Cytokine storm in Covid-19

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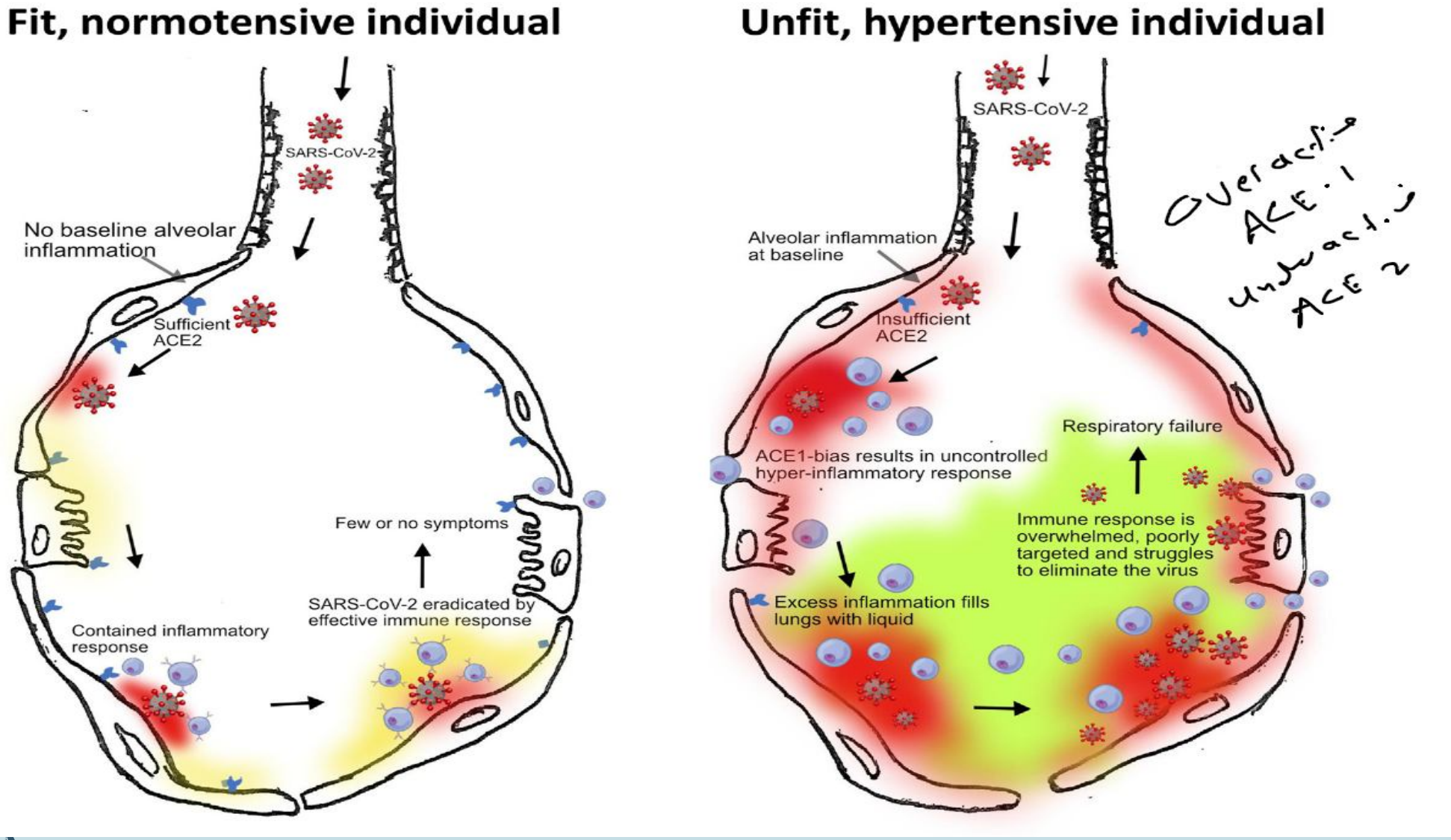
MB ChB (Stell)

Disease spectrum

1. Asymptomatic
   - viral replication phase with minor non specific symptoms

2. Pulmonary phase
   - Late viral phase and early hyperinflammation/cytokine storm phase
   - Hospital presentation

3. Cytokine storm phase
   - Severe Covid signs and symptoms, higher FiO2 requirement and support
   - Usually need high care and/or ICU
   - Decreasing viral load at this point but worsening clinical condition due to host response


Fit, normotensive individual
SARS-CoV-2
No baseline alveolar inflammation
Sufficient ACE2
Few or no symptoms
SARS-CoV-2 eradicated by effective immune response
Contained inflammatory response
Unfit, hypertensive individual
SARS-CoV-2
Alveolar inflammation at baseline
Insufficient ACE2
ACE1-bias results in uncontrolled hyper-inflammatory response
Respiratory failure
Immune response is overwhelmed, poorly targeted and struggles to eliminate the virus
Excess inflammation fills lungs with liquid

Why is this important?

Severe and critical covid 19 is caused by overwhelming immune response with inflammation and damage to multiple organs particularly the lung parenchyma

1. Type 1 respiratory failure
2. ARDS
3. MOD

This is what we help our patients get through.

Cytokine release storm(CRS)

1993:Initially described by Ferrara et al in graft-vs-host disease

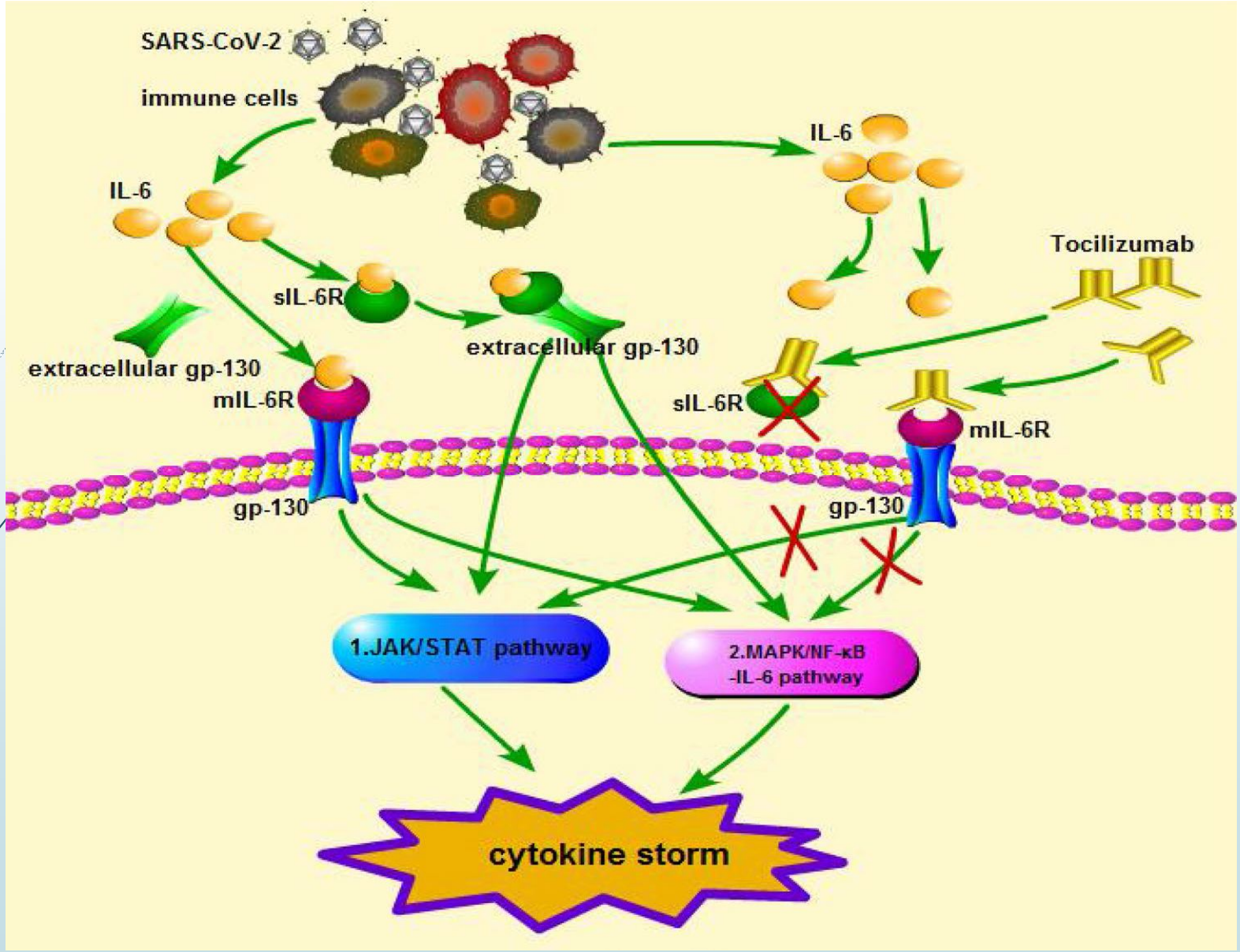
2003: SARS

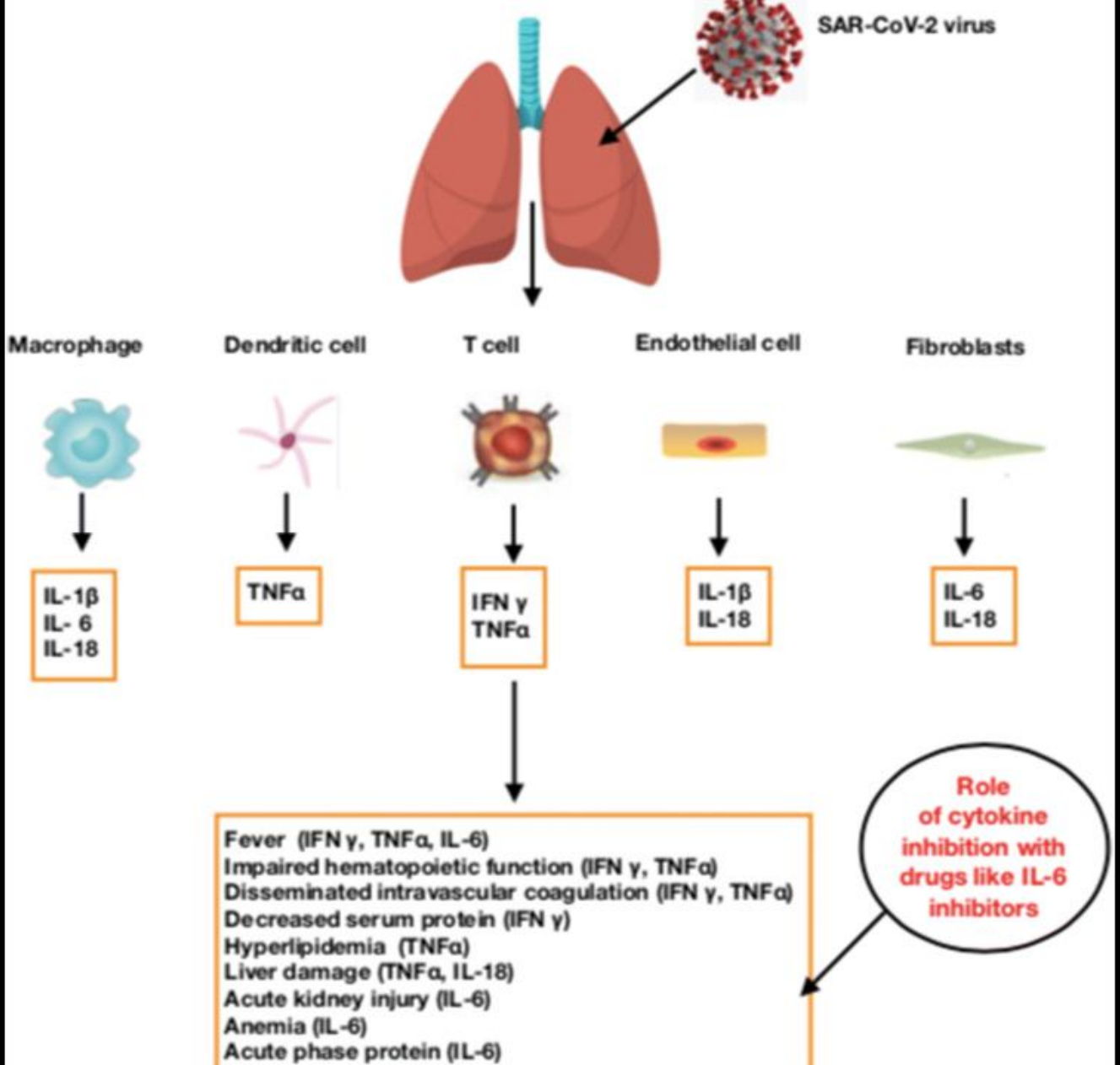
Associated with high mortality and multi-organ failure

Also seen in Kawasaki disorder, Toxic shock syndrome in children

Pathophysiology: immune system overwhelming response to antigen presentation and stimulation of the adaptive immune system

Chemokines in Covid: interleukin (IL)-1, ***IL-6***, IL-12, and IL-18, ***TNFa***


SARS-CoV-2
immune cells
IL-6
IL-6
Tocilizumab
sIL-6R
extracellular gp-130
extracellular gp-130
mIL-6R
sIL-6R
mIL-6R
gp-130
gp-130
1.JAK/STAT pathway
2.MAPK/NF-kB
-IL-6 pathway
cytokine storm


SAR-CoV-2 virus
Macrophage
Dendritic cell
T cell
Endothelial cell
Fibroblasts
IL-1β
IL- 6
IL-18
TNFα
IFN γ
TNFα
IL-1β
IL-18
IL-6
IL-18
Fever (IFN γ, TNFα, IL-6)
Impaired hematopoietic function (IFN γ, TNFα)
Disseminated intravascular coagulation (IFN γ, TNFα)
Decreased serum protein (IFN γ)
Hyperlipidemia (TNFα)
Liver damage (TNFα, IL-18)
Acute kidney injury (IL-6)
Anemia (IL-6)
Acute phase protein (IL-6)
Role of cytokine inhibition with drugs like IL-6 inhibitors

IL 6 Inhibitors

Multiple RCTs are currently being done to validate the use and benefit of these agents in multiple countries across the world.

Use of these agents only experimental in some hospitals currently.

Pro's:

1. Single IV dose needed
2. Could potentially influence mortality and morbidity outcomes as well as decongest ICU's

Cons:

1. Expensive
2. Side effects: infections(Particularly TB), neutropenia, thrombocytopenia, liver impairment

In summary

- Cytokine storm is the major pathophysiological determinant of severity of disease in Covid 19
- IL 6 Inhibitors could play a major role in disease mortality and morbidity if their effectivity can be validated from the current RCTs being done
- Should we start measuring IL 6 levels in the sicker patients?


We Will GetThrough This Storm
Stephen Pishner

Original Investigation

ONLINE FIRST FREE

June 8, 2020

Clinical Characteristics of 58 Children With a Pediatric Inflammatory Multisystem Syndrome Temporally Associated With SARS-CoV-2

Elizabeth Whittaker, MD[1,2]; Alasdair Bamford, MD[3,4]; Julia Kenny, MD[5,6]; et al

Author Affiliations | Article Information

JAMA. Published online June 8, 2020. doi:10.1001/jama.2020.10369

Original Investigation

ONLINE FIRST FREE

June 3, 2020

Epidemiology, Clinical Features, and Disease Severity in Patients With Coronavirus Disease 2019 (COVID-19) in a Children's Hospital in New York City, New York

Philip Zachariah, MD, MSc[1,2]; Candace L. Johnson, MD[1,2]; Katia C. Halabi, MD[1]; et al

Author Affiliations | Article Information

JAMA Pediatr. Published online June 3, 2020. doi:10.1001/jamapediatrics.2020.2430

Clin Drug Investig. 2020 Apr 26 : 1–8.
doi: 10.1007/s40261-020-00917-3 [Epub ahead of print]

PMCID: PMC7183818
PMID: 32337664

Rational Use of Tocilizumab in the Treatment of Novel Coronavirus Pneumonia

Shengyu Zhang,[1] Lei Li,[2] Aizong Shen,[1] Yongwu Chen,[1] and Zhigang Qi[3]

Author information ▸ Copyright and License information Disclaimer

Pharmaceut Med. 2020 Jun 13;1-9. doi: 10.1007/s40290-020-00342-z. Online ahead of print.

IL-6 Inhibitors in the Treatment of Serious COVID-19: A Promising Therapy?

Shubham Atal [1], Zeenat Fatima [2]

Affiliations + expand

PMID: 32535732 PMCID: PMC7292936 DOI: 10.1007/s40290-020-00342-z