Therapeutic immunocompromise in the age of COVID 19: When is your patient at risk?

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Disclosures

	Company/Organization	Details
I am a member of an **Advisory Board or equivalent** with a commercial organization.	Emerade Sanofi-Genzyme Liffey Biotech Immunology CSO	Adboard member Adboard member Advisor for development of therapeutic molecule for allergic hypersensitivities
I am a member of a **Speaker's Bureau**	n/a	
I have **received payment from a commercial organization** (including gifts or other consideration or 'in kind' compensation).	n/a	

Objectives

- Describe the immunological events occurring in mild, moderate and severe COVID infection
- Discuss the risks of COVID-19 in patients on biological immunosuppression and know the knowledge gaps
- Develop a clinical reasoning strategy to offer patients of the "best" options during the pandemic

Case 1

- 28 year old female with IBD, on treatment with anti-TNF-R inhibitor. In March, because of fears of severe COVID-19 in immunosuppressed patients, she stopped taking the medication and now has a significant flair of her disease.
- What do you advise?

Poll 1
For this patient with IBD would you

- 1. Suggest she restart her anti-TNF-R therapy as her disease is worse than COVID?
- 2. Suggest she not restart her therapy as it would increase her risk for severe COVID-19
- 3. Suggest she restart her medication and self –isolate
- 4. Suggest she should be self-isolating anyway because of her underlying autoimmune disease and provide a medical letter for her employer.

Case 2

- 12 year old boy with nephrotic syndrome treated with rituximab, now in remission. However, B cell numbers have not recovered and he requires SCIg weekly which he receives at home.
- Since the start of the pandemic he has been at home and in September mother decided to home school him but this is causing strain on the family.
- Should he attend school in January? The mother asks for a medical note to keep him home from school.
- What do you do?

Poll 2
Should this child return to school?

- 1. yes
- 2. yes but should be isolated for class activities
- 3. No and I will provide a medical letter for the family
- 4. No It is mom’s decision. No medical letter needed

Case 3

- 60 year old female with multiple sclerosis. She has been experiencing increased frequency of relapses of her disease and the neurologist wants her to start cladribine. She comes to you for advice.
- Her current medications are glatiramer acetate and fingolimod. She developed liver toxicity while taking interferon-β1a and it was discontinued.
- She needs to know if she will have to stop working and self-isolate if she take this medication and will require a note from her MD if this is the case.
- What do you do?

Poll 3

Should this patient start this medication during COVID-19 and what should happen regarding her work?

- 1. She should start the medication and continue her activities per usual
- 2. She should not start this medication at present
- 3. She should start, self isolate and a medical letter should be provided.

COVID-19

- SARS-Co-V2 infection results in multiple different clinical outcomes
  - Asymptomatic infection
  - Mild self-resolving infection
  - Moderate but self resolving infection
  - Moderate self resolving infection with prolonged period of recovery secondary to loss of energy, persistent headache, insomnia.
  - Moderate to severe requiring hospitalization, oxygen therapy
  - Severe requiring ICU and intubation
  - Severe and fatal infection
  - Post-infectious multisystem inflammatory disease

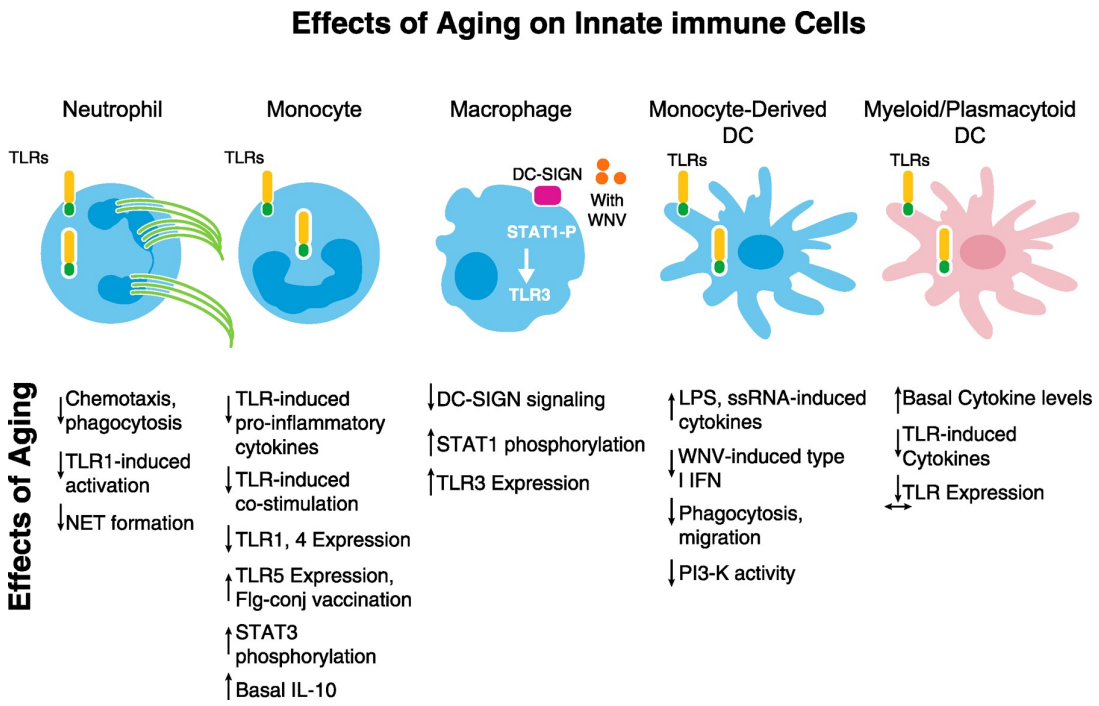
Risk factors for COVID-19

- Everyone at risk for infection.

- Mortality risk factors: male, age >65, smoking
  - Severity risk factors:
    - hypertension
    - diabetes
    - obesity is a risk factor for hospitalization in patients<60 years of age.
    - Immunosuppressive condition (includes the use of corticosteroids within 2 weeks of admission to hospital, underlying malignancy, post transplant).

Immunity and Aging

Innate Immunity



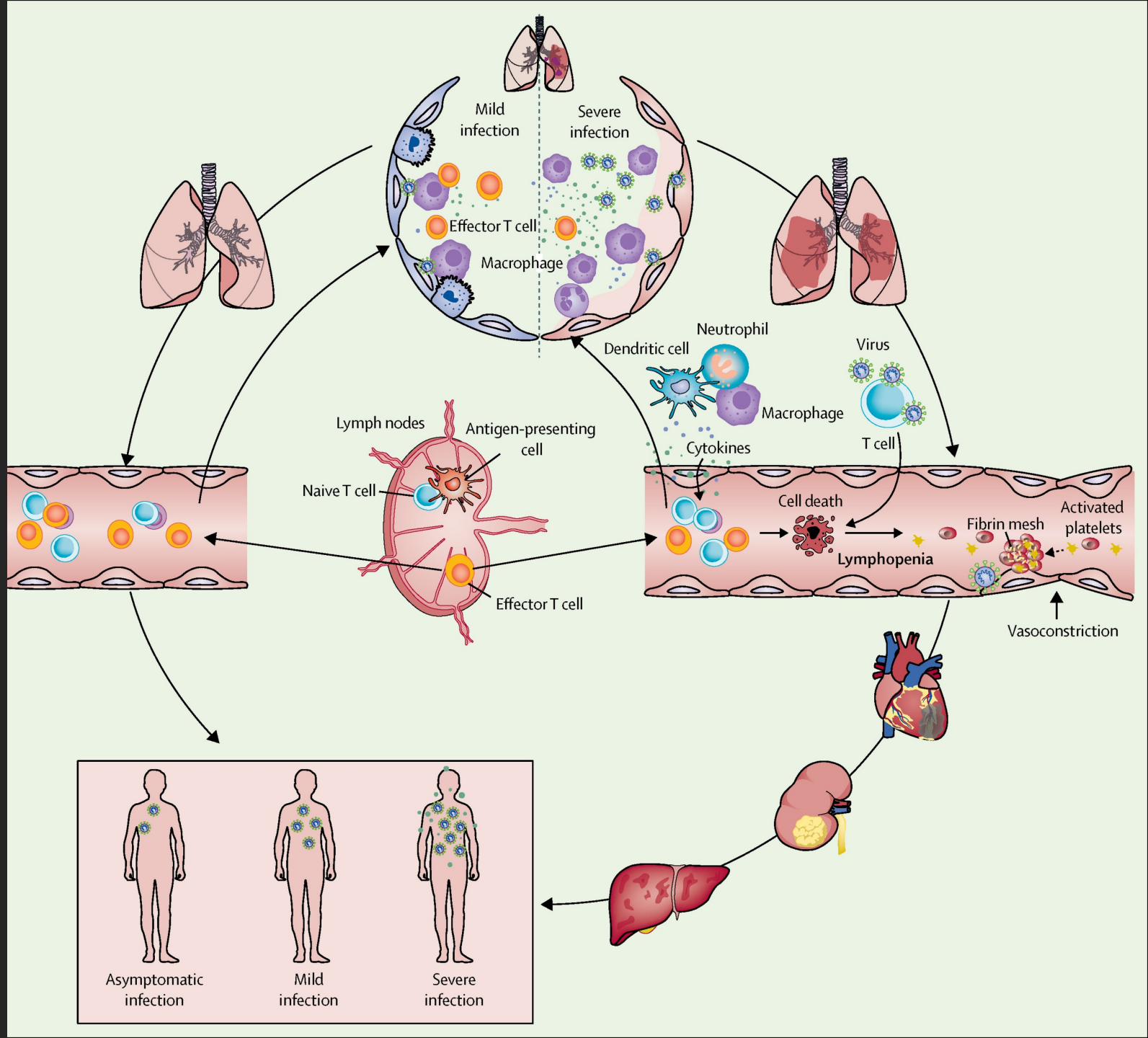
Taken from Montgomery and Shaw 2015. J Leuk Biol

Adaptive Immunity

- Increased antigen experienced T and B cells
  - Naïve cells less frequently found
- T cells from humans >age 60 more likely to form inhibitory complexes when activated-reducing overall functioning
- Sequential loss of costimulatory receptors on T cells
- As cells age, increased frequency of DNA damage, therefore reducing the proliferative potential of these cells may be protective

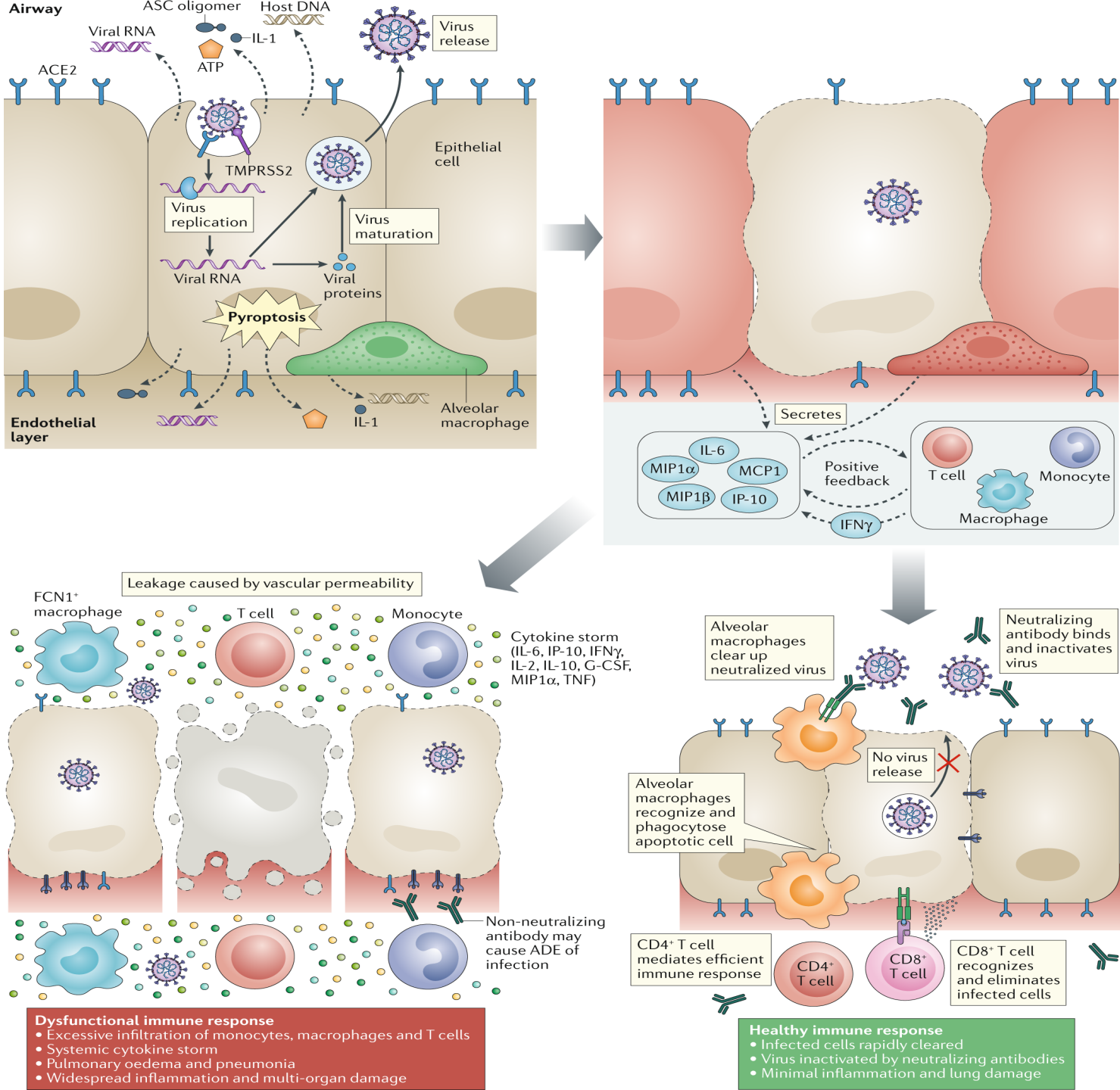
Immune system and COVID-19

taken from Li et al *The Lancet* Volume 395 Issue 10235 Pages 1517-1520 (May



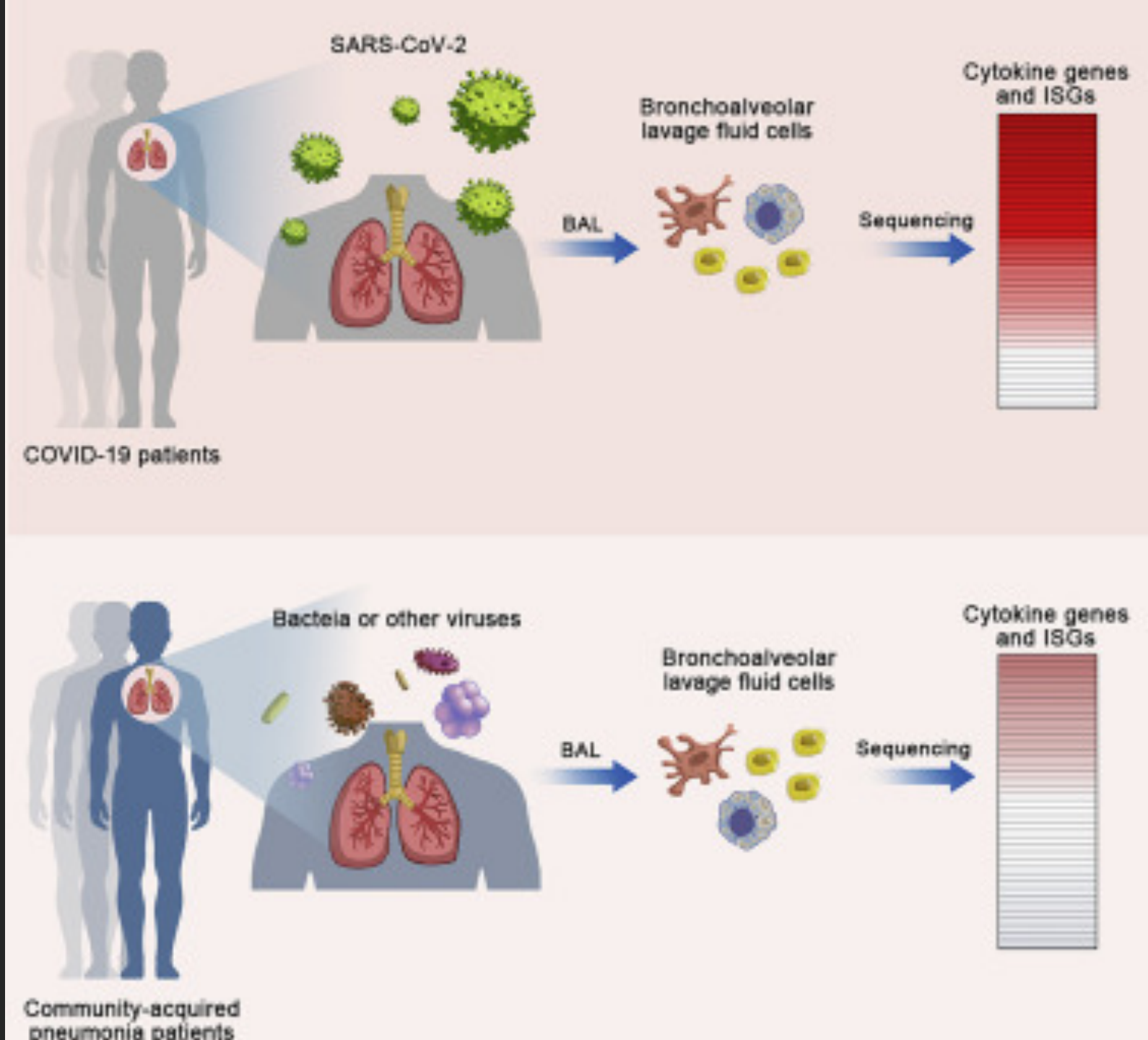
Chronology of events during SARS-CoV-2 infection.

Taken from Zirui et al *NatureReviewsImmunology* **volume 20**, pages363–374(2020)

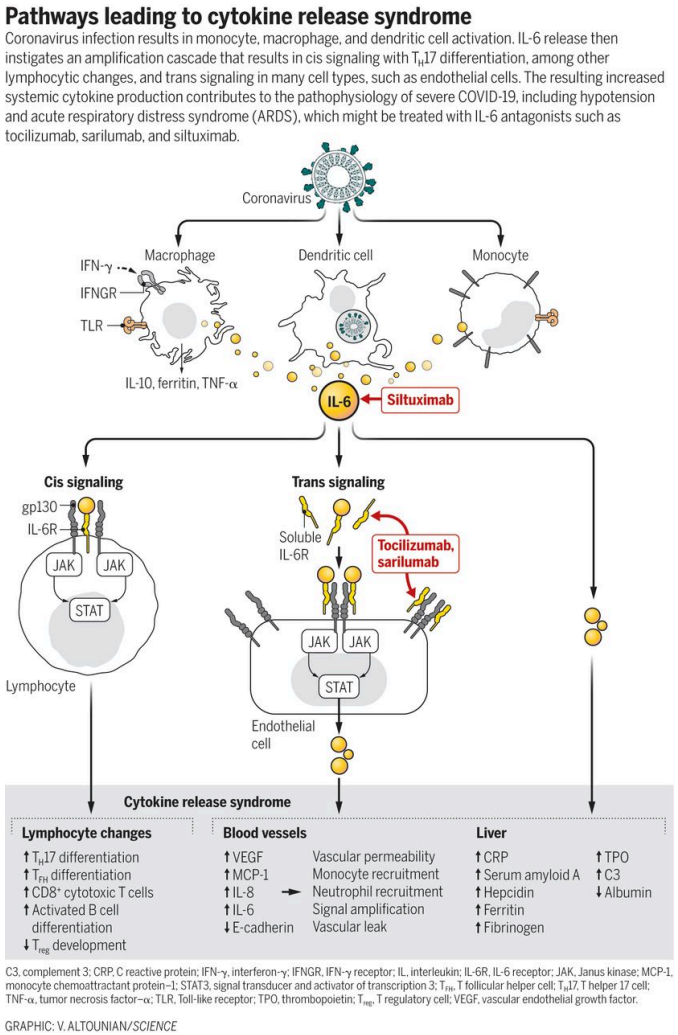


Pulmonary cytokines in SARS CoV-2-severe Covid

Taken from Zhou et al, 2020 Cell Host Microbe Volume 27, Issue 6, 10 June 2020, Pages 883-890.e2

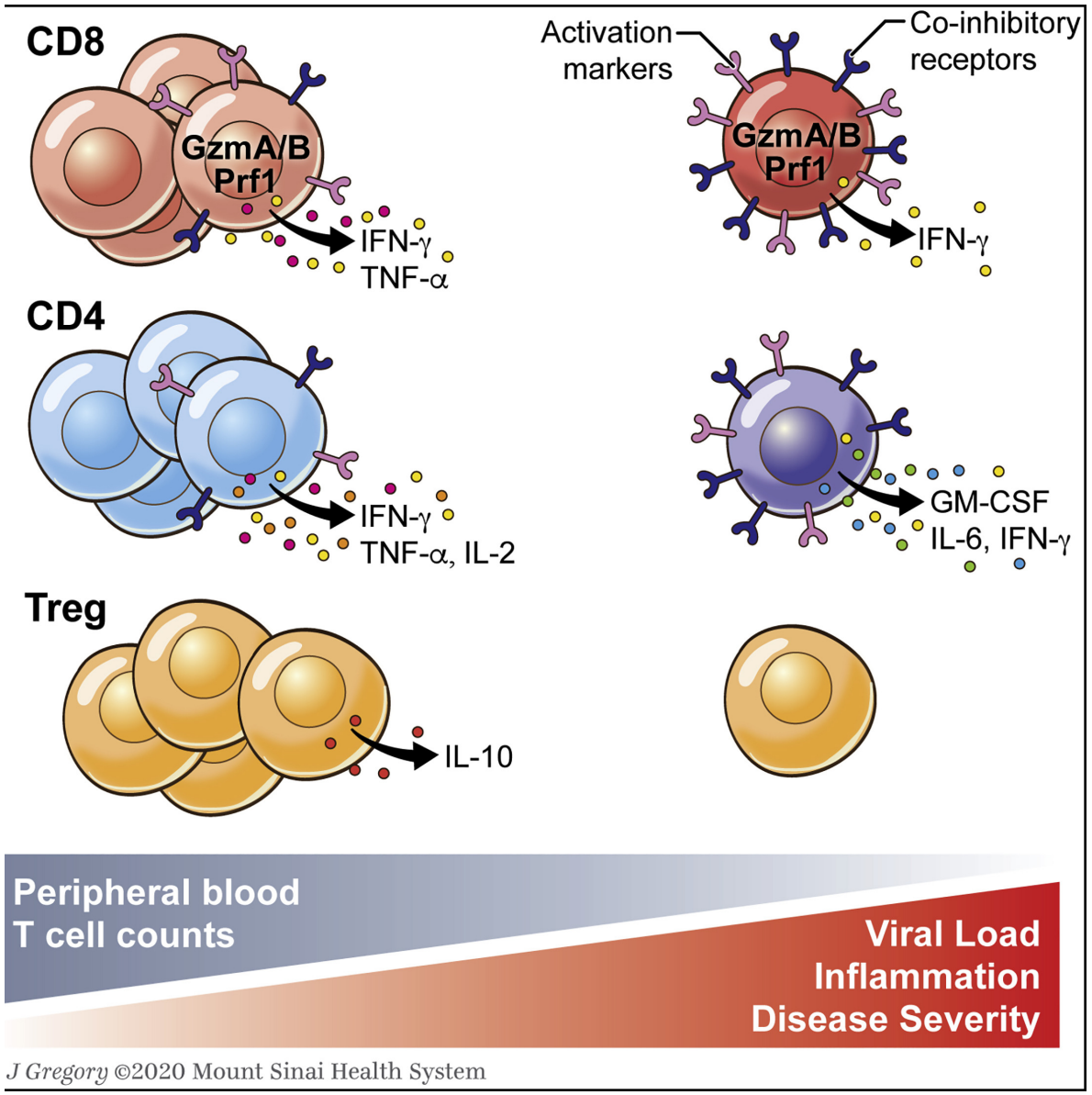


Pathways leading to cytokine release syndrome



By John B. Moore, and Carl H. June Science 2020;science.abb8925

Science AAAS

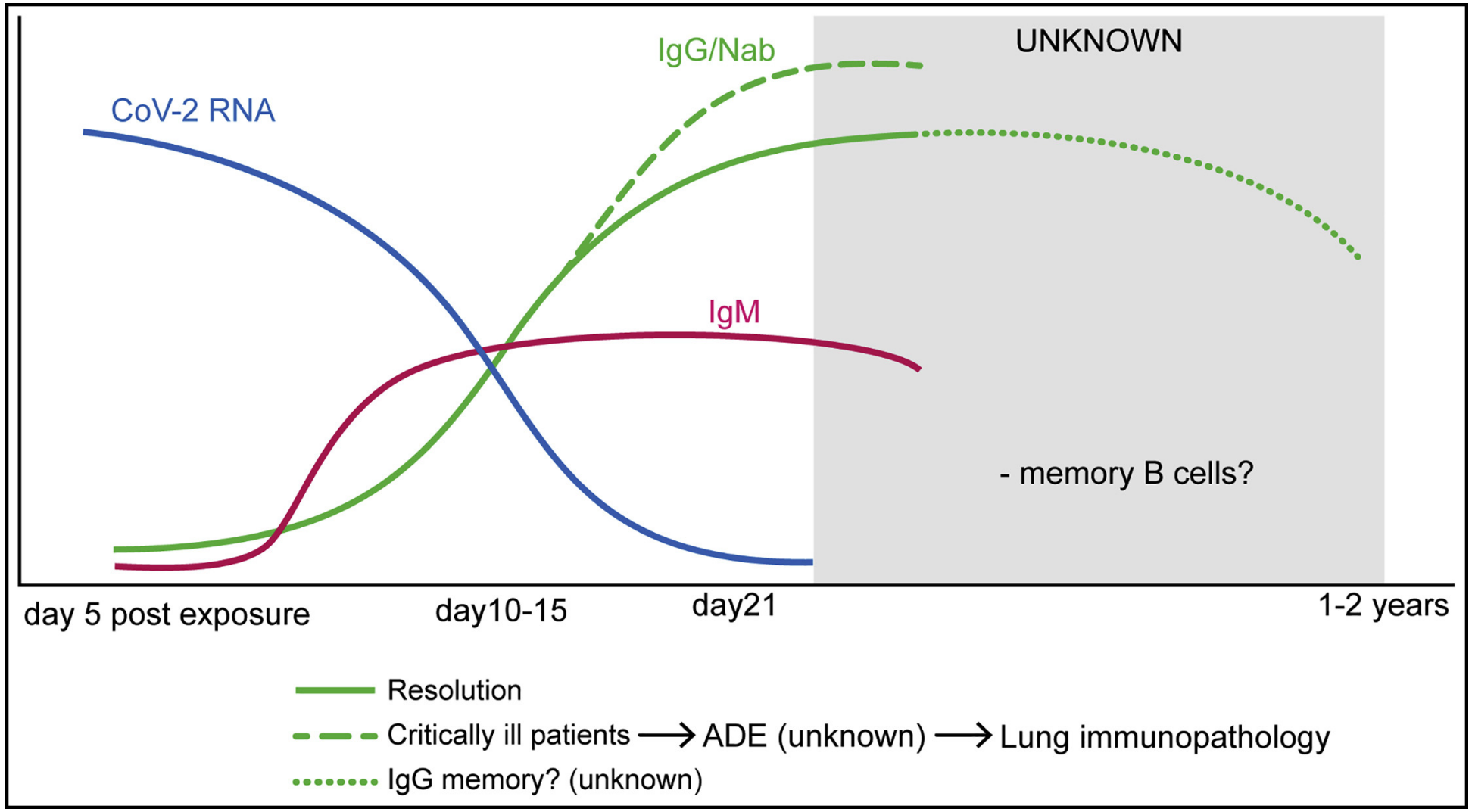


T cells and SARS-CoV-2

Taken from Varnet etal *Immunity* 2020 52910-941DOI: (10.1016/j.immuni.2020.05.002

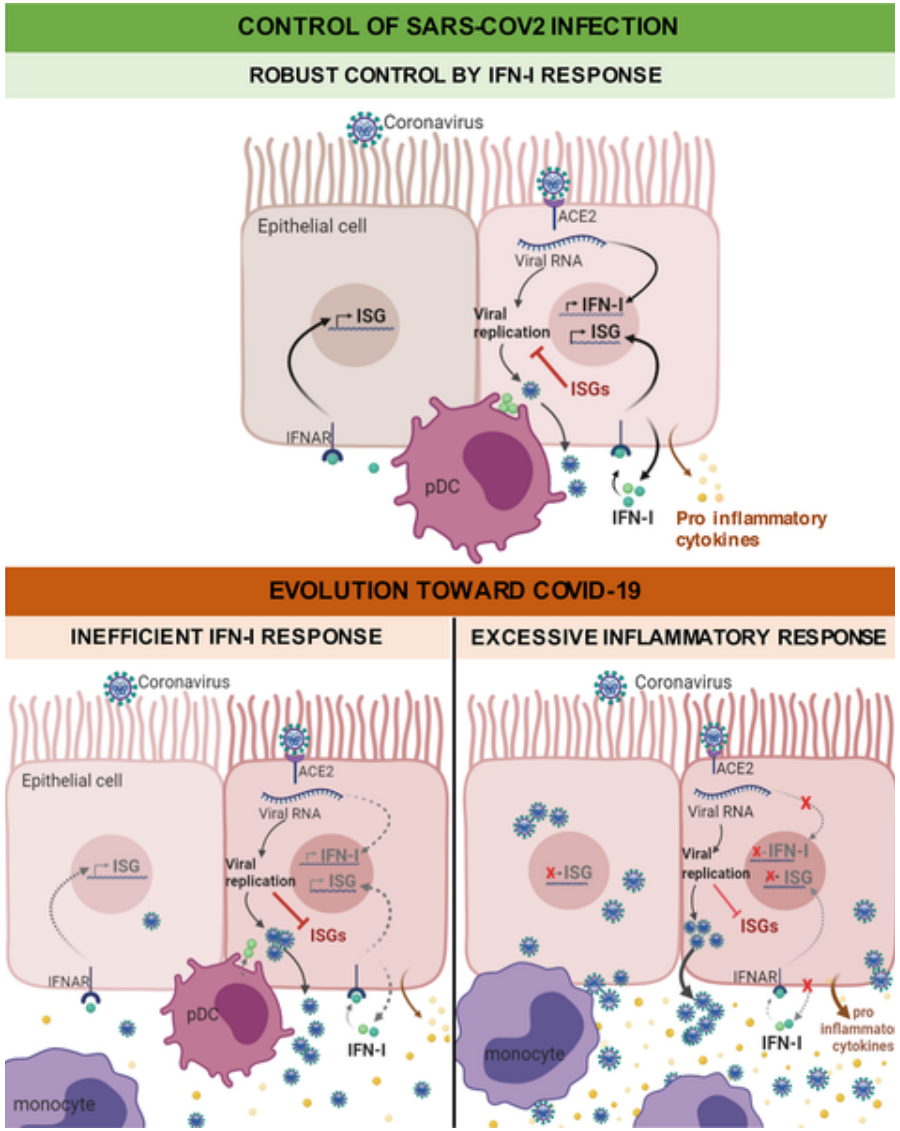
B Cells and SARS Co-V-2 Taken from Varnet etal *Immunity* 2020

52910-941 DOI: (10.1016/j.immuni.2020.05.002



Summary

- Severe COVID-19 results from excessive activation of innate immune cells especially macrophages/dendritic cells resulting in uncontrolled cytokine release and pulmonary inflammation.
- T cells play a key role in elimination of the virus and control of inflammation
- B cells produce antibodies which may help to prevent subsequent infection. B cells are a source of inflammatory cytokine which may worsen disease



Taken from Ribero et al PLOS Pathogens 2020

Immune response modifiers and COVID-19

- Evidence from multiple studies suggests that treatment with anti-TNF, anti-IL1, anti-IL6 disease modifying biological therapies (DMARDS) was NOT a risk factor for symptomatic or severe COVID-19.
- Case report: MS patient treated with alemtuzumab (wipes out B and T cells)-only moderate symptoms with COVID 19 in 28 year old female
- In a meta analysis of patients with autoimmune diseases, the use of corticosteroids was associated with increased risks for severe outcomes with COVID infection

In this same study the use of DMARDS, especially anti-TNF was potentially protective for severe COVID

Patients with inborn errors of immunity and COVID

- Evidence suggests that patients with genetic potentially deleterious variants in genes in the type 1 interferon pathway have increased risk for severe COVID-19.
- Patients with inborn errors of immunity affecting the humoral immune system do not appear to have increased susceptibility for severe COVID-19

Returning to case 1

- 28 year old female with IBD, on treatment with anti-TNF-R inhibitor. In March, because of fears of severe COVID-19 in immunosuppressed patients, she stopped taking the medication and now has a significant flair of her disease.
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Case 2 revisited

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Case 3 re-examined

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