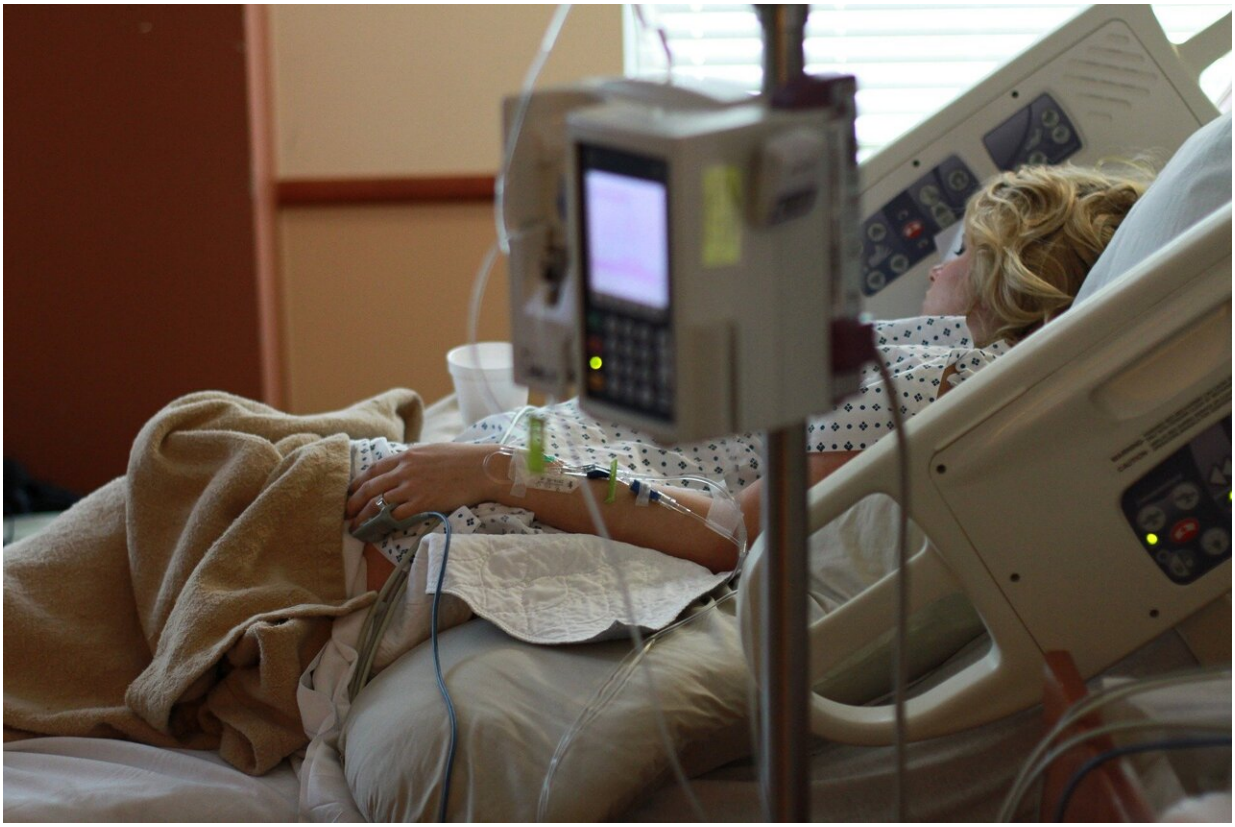
Expert reaction to high proportion of blood clotting in COVID-19 patients

May 19 2020



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Earlier this week, the BBC reported that one third of COVID-19 patients developed dangerous blood clots. While current treatments are mainly focusing on anti-viral and potentially anti-inflammatory treatments, these

only address the direct effects of the virus. If the virus is a flood, these treatments controlling the flood but not considering damage caused. In addition to the drugs that treat the immune system overdrive or neutralising the virus, there is an urgent need to focus on medications that address this clot formation including the use of blood thinners, and clot busting agents, especially the right dose and the right patient.

Is the figure of 'one third' of COVID-19 patients developing blood clots a realistic one? Why is it such a high proportion?

Case series have now been reported from multiple countries quoting a figure as high as 40 % in patients in intensive care. Patients on the ward also have higher prevalence even if not of the same magnitude as the patients on intensive care.

This excess thrombosis has been confirmed in autopsy reports where more extensive thrombosis has been noted in the lungs and thrombosis was noted in blood vessels of other organs.

Are the blood clots different from the ones we routinely see in clinical practice?

A view is developing that the pulmonary artery thrombi in these patients probably represent de novo thrombus formation, unlike the typical clots which represent an embolic phenomenon. In other words, the clots of formed by new deposits in blood vessels rather than clots formed in other parts of the body that migrated. This might explain the slow onset of breathlessness. In some patients, a more typical rapid onset breathlessness secondary to rapid occlusion of the pulmonary vascular tree has been seen.

I suspect a combination of both is common across the patient group, with the smaller peripheral thrombi representing de novo thrombus formation. The thrombi in the larger arteries probably are embolic in origin.

What about treatment strategies for the thrombosis?

An assumption has been made that managing the excess cytokines, and immune activation can address thrombosis. This is a misconception as our experience with other thrombotic conditions, including arterial and venous thrombosis shows that addressing the cause does not clear the clot. The clot is cleared through turnover process called fibrinolysis that is intrinsic to the coagulation process. This can also be facilitated by external medications called clot busters (tissue plasminogen activator or streptokinase)

In the context of thrombosis secondary to modest inflammation or secondary hypercoagulability that is inherited or acquired , anticoagulation is the mainstay of treatment. Primarily they can address the consequences in the coagulation system, i.e. prevent progression and recurrence of thrombosis.

There is also considerable debate if all patients should receive therapeutic anticoagulation. On the other hand, there are concerns about the potential risk of bleeding. A randomised trial is underway, although the trial does not require screening despite the high reported prevalence.

A great emphasis has been put on anti-viral and anti-inflammatory strategies, but sadly studies addressing coagulation have struggled to be badged as 'important'. While anti-viral and potentially anti-inflammatory strategies may the control the 'flood,' i.e. viral infection and related cytokine storm, the 'flood damage' i.e. fibrin in the alveoli and bloodstream needs to be addressed by alternate mechanisms.

What do scientists think is the mechanism causing the increase in blood clotting in COVID-19 patients?

A consistent finding is elevated d-dimers, typically between 4 to 10-fold increase are seen. Also, increases as high as 100 to 150 fold have been seen in the very sick patients. Elevated d-dimers have been associated with higher mortality and morbidity. The relationship with the severity of lung disease is not clear.

Several explanations have been put forward, and the mechanisms responsible for the excess thrombosis or coagulation abnormalities in COVID-19 are not entirely elucidated.

Three possible mechanisms can be considered.

1. Coagulation abnormalities may be secondary to the cytokine storm. This appears to be the most prevalent belief, but it is interesting to note that patients do not have a concurrent decrease in fibrinogen or platelets. Typically, the coagulopathy of a cytokine storm tends to be consumptive with low fibrinogen, low platelets, and elevated d-dimers.
2. The second possibility is that the endothelium is damaged because of adjacency to the alveolar epithelium, and there is a spill-over of the severe inflammation, a bystander effect. This mechanism can explain the excess of pulmonary arterial thrombosis seen in this group of patients. Typically in this situation, there is an increase in fibrinolysis inhibitors in the alveoli with a spill into the circulation.
3. The third possibility is that there is direct infection of the endothelial cells. There has been a case report demonstrating this possibility. .

What about investigations for pulmonary artery thrombosis?

CT Pulmonary angiogram can demonstrate thrombi in pulmonary vasculature until the sub segmental level. It has been challenging in these patients as they are breathless with resulting motion artefacts, and the presence of lung pathology makes the smaller thrombi more challenging to visualise

If one accepts that the pulmonary thrombi are developing de novo, screening for them will become important as patients are unlikely to present with the more traditional clinical symptoms.

In our institution, a review of data shows that elevated d-dimers can predict the presence of pulmonary artery thrombosis.

At a minimum patient with high d-dimers, about 4 to 6 times the upper limit of normal should have a CTPA and anticoagulation will address the contribution from PAT.

What other treatments are possible for blood clotting?

Typically, we tend to manage blood clots with anticoagulants, but the clots can be lysed with thrombolytic agents. Thrombolysis for pulmonary embolism can be done as systemic therapy by administering the drug through a peripheral vein or catheter-directed..

There have been a few case series of intravenous tissue plasminogen activator with transient improvement in oxygenation. Most of the studies have been conducted in patients hospitalised in intensive care for long periods, and the lack of effect in clinical outcomes may potentially be related to fibrosis. There is also a study of nebulised tissue plasminogen

activator to see if this helps improve oxygenation through lysis of fibrin membranes in the alveoli and small vessel thrombosis.

Provided by The Physiological Society