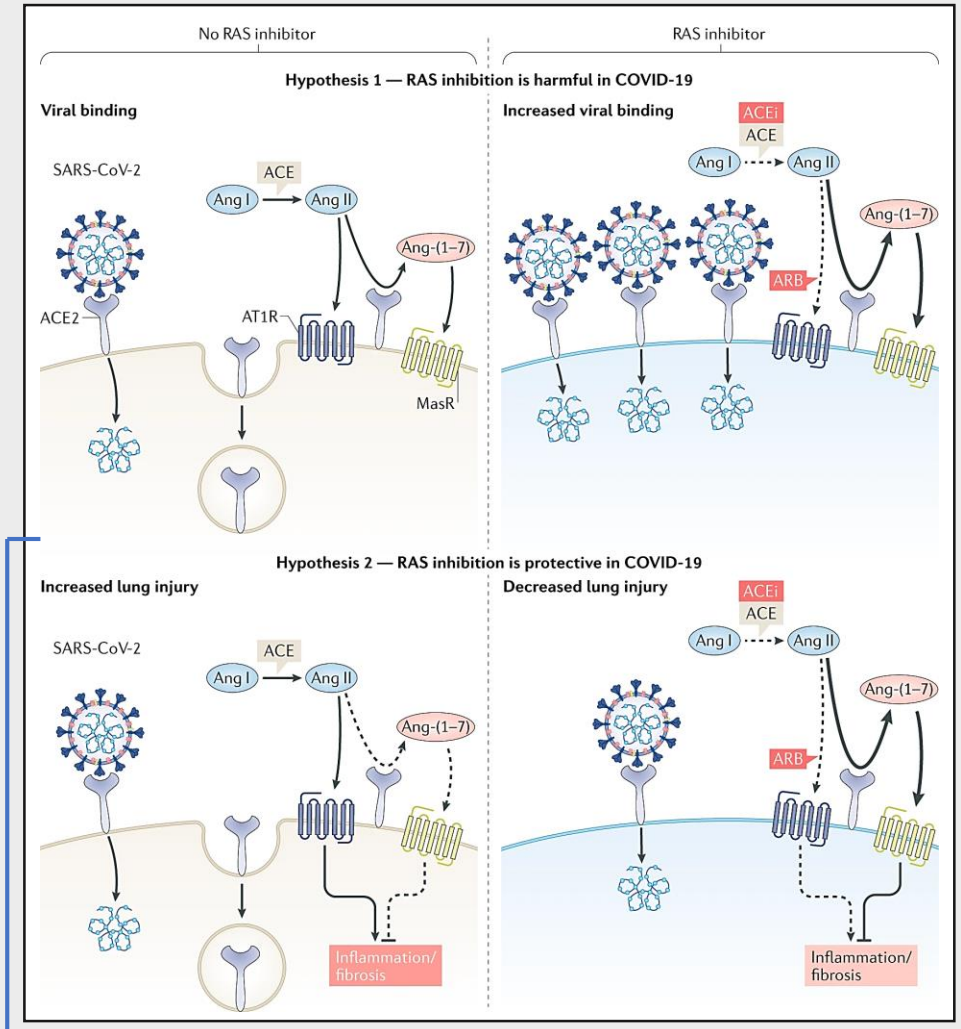
- *What is the incidence of AKI in hospitalised patients with covid-19, both in and outside of the intensive care unit?*
- *What, if any, are the typical clinical, laboratory, and urinary features that characterise AKI in the setting of covid-19?*
- *What are the long term effects of covid-19 on renal function?"*

LOCAL DATA IS SCANTY

Local stats describing AKI incidence in COVID and not just chronic kidney disease (CKD)

Unclear at present whether local data supports the finding that AKI is a marker of severe disease and an independent predictor of mortality given our context specific patient characteristics

What does this mean for clinical practice in the EC beyond maintaining fluid status and avoiding nephrotoxins ?



Possible effects of renin–angiotensin system inhibition on COVID-19. The competing hypothetical mechanisms by which inhibition of the renin–angiotensin system (RAS) with an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin-receptor blocker (ARB) might be harmful (upper panels) or protective (lower panels) in COVID-19

Due to their effects on the Renin-Angiotensin System (RAS), there is theoretical concern and argument for and against the use of ACE-inhibitors and ARBs – further evidence as to the clinical implications of these medications is required to determine their use (7,8)**.**

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Hyperglycaemia and Diabetes

Diabetes is an independent risk factor for severe disease, rapid progression and poor prognosis

New onset hyperglycaemia in the setting of COVID-19 suggests an increased risk of severe disease

Hyperglycaemia in a previously well controlled diabetic may be as a result of pre-symptomatic COVID-19

JCEM **Diabetic Ketoacidosis in COVID-19: unique concerns and considerations**

Diabetes/Metabolism Research and Reviews **Diabetes is a risk factor for the progression and prognosis of COVID -19**

Project ECHO University of Cape Town South Africa **COVID-19 ECHO CLINIC: LOCAL HAZARD RATIOS FROM COVID-19**

Patients with diabetes are at greater risk of: **Severe pneumonia**, an excessive and **uncontrolled inflammatory response** and their dysregulated glucose metabolism worsens their **hypercoagulable state(13)**. The same response was recognised in diabetics during SARS 2003 and H1N1 outbreaks (1).

With about half a billion diabetics worldwide, diabetes is the leading non-communicable, chronic disease associated with the pandemic(1).

During the 1st phase of infection, diabetics may have a milder disease onset with fewer symptoms(9) and this may result in a delay in seeking care, also potentially worsening prognosis. The mechanism for this is postulated to be due to altered immune responses in diabetics and is also seen in other disease phenotypes (1,14).

"The interaction between Covid-19 and diabetes could also be bi-directional, with SARS-CoV-2 potentially worsening pre-existing diabetes or even predisposing to diabetes in non-diabetics(1)."

ACE-2 receptors are expressed widely through the body, including in the liver and endocrine pancreas, and its effects in these organs may result in impaired insulin secretion(15) and dysregulation of glucose metabolism (16).

Evidence for this dysregulation is demonstrated in the range of COVID-19 hyperglycaemic presentations (12):

1. Simple and complicated hyperglycaemia in patients not previously known to be diabetic
2. DKA in type II (well or poorly controlled) diabetics who have never been in DKA previously
3. Precipitating DKA in type I diabetics
4. HHS and mixed DKA

Those with dysregulated glucose metabolism appear to do worse during the excessive and uncontrolled inflammatory response. This is evidenced by raised cytokines (specifically IL6) and increased hypercoagulability corresponding with clinical deterioration(12).

With the suspected injury to the endocrine pancreas and host inflammatory response, there are concerns that following infection with SARS-CoV2 and full recovery, that there may be an increased risk of developing subsequent diabetes(7) – longitudinal analysis over the next few years will provide more information as to this identified risk.

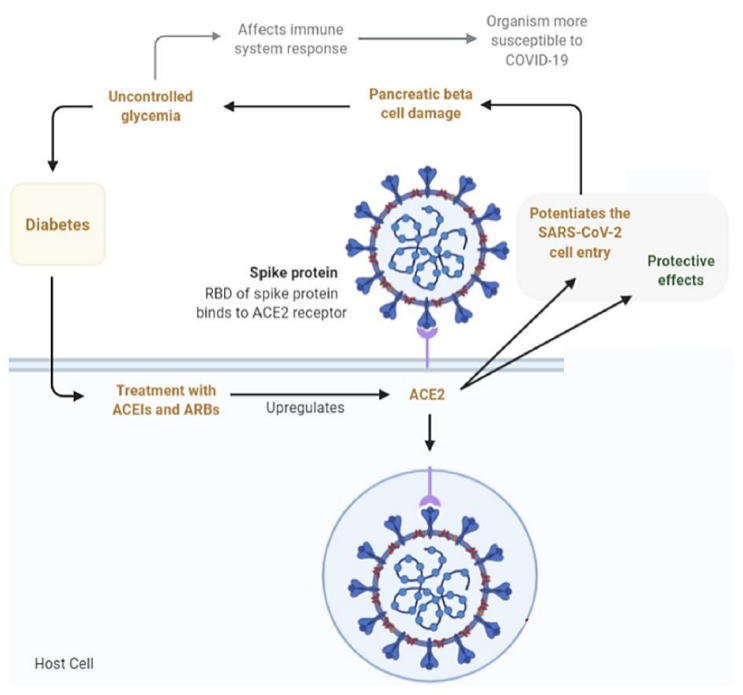
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Glucose Dysregulation

New onset hyperglycaemia may indicate underlying COVID-19 infection

Covid-19
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Pathophysiology

COVID-19 disease precipitates atypical presentations of diabetic emergencies (mixed DKA and hyperosmolar states)

This may be due to the disturbed glucose homeostasis as a combined result of pancreatic beta cell damage affecting the secretion of insulin and the COVID-19 effects on the liver.

Homeostasis is likely further disturbed by the systemic inflammatory response, sepsis and use of steroids in the management of those requiring oxygen therapy.

People with COVID-19 infection appear to have a greater risk of hyperglycaemia with ketones

Significant insulin resistance is seen in some patients with type 2 diabetes (16)

Patients with diabetes or hyperglycaemia have fourfold higher in-hospital mortality rate compared to those without evidence for diabetes or uncontrolled hyperglycaemia (17)**.**

COncise adVice on Inpatient Diabetes (COVID:Diabetes):
FRONT DOOR GUIDANCE
DIABETES UK KNOW DIABETES. FIGHT DIABETES.
ABCD

COncise adVice on Inpatient Diabetes (COVID:Diabetes):
GUIDANCE FOR MANAGING INPATIENT HYPERGLYCAEMIA
DIABETES UK KNOW DIABETES. FIGHT DIABETES.
ABCD

COncise adVice on Inpatient Diabetes (COVID:Diabetes):
GUIDELINE FOR MANAGING DKA USING SUBCUTANEOUS INSULIN
(where intravenous insulin infusion is not possible)
DIABETES UK KNOW DIABETES. FIGHT DIABETES.
ABCD

Management

Early identification and management of hyperglycaemia in COVID-19 patients is necessary to improve outcomes(13).

Although patients may require IV insulin infusion, the infusion pumps may be in use elsewhere for sedation or medication in the critically ill. Where this is a limitation, depending on the degree of insulin resistance, modified subcutaneous regimens may be required (18).

Fluid requirements may differ in those with DKA/HHS and evidence of “lung leak,” myocarditis or those with AKI(18).

Where ketosis persists despite treatment in line with usual protocols and where and there is a concern regarding fluid quantity consider using 10-20% glucose (18).

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