What can go wrong in severe COVID?

1. T cell exhaustion
2. Cytokine storm aka cytokine release syndrome (CRS)
3. Bradykinin storm
4. Antibody-dependent enhancement (ADE)
5. Auto-antibodies

1. T cell exhaustion in COVID

- **CD8+ T cells (and natural killer cells) may have exhaustion characteristics in severe patients,** with high expression of inhibitory receptors (IRs) such as PD-1, upregulation of exhaustion-associated genes (such as HAVCR2 (TIM-3) and LAG3), decreased expression of pro-inflammatory cytokines (e.g. IFN-γ and IL-21), increased anti-inflammatory cytokines (IL-10) and increased apoptosis. There is a correlation between viral load and exhaustion severity in CD8+ T cells.
- **However, whether T cells are truly exhausted during COVID-19 has been a controversial issue, particularly as some severe patients show no sign of T cell exhaustion.**
- **Why does it occur in some severe patients and not others?**
- Expression of inhibitory receptors (IRs), such as PD-1, correlates with worse clinical outcomes but it is unclear whether their upregulation in COVID-19 patients is causative in leading to T-cell exhaustion.
- Instead, sustained overexpression of IRs may prevent a hyperactive host immune response through counteracting T-cell function, possibly through the anti-inflammatory cytokine IL-10.
- PD-1 was found to be upregulated on both serum CD8+ and CD4+ T cells in severe compared with mild COVID and increased exponentially with the period of illness in ICU patients. Nevertheless, some studies have found no association of PD-1 with T cell exhaustion.

2. The cytokine storm

- The cytokine storm, aka cytokine release syndrome (CRS), hypercytokinaemia or cytokine storm syndrome are known as life-threatening systemic inflammatory syndromes involving elevated levels of circulating cytokines and immune-cell hyperactivation.
- **No single definition of the cytokine storm is widely accepted and there is much disagreement about how the 'cytokine storm' differs from a hyperactive inflammatory response. Many scientists have called for a precise definition.**
- **Where there is no precise medical definition for a diagnosis, we should be cautious.**
- For reasons that are not yet clear, the SARS-CoV-2 virus seems more likely to result in excessive cytokine release compared to diseases caused by other viruses, possibly due to specific dysregulation of the type-I interferon (IFN) response and its downstream cytokine signatures, rarely seen in other viruses.
- But does this amount to a 'cytokine storm'? Without a definition, we can't be certain. Nevertheless, it is taken to mean 'acute overproduction and uncontrolled release of pro-inflammatory cytokines and chemokines, both locally and systemically', i.e. it is indistinguishable from severe COVID!
- It is important to remember that circulating cytokine levels can be difficult to measure because cytokines have short half-lives, systemic levels may not accurately reflect local microenvironment, tissue concentrations (e.g. the pulmonary compartment)

Scientific opinion doubting the existence of a cytokine storm in COVID-19

- **A study by Gao et al found evidence that COVID-19 does not cause a 'cytokine storm'.**
- **The virus kills by directly injuring the lung, whereas the cytokine storm would be expected to cause multi-organ inflammatory disease and organ failure, which is not occurring** (Gao, CA. et al. "Machine learning links unresolving secondary pneumonia to mortality in patients with severe pneumonia, including COVID-19." J Clin Invest. 2023 Apr 27;e170682).
- A systematic review of 47 studies reporting the cytokine storm in COVID, concluded that '(we) found high variability in CRS definitions and associated biomarker cut-off values... We call for a standardized definition of CRS, especially in COVID-19 patients'. (Mangalmurti N, Hunter CA. Cytokine Storms: Understanding COVID-19. Immunity. 2020 Jul 14;53(1):19-25)
- 'Cytokine storm has no definition. A critical evaluation of the term cytokine storm and its relevance to COVID-19 is warranted……. Although the term *cytokine storm* conjures up dramatic imagery and has captured the attention of the mainstream and scientific media, the current data do not support its use.' (Sinha P, et al. Is a 'cytokine storm' relevant to COVID-19? JAMA Intern Med 2020; 180:1152–1154)
- 'It is uncertain whether the elevated levels of pro-inflammatory cytokines in severe disease are reflecting damage or are protective' (Niedźwiedzka-Rystwej P, et al. Immune Signature of COVID-19: In-Depth Reasons and Consequences of the Cytokine Storm. Int J Mol Sci. 2022 Apr 20;23(9):4545).
- 'Distinguishing between protective inflammatory responses and pathologic cytokine storm…..is quite challenging' (Fajgenbaum DC, June CH. Cytokine Storm. N Engl J Med. 2020 Dec 3;383(23):2255-2273).

What is claimed to cause a cytokine storm? The views from published studies 1/2

- Genetic factors, such as familial haemophagocytic lymphohistiocytosis (HLH), which lead to problems in immune system cells.
- Pre-existing comorbidities (hypertension, diabetes, cardiovascular diseases, respiratory diseases, older age, male gender). These conditions are known to perturb the levels of cytokines, chemokines and angiotensin-converting enzyme 2 (ACE2), an essential receptor involved in SARS-CoV-2 entry into the host cells.
- Concomitant infections, such as influenza.
- People with certain autoimmune syndromes e.g. lupus erythematosus, when the excessive cytokine are known as ‘macrophage activation syndrome’ (MAS), as the proinflammatory cytokines are secreted from activated macrophages, likely due to rapid replication of the virus.
- Some medical therapies, e.g. CAR-T therapy for leukaemia or following transplants.
- Elevated angiotensin II (because SARS-CoV-2 hijacks the ACE2 receptor) increases cytokine release
- Mast cell activation syndrome (MCAS) due to virus-induced mast cell activation, leading to release of histamine, proteases, cytokines, chemokines, prostaglandin D2 and leukotrienes, inducing their own positive feedback loop. Autopsy studies showed accumulation of mast cells in the lungs.
- Molecular mimicry, where the spike protein mimics 1) anti-inflammatory cytokines, tricking the body into thinking that they have already been released or 2) PARPs, which are antigens for MHCs.
- Excessive oxidative stress.

What is claimed to cause a cytokine storm? The views from published studies 2/2

- Activation of ACE2, a disintegrin, metalloprotease 17 and matrix metalloproteinase-9 (MMP-9).
- Non-spike viral proteins, which enter the body through receptors other than ACE2.
- Antibody-dependent enhancement (ADE), which itself triggers additional pro-inflammatory cytokines.
- Silent hypoxaemia, which may lead to molecular changes exacerbating coagulopathy and cytokine release.
- Hyperferritinaemia (one result of hyperactivation of macrophages) induces the production of cytokines and chemokines, which aggravates the positive feedback loop.
- Components of neutrophil traps (NETs) may be involved in the pathogenesis of cytokine storm through the interplay between inflammation and thrombosis in the affected lungs.
- Virus replication leads to pyroptosis (inflammatory cell death), which triggers the release of pro-inflammatory cytokines and affects macrophage and lymphocyte functions, causing peripheral lymphopaenia.

When this many potential causes are suggested, it is clear that no-one knows precisely.

Certainly, starting COVID in an inflammatory state (pre-existing comorbidities, including autoimmune conditions) is likely to promote excessive cytokine release.

Similarly, a pre-existing dysregulated immune system will not have in place the normal checks and balances to counter excessive inflammation.

What does excessive cytokine release do?

- **The key feature of excessive cytokine release is delayed production of type I and type III IFNS followed by over-activation of IFNs and depleted T cell activation.**
- The cytokines (principally IL-6, IL-1, IL-10, TNF-α and type II IFNγ) and chemokines interact with the complement and coagulation systems to induce leakage of plasma, increased vascular permeability, disseminated intravascular coagulation (DIC), acute respiratory distress syndrome (ARDS), multi-organ failure and death.
- **These cytokines drive a positive feedback loop** by activating other innate and adaptive immune cells and increased myelopoiesis (production of monocytes and neutrophils from bone marrow), which in turn produce more pro-inflammatory cytokines, causing PANoptosis (the innate immune inflammatory cell death pathway) through activation of caspase 8. Similarly, the depleted T lymphocytes allow uncontrolled cytokine release inducing inflammatory injury and organ failure.
- TNF and IFNγ signalling can drive lymphopaenia and immunosuppression and deplete germinal centres in the spleen and lymph nodes, which can limit B cell affinity maturation, isotype switching and production of mature and neutralising antibodies.
- IL-6 is a platelet augmentation factor and stimulates production of vascular endothelial growth factor (VEGF) in the endothelium and histamine production by mast cells, leading to increased vascular permeability, hypotension, hypoxia and peripheral oedema, while IL-1 may stimulate the release of other pro-inflammatory cytokines, nitric oxide and inflammatory arachidonic acid products such as prostaglndins and thromboxane A2.

3. Bradykinin storm in severe COVID

- **Bradykinin is a vasoactive peptide that helps to regulate blood pressure and promotes inflammation.** It causes arterioles to dilate via the release of prostacyclin, nitric oxide, and endothelium-derived hyperpolarizing factor and makes veins constrict, via prostaglandin F2, thereby leading to leakage into capillary beds, due to the increased pressure in the capillaries.
- **A bradykinin storm is said to be an important factor in many COVID-19 fatalities.**
- **The SARS-CoV-2 virus downregulates the body's ability to break down bradykinin**
- As bradykinin accumulates, the more serious COVID-19 symptoms appear, including arrhythmias, low blood pressure and neurological symptoms such as dizziness, seizures, delirium and stroke. At high levels, bradykinin can lead to a breakdown of the blood-brain barrier, thereby allowing toxic compounds into the brain.
- **Again, no precise definition of a bradykinin storm exists!**

How does the bradykinin storm work?

- **Mounting clinical data suggest COVID-19 is primarily a vascular endothelial disease rather than a respiratory one, i.e. a disease of the lining of the blood vessels.**
- **Bradykinin actually increases vascular permeability (blood vessel leakage), which can lead to death.**
- Bradykinin causes arterioles to dilate via the release of prostacyclin, nitric oxide, and endothelium-derived hyperpolarising factor and makes veins constrict via prostaglandin F2, leading to leakage into capillary beds due to the increased pressure in the capillaries. It is controlled by the renin-angiotensin system (RAS), which is a central regulator of renal and cardiovascular functions. Over-activation of the RAS leads to renal and cardiovascular disorders, such as hypertension and chronic kidney disease, the major risk factors for stroke, myocardial infarction, congestive heart failure, progressive atherosclerosis and renal failure.
- In the lungs, leakage leads to fluid buildup that can trigger inflammation when immune cells also leak out into the lungs. Bradykinins can also mimic ACE inhibitors, drugs to reduce blood pressure, by lowering blood pressure and reducing the sense of taste and smell.

4. Antibody-dependent enhancement (ADE)

- ADE can also be known as immune enhancement, antibody-dependent cellular cytotoxicity and pathogenic priming.
- **ADE is where the virus binds to suboptimal antibodies, which facilitate its entry into host cells, thereby promoting viral replication and enhancing the severity of the infection.**
- ADE allows the virus to avoid innate immune sensors and pattern recognition receptors. i.e. **it is an immune evasion strategy.**
- In a healthy immune system, an inhibitory signal, known as antibody feedback, is generated as the antigen/antibody complex binds to the B cell receptor. Where the immune system is dysregulated, antibody feedback may not occur.
- **Antibody-dependent enhancement (ADE) has been associated with severe infection and poor disease outcomes in many viral infections, particularly with respiratory viruses.**
- It has been suggested that ADE is one of the mechanisms causing hyperactivation of macrophages and monocytes, leading to excessive cytokine production.
- Several experts have warned of the potential problems of ADE with antibody therapies and vaccines that trigger antibody production. For example, vaccinations against Dengue virus and a coronavirus affecting cats were deemed unsuccessful because they resulted in antibody-dependent enhancement that made the infection worse in those that had been vaccinated when compared to those that had not been vaccinated.

Antibody-dependent enhancement (ADE) in COVID-19

- **Again, there are no diagnostic criteria for ADE. Consequently, we have no idea whether it is occurring or not.**
- '…no definitive clinical data is available that indicates the occurrence of ADE during....SARS-CoV-2 infection.' (Ahmad T, et al. COVID-19: The Emerging Immunopathological Determinants for Recovery or Death. Front Microbiol. 2020 Dec 1;11:588409)
- 'ADE has been observed in many viral infections and is supposed to complicate the course of COVID-19. However, the evidence is insufficient.' (Ziganshina MM, et al. Antibody-Dependent Enhancement with a Focus on SARS-CoV-2 and Anti-Glycan Antibodies. Viruses. 2023 Jul 20;15(7):1584)
- '…**multiple studies do not support [ADE's] occurrence (in SARS-CoV-2 infection)**' (Al Dossary R. Antibody Dependent Enhancement of SARS-CoV-2 Infection in the Era of Rapid Vaccine Development. Med Arch. 2022 Oct;76(5):383-386)
- '[A meta-analysis] finding demonstrates that SARS-CoV-2 may not trigger ADE at the population level' (Gan L, et al. Does potential antibody-dependent enhancement occur during SARS-CoV-2 infection after natural infection or vaccination? A meta-analysis. BMC Infect Dis. 2022 Sep 19;22(1):742).
- "At present, there are no known clinical findings, immunological assays or biomarkers that can differentiate any severe viral infection from immune-enhanced disease, whether by measuring antibodies, T cells or intrinsic host responses." (Arvin AM, et al. A perspective on potential antibody-dependent enhancement of SARS-CoV-2. Nature. 2020 Aug;584(7821):353-363)
- ADE remains a concern for vaccination and the use of therapeutic neutralising antibodies from donors, but apparently not so much for COVID itself.

5. Autoantibodies

- **Autoantibodies are rogue antibodies produced by our immune system that are directed against our own body, potentially causing considerable damage and destroying the body's healthy cells and trigger an autoimmune disease.**
- **The production of autoantibodies is well known in viral infections but the precise mechanism is largely unknown.**
- **Scientists are unclear whether autoantibodies arise as part of the viral strategy of immune evasion or whether they are a product of a dysfunctional immune system.**
- It may occur through molecular mimicry, one of the leading mechanisms by which disruption of immune tolerance, and hence autoimmunity, is triggered. Many autoimmune diseases are caused by infection-driven autoantibodies such as arise following malaria.
- Autoantibodies may arise from a predominantly extrafollicular B cell immune response. Extra-follicular B cell activation lacks essential checkpoints to prevent autoreactivity and hence is more prone to generating autoantibodies. The antibodies are also predominantly non-neutralising.
- Production of autoantibodies increases with age and occurs at a much higher frequency among men than women.

‘Rogue antibodies’ picked up by the Mail

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Is this why some people get sicker than others with Covid-19? Immune cells called autoantibodies could help explain our vulnerability to infection

By ADELE WATERS FOR THE DAILY MAIL
UPDATED: 02:15, 25 January 2022

- ‘Proteins that attack us from within’ sounds more like a description for a new sci-fi film than a very real threat to humankind.
- But autoantibodies — also known as ‘rogue’ antibodies — are just that.
- They are immune cells that turn against us, instead of defending our bodies against infection, they attack our healthy tissues and vital organs.
- This process is responsible for a long list of autoimmune diseases such as rheumatoid arthritis.’

Autoantibodies in severe COVID

- **Severe COVID may display similarities to autoimmune conditions and numerous case reports have described development of new autoimmune disease following COVID infection,** such as rheumatoid arthritis and psoriatic arthritis.
- A Russian post-mortem study of COVID-19 patients found a classic pattern of autoimmune damage in the lungs, kidneys, liver, adrenal gland and intestines.
- In COVID-19, development of autoantibodies may explain some of the delay in the onset of severe symptoms and the development of lung and heart/circulation problems as well as multi-organ failure.
- In patients with obesity (a risk factor for severe COVID), the majority of SARS-CoV-2-specific antibodies are autoimmune and not neutralising. Autoantibodies are linked to Long COVID and are associated with neurocognitive symptoms, fatigue, myalgia and breathing difficulties during low-intensity exercise. Some of these patients go on to develop autoimmune thyroiditis, diabetes insipidus or type 1 diabetes.
- Autoantibodies against the spike protein promoted autoimmune thyroiditis, and there was cross-reactivity with central nervous system (CNS) proteins such as neurofilament protein, beta-amyloid and alpha-synuclein, all implicated in neurodegenerative disease.

Types of autoantibody seen in severe COVID

- **Autoantibodies to type I interferons**: 10-15% of COVID patients with critical pneumonia have neutralising autoantibodies against type I IFNs and they were found in nearly 20% of COVID deaths. Pre-existing autoimmune antibodies were detected prior to infection and appear to increase the severity of COVID-19 infection, suggesting that their existence, should be considered a comorbidity, predisposing towards severe COVID. They are more commonly found in the elderly.
- Autoantibodies to phospholipids and phospholipid-binding proteins can cause antiphospholipid syndrome, a potentially life-threatening autoimmune thromboinflammatory disease with coagulopathy, presenting as thrombotic arterial and venous occlusions, pulmonary embolism and strokes. A study of hospitalised patients showed that >50% had autoantibodies to phospholipids.
- Autoantibodies to ACE2, which decreased ACE2 activity and could lead to an increase in angiotensin II, causing a proinflammatory state.
- Autoantibodies to annexin A2 prevent Annex A2 from keeping cell membranes stable and ensuring the integrity of small blood vessels in the lungs. Seen particularly in patients who died of COVID.
- Autoantibodies to tight junction proteins (occluding, zonulin, betacatenin, S100B) which are responsible for maintaining the integrity of lung, gut and blood-brain barriers. Without this integrity, the virus can spread more quickly throughout the body, promoting systemic cytokine production. Permeability of the immune barriers is known as an independent risk factor for autoimmune disease.
- High prevalence seen of antinuclear antibodies, antineutrophil cytoplasmic antibodies and ASCA immunoglobulin A antibodies.

Autoimmune disease and COVID: clinical evidence and potential mechanisms

- Professor Yehuda Shoenfeld, well known researcher in autoimmunity, has found that **SARS-CoV-2 triggers autoimmunity in some predisposed individuals.** He identified three common determinants that underlie the pattern of immune dysregulation that spirals into autoimmune disease in genetically susceptible individuals:
  - Cytokine storm associated with severe infection, coupled with high circulating levels of iron in the form of ferritin (hyperferritinaemia) that's often associated with severe disease.
  - The production of disease-causing autoantibodies, these being specific types of protein produced by B cells of the adaptive immune system that attack particular (self) proteins (e.g. interferon, specific glycoproteins) that are needed for healthy function.
  - Underlying genetic predisposition, notably people with a particular genetic variation (polymorphism) in the human leukocyte antigen (HLA) (HLA-DRB1).
- Studies by Shoenfeld's research group and others have also identified associations between particular types of autoimmune diseases developing after severe COVID disease. These include immune thrombocytopenic purpura (ITP), Guillian-Barrė syndrome (GBS), Miller Fisher syndrome (MFS), and, in children, Kawasaki-like disease.

What can go wrong in severe COVID: summary

- T cell exhaustion, the cytokine storm, the bradykinin storm and antibody dependent enhancement have all been cited in connection with severe COVID-19.
- There is no clinical definition of any of these, suggested mechanisms vary and some scientists are extremely wary of using the terms as they are emotive and imprecise.
- Autoantibodies may be produced during severe COVID-19. Autoantibodies to interferons may be particularly damaging to the immune response to COVID.

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