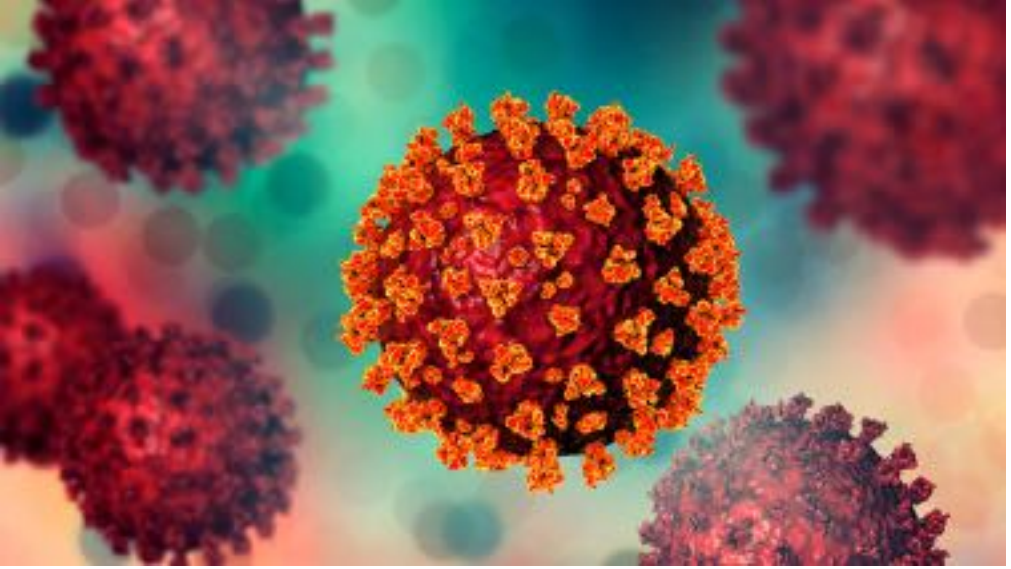
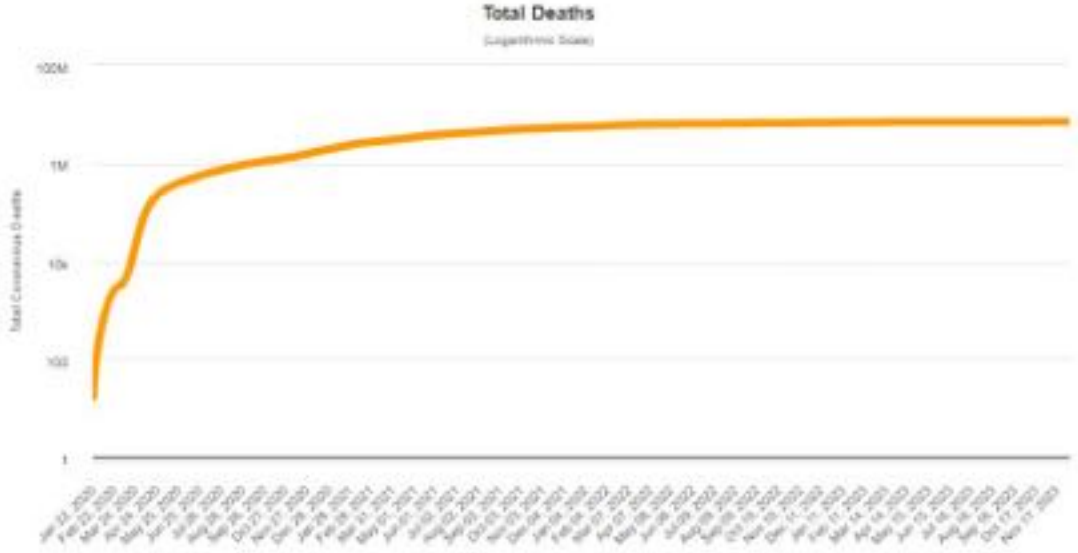


POST COVID HUS

The coronavirus disease 2019 (COVID-19) pandemic caused by SARS-Cov2 has affected millions of people worldwide.

As of April 2023, over 670 million cases had been diagnosed worldwide, with nearly 7 million deaths.

Is it over? **NO**, while vaccine rollout has been successful in reducing both the incidence and the severity of the disease, COVID-19 is far from contained, with around 1000 daily deaths still attributed globally to COVID-19 infection.

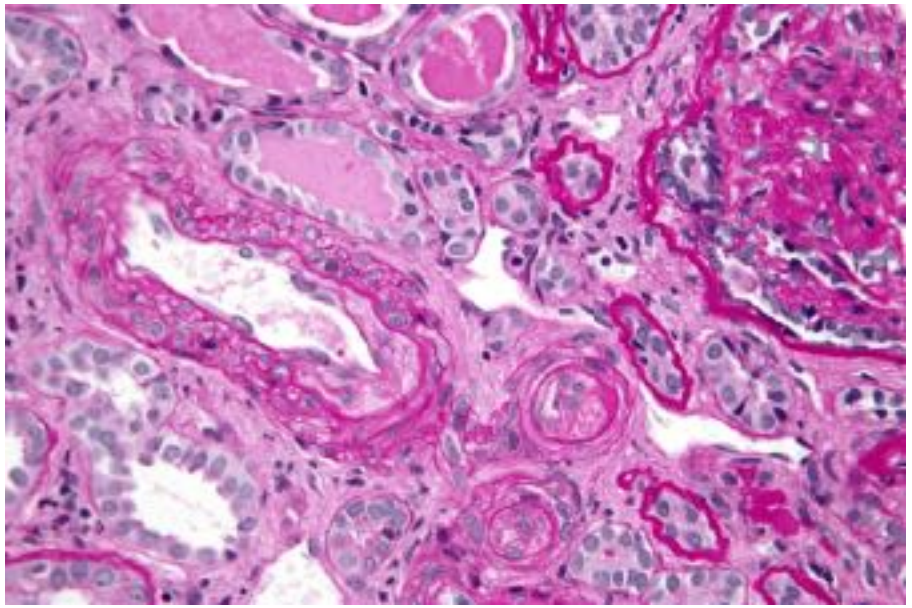


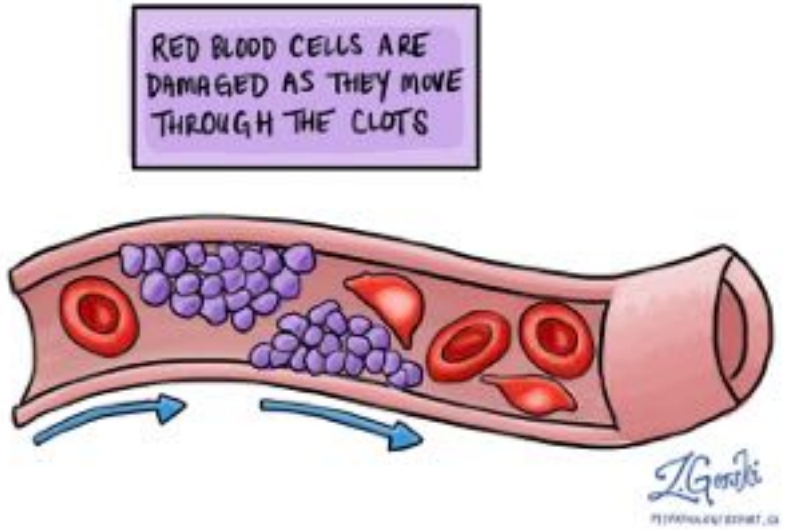
- In addition to pulmonary involvement, infected individuals may present with a wide range of extrapulmonary manifestations, including acute kidney injury (AKI), thrombotic complications, myocardial insufficiency and arrhythmias, acute coronary syndromes, gastrointestinal symptoms, hepatocellular injury, hyperglycemia and ketosis, neurologic disease, ocular symptoms, and dermatologic complications.

- AKI is common in patients with COVID-19, but its exact mechanism remains unclear. While acute tubular injury appears to be the most common histopathologic finding on renal biopsy, it has been suggested that thrombotic microangiopathy (TMA) can also occur.

What is TMA?

TMA syndromes share certain pathological and clinical features. The most important pathological feature is widespread thrombosis in capillaries and arterioles, clinically manifested by microangiopathic hemolytic anemia (MAHA), thrombocytopenia, and organ damage (AKI, neurological abnormalities).





Classification of TMA: TMA can be classified into the following forms:

- **Thrombotic thrombocytopenic purpura (TTP)** resulting from an inherited or acquired deficiency of ADAMTS13;

- **Typical hemolytic uremic syndrome** caused by Shiga toxin-producing Escherichia coli (STEC-HUS);

- All other forms grouped under the common term **atypical HUS (aHUS).**

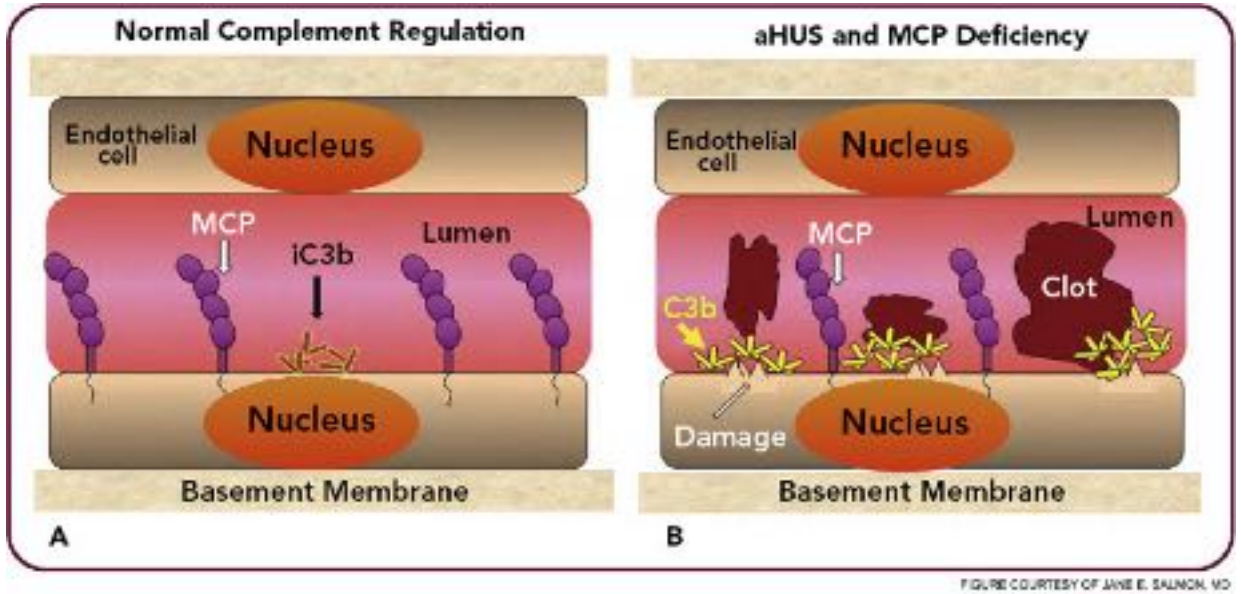
aHUS can be either ***primary/hereditary*** with uncontrolled activation of the alternative complement pathway (due to a pathogenic complement gene mutation) or ***secondary/acquired***.

The classification into primary/hereditary and secondary/acquired TMA is not absolute, as hereditary TMA requires a trigger factor, and acquired TMA may also have a genetic background.

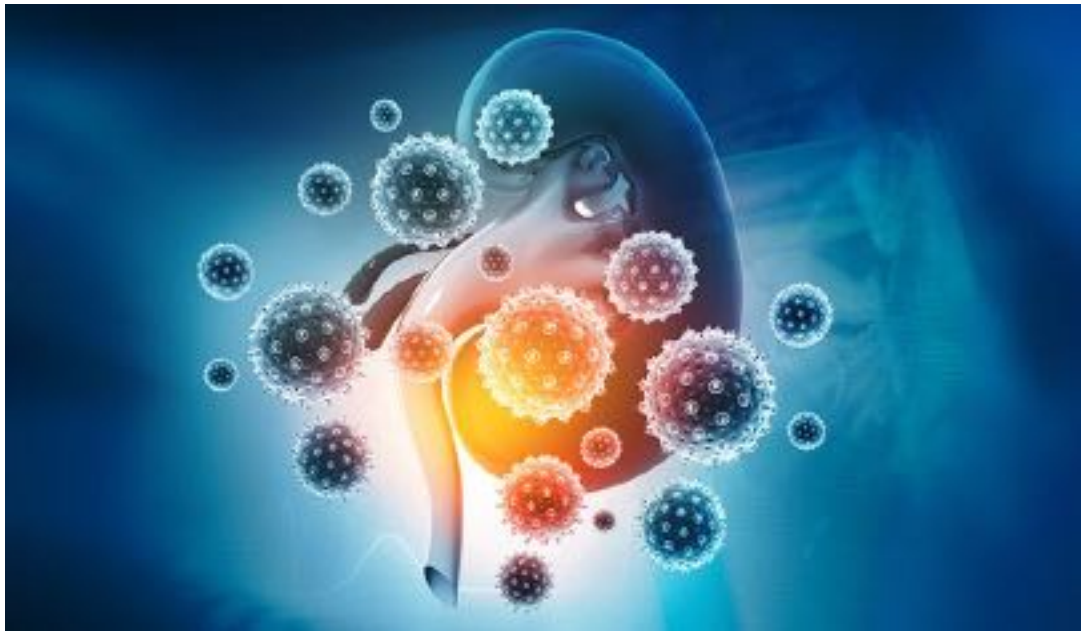
Atypical HUS is a thrombotic microangiopathy most commonly presenting in children.

- The pathophysiology is largely attributed to accelerated activation of the alternative complement system leading to endothelial dysfunction and subsequent thrombotic microangiopathy with end-organ damage.

- This can occur either by inherited mutations in the complement regulatory genes or by acquired autoantibodies to complement regulatory proteins, most commonly against complement factor H.



Can COVID cause thrombotic microangiopathy?



International Journal of
Molecular Sciences

MDPI

Review

Coronavirus Disease 2019-Associated Thrombotic Microangiopathy: Literature Review

Marija Malgaj Vrečko [1,2], Andreja Aleš Rigler [1,2] and Željka Večerić-Haler [1,2,*]

Review of global literature revealed 46 cases of TMA in association with COVID-19. Among identified cases, 18 patients presented as thrombotic thrombocytopenic purpura (TTP) and 28 cases presented as atypical hemolytic uremic syndrome (aHUS).

Of the 28 patients:

- Three had relapsing disease (presumed primary aHUS) with previously diagnosed pathogenic genetic complement abnormalities

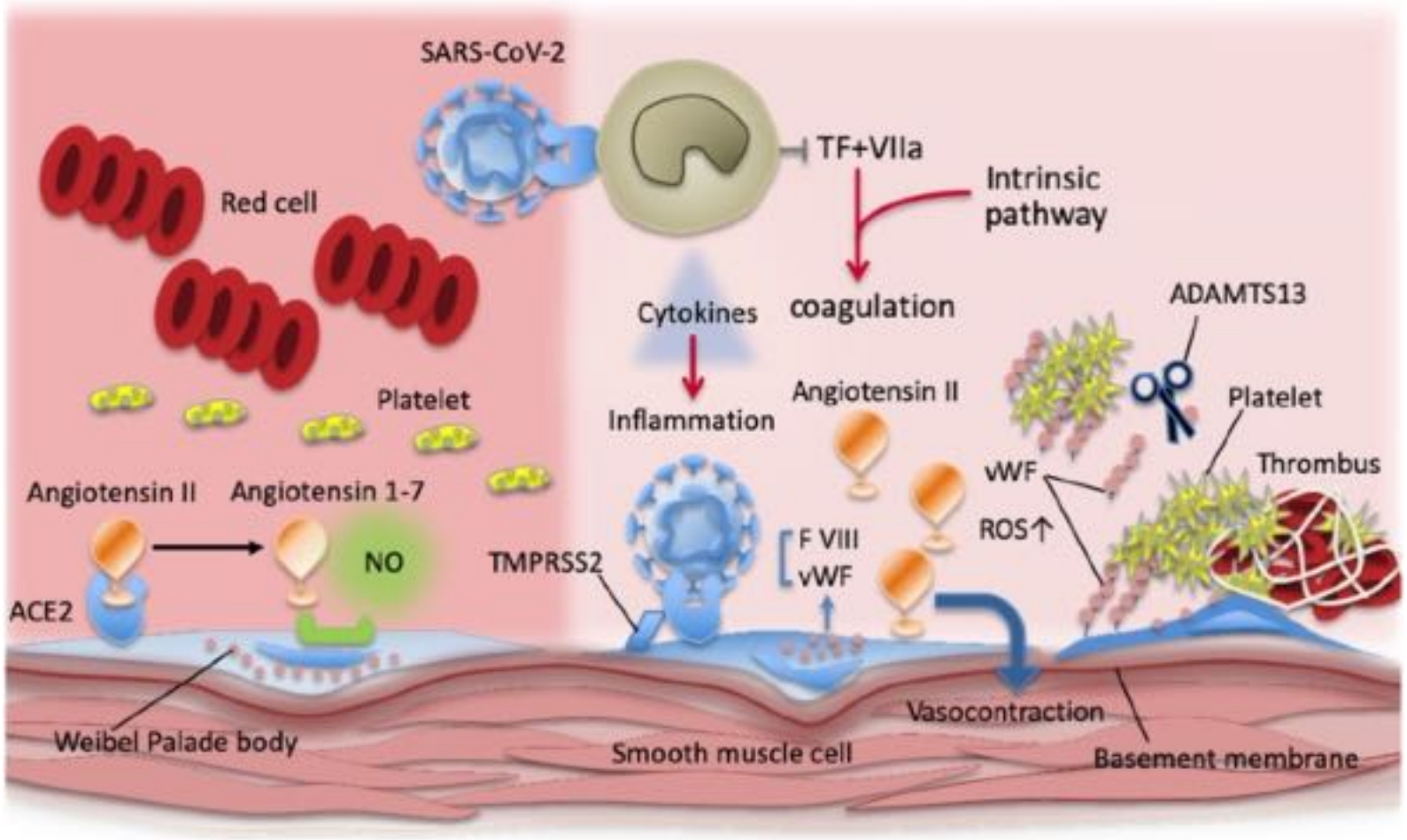
- Three patients with no previously known aHUS, there were likely pathogenic complement gene variants associated to an altered regulation of the complement alternative pathway detect

- One patient had the risk haplotype in the CFH gene, which predisposes to aHUS

- Seven patients showed laboratory evidence of functional dysregulation of the alternative complement pathway, although no genetic analysis of the complement system was performed

- In the other 14 patients, No complement abnormalities were detected

So, COVID-19 likely represents a second hit of aHUS that manifests in a certain proportion of genetically predisposed individuals.



Kurian et al. Journal of Medical Case Reports (2021) 15:587
https://doi.org/10.1186/s13256-021-03144-2

Journal of Medical Case Reports

CASE REPORT Open Access

Case series: coronavirus disease 2019 infection as a precipitant of atypical hemolytic uremic syndrome: two case reports

Christine J. Kurian[1*], Zachary French[1], Patrick Kukulich[1], Matthew Lankiewicz[2], Sushil Ghimire[3], Omar H. Maarouf[4], Sanaa Rizk[5] and Ruben Rhoades[5]

It reported two patients presenting with atypical hemolytic uremic syndrome precipitated by COVID 19 infection.

- The first patient, a 25-year-old Hispanic male, had one prior episode of thrombotic microangiopathy presumed to be atypical hemolytic uremic syndrome precipitated by infuenza A, and re-presented with thrombocytopenia, microangiopathic hemolytic anemia, AKI, with confirmed coronavirus disease 2019 positivity.

- The second patient, a 31-yearold Caucasian female, had no personal history of thrombotic microangiopathy, though reported a family history of suspected atypical hemolytic uremic syndrome. She presented with similar laboratory derangements, AKI requiring hemodialysis, and confirmed coronavirus disease 2019 positivity.

Both patients were treated with eculizumab with complete resolution of their hematologic and renal complications.

Cureus

Open Access Case Report

DOI: 10.7759/cureus.27962

COVID-19: A Rare Cause of Hemolytic Uremic Syndrome

Kimberly Boldig [1], Rishu Batra [2], Augusto Villegas [3]

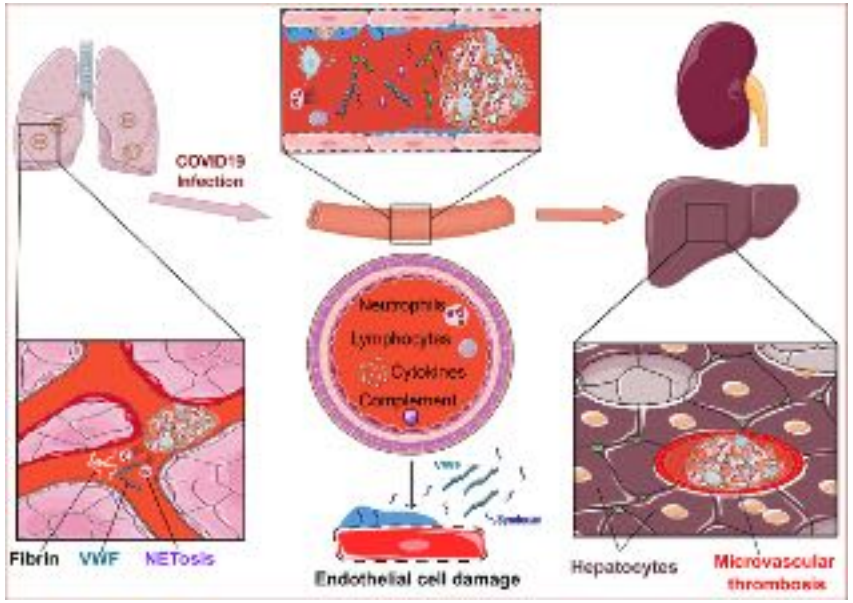
1. Internal Medicine, University of Florida College of Medicine – Jacksonville, Jacksonville, USA 2. Internal Medicine, Orange Park Medical Center, Orange Park, USA 3. Hematology and Oncology, Florida Cancer Specialists and Research Institute, Fleming Island, USA

Review began 08/02/2022
Review ended 08/08/2022
Published 08/13/2022

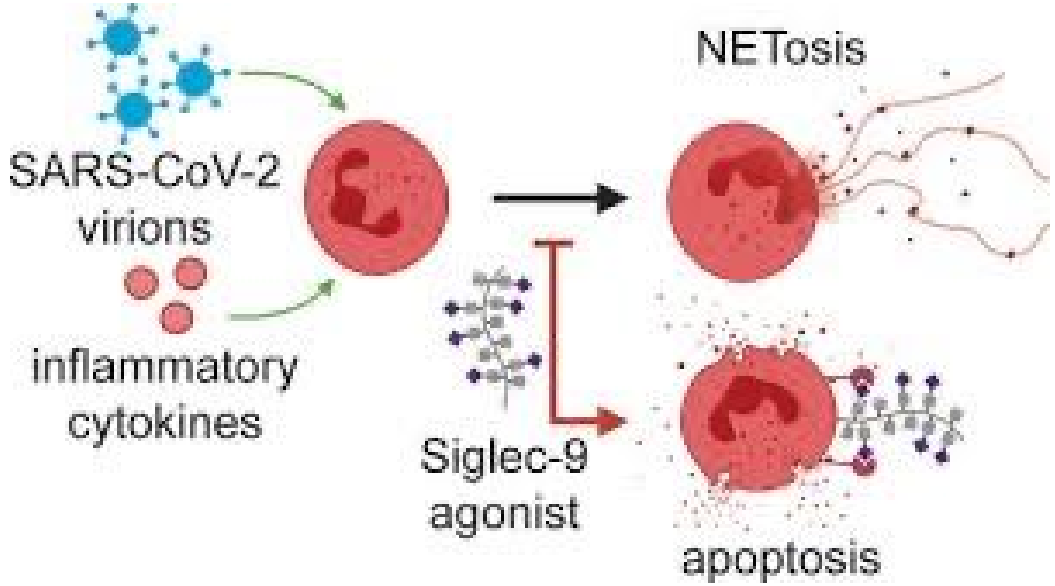
A case of a 36-year-old woman with a previous history of aHUS, who was now in remission but undergoing treatment with eculizumab. She tested positive for COVID-19 after developing symptoms of an upper respiratory tract infection. Within three days, she presented with acute hypoxic respiratory failure and acute renal failure.

Multiple theories have been proposed for the mechanism of aHUS precipitated by COVID-19 is unknown.

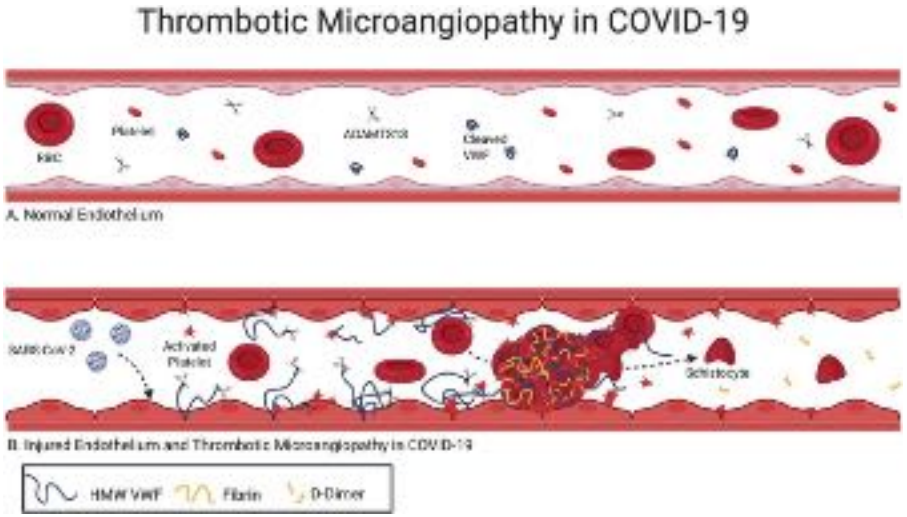
- Direct endothelial damage by COVID-19 may be a contributing mechanism to its precipitation of aHUS. One case report notes severe endothelial injury in lung tissue of seven patients who died from COVID19, which was unique when compared with lungs from patients with infuenza A or uninfected controls



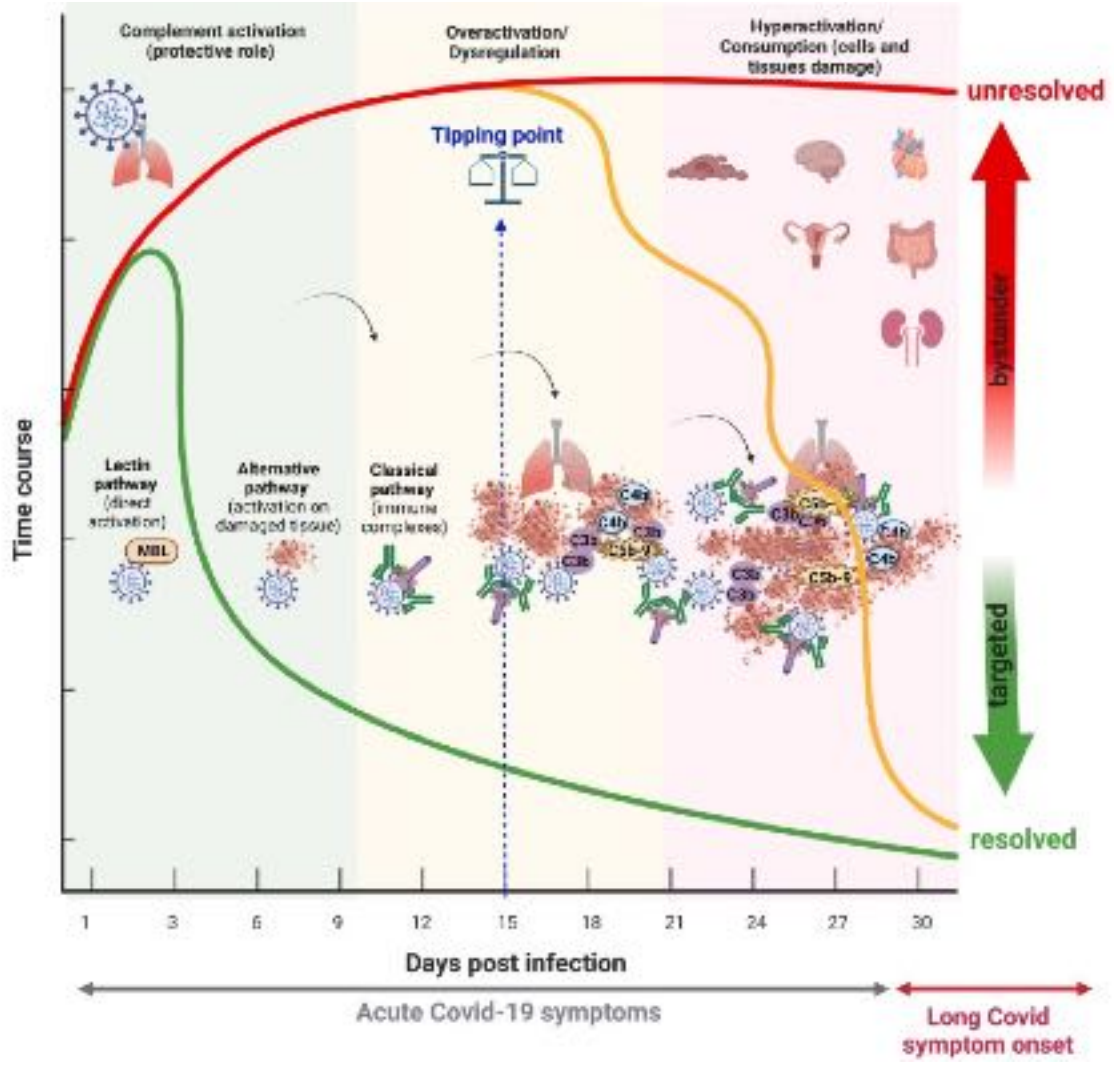
Another report proposes the mechanism of endotheliitis by COVID-19 being not only due to direct effects of viral involvement and the subsequent inflammatory response, but also via induction of apoptosis. A potential mechanism for this may be binding to the SARS-CoV-2 receptor, angiotensin-converting enzyme 2 (ACE2), which is highly expressed on vascular endothelial cells.



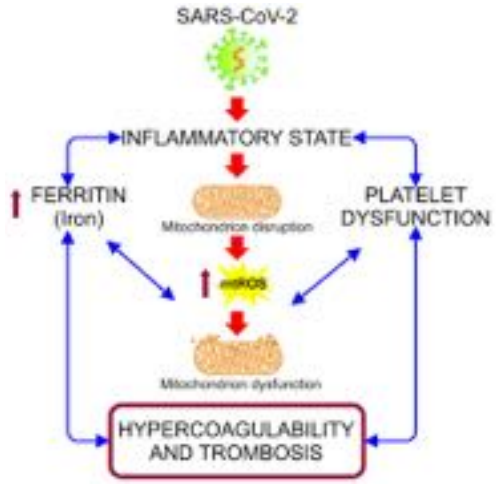
Complement activation by COVID19 is another leading theory regarding the mechanism of aHUS precipitated by COVID-19. For example, one case report detailed the findings that lung and skin tissue of patients with severe COVID-19 infection with either respiratory failure or purpuric skin rash had substantial deposits of complement cascade proteins within the microvasculature, suggesting a systemic activation of the complement pathways by COVID-19



the spike protein may directly activate the alternative complement pathway. This is supported by a report of four COVID-19 patients being successfully treated with eculizumab for severe pneumonia and acute respiratory distress syndrome (ARDS).



The progression and severity of TMA in patients with COVID-19 could also be due to significant hypercoagulation. The pathophysiology of coagulopathy associated with COVID-19 is complex and currently not fully understood. Until recently, it appeared to be related to an enhanced inflammatory response to viral infection rather than to the specific viral properties of SARS-CoV-2. However, recent research has shown that viral spike protein causes significant ultrastructural changes in whole blood under experimental conditions, leading to extensive spontaneous fibrin network formation and severe impairment of fibrinolysis. Such impairment of clotting in acute COVID-19 infection could contribute significantly to the persistence of microclots in COVID-19 patients, which may also be of major clinical significance for the course and outcome of COVID-19-associated TMA.



Treatment of TMA generally relies on four modalities: therapeutic plasma exchange (TPE), immunosuppression, monoclonal antibodies, and treatment of the underlying cause.

Eculizumab is a monoclonal anti-C5 antibody that blocks the formation of the MAC on endothelial cells surfaces and has revolutionized the prognosis of renal TMA known as atypical Haemolytic and Uremic syndrome. A previous report has suggested the safety and potential benefits of Eculizumab in COVID 19.

COVID-19-associated TMA represents a new, distinct entity that may present as TTP or aHUS and probably deserves a special, additional place in the classification

THANK YOU

MIS-C associated with COVID-19
US Centers for Disease Control and Prevention[37]
<21 years
Fever and elevated inflammatory markers
Clinically severe illness requiring hospitalisation; and multisystem (two or more) organ involvement (cardiac, renal, respiratory, haematological, gastrointestinal, dermatological, or neurological)