Speaker Academic information

Dr. Maria Zavala is a research professor and academic coordinator at the international program of medicine in Universidad Autonoma de Guadalajara.

Graduated as MD and PhD in Biomedical Sciences and Immunology (UAG and UDG respectively)

Currently, she participates in the 2019-2020 cohort for global clinical scholars' research training at Harvard Medical School

Her research interests are primarily focused in immunopathological consequences of autoimmune diseases and infectious diseases, previously worked with genetic variations and proteomic profiles, including autoantibodies and proteins related to the immune response

My goal is to ultimately integrate information from genetic, epigenetic and proteomic variations into useful tools for clinical research in order to improve diagnosis, treatment, and prognosis of human diseases with acute or chronic affection of the immune response

Information about her publications are available at https://www.ncbi.nlm.nih.gov/pubmed/?term=Zavala-Cerna.

GLOBAL DEVELOPMENT LEARNING NETWORK

GDLN LAC

UNIVERSIDAD AUTONOMA DE GUADALAJARA

Immune Response during COVID-19

MARIA G. ZAVALA-CERNA MD PHD

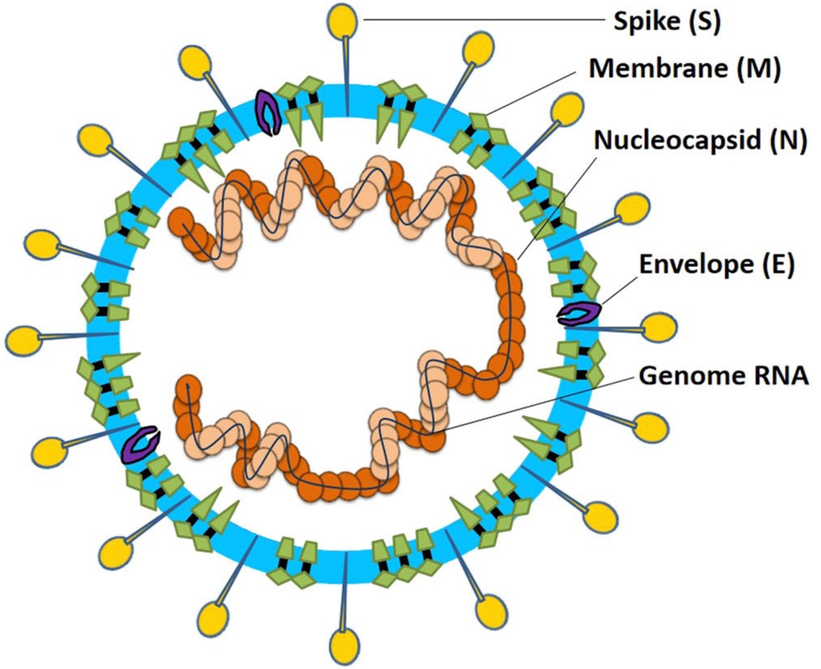
maria.cerna@edu.uag.mx

Learning Objetives

- Coronavirus and human infectious disease
- General overview of the immune response
- Immune response during COVID-19 (different scenarios)
- Considerations and opportunities for treatment in severe cases
- Considerations for prevention in at risk population
- Concluding remarks

Coronavirus (CoV) virion structure

- Enveloped, non segmented, positive sense single stranded RNA virus
- 26-32 kilobases (largest known)
- 4 structural proteins: N (phosphorylated), spike proteins (S), and transmembrane proteins (M and E)
- 4 genera, although human infections are caused by α and β genera (SARS-COV-2)



	orf1ab	S	ORF3a	E	M	ORF6	ORF7a	ORF8	N	ORF10
SARS-CoV-2										
Bat-SL-CoV	95%	80%	91%	100%	98%	93%	88%	94%	94%	-
SARS-CoV	86%	76%	72%	94%	90%	68%	85%	40%	90%	-
MERS-CoV	50%	35%	-	36%	42%	-		-	48%	-

Figure 1. Comparison of SARS-CoV-2 (Wuhan-Hu-1) Genome Structure with Its Closest Bat Relative (bat-SL-CoVZXC21), Tor2 SARS-CoV, and HCoV-EMC MERS-CoV

Li G. 2020, Grifoni A. 2020

The infectious disease COVID-19

- Virus reproductive number R_0 = 3.28 (Influenza R_0=2.4)

- SARS-CoV-2 use host receptor angiotensin-converting enzyme 2 (ACE2) to enter the cells. High expression of this receptor is in human oral pharynx, upper airway, and type 2 pneumocytes in the lungs

- Once activated ACE2 can be cleaved and released into the circulation: increase lung vascular permeability and directly interact with macrophages

Harapan 2020

The infectious disease COVID-19

- Clinical manifestations: fever, headache, dry cough, smell & taste disorders, fatigue, myalgia, diarrhea, pneumonia, acute respiratory distress syndrome (ARDS), sepsis, multiple organ failure, and death

- Risk factors for severe disease: male, >60 years old, chronic comorbidities (hypertension, cardiovascular disease, obesity, and diabetes)

- Mortality rate 0.5-8%, depending on the availability of diagnostic testing and capacity of the health care system

- Histopathology: inflammatory cell infiltration and edema, with pathological changes in alveolar epithelial cells and alveolar type 2 pneumocytes, with damage to pulmonary arteriolar walls

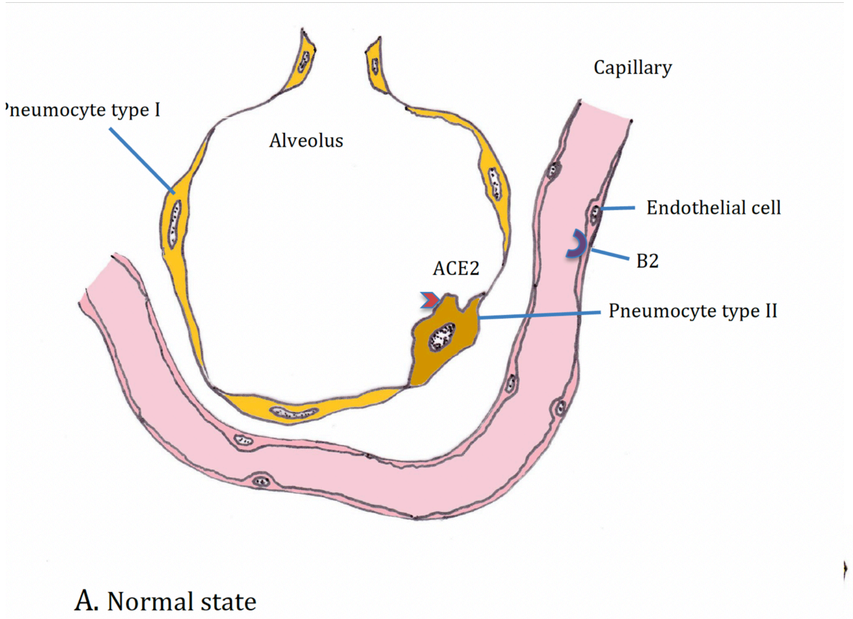
Mehta P, 2020

Table 2. Distribution of ACE2 and TMPRSS2 in organs, and symptoms of COVID-19 (percentage indicate estimated frequency in COVID-19 patients).

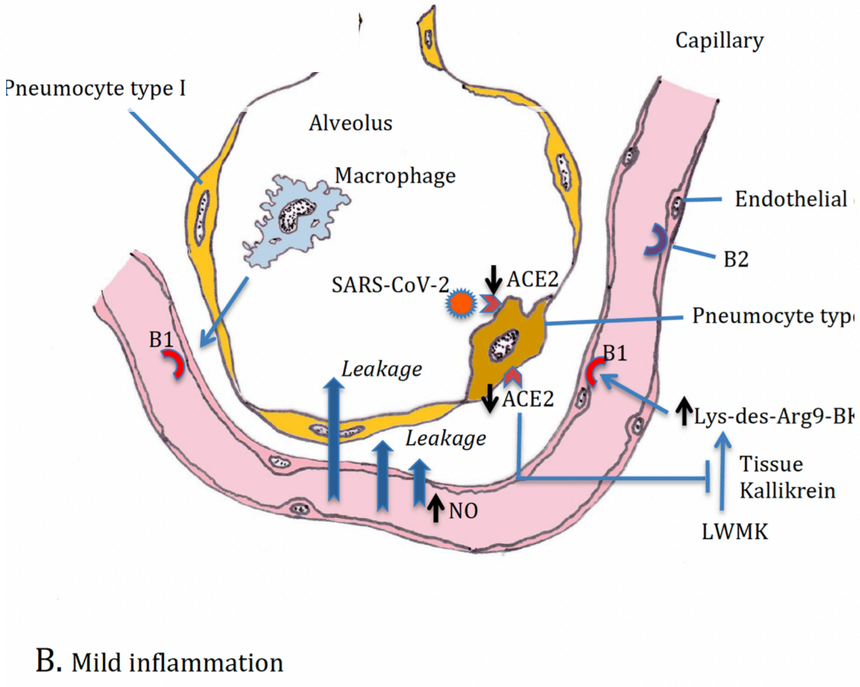
ACE2/TMPRSS2 Distribution	Symptoms/Lab Findings
Lymphocytes/Dendritic Cells	Fever (>99%), fatigue (70%), myalgia, lymphopenia
Lung (type 2 pneumocytes, bronchial epithelium)	Dyspnea (31%), dry cough (60%), respiratory failure
GI Smooth Muscle	Nausea (30%), Diarrhea
Myocardium	Myocarditis, heart failure, arrhythmias
Vasculature (smooth muscle)	Vasculitis, thrombosis, microangiopathy
Neurons	Anosmia, hypogeusia, encephalopathy, seizures, myopathy
Liver	Abnormal liver function
Kidney	Renal dysfunction

Liu , 2020

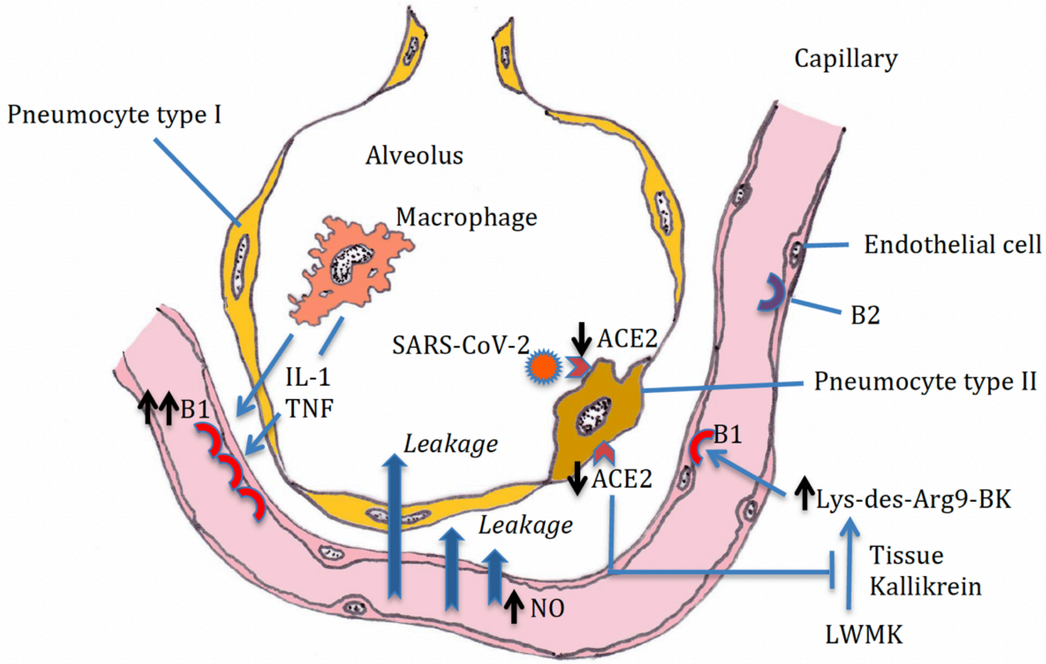
Tissue pathological changes



A. Normal state



B. Mild inflammation



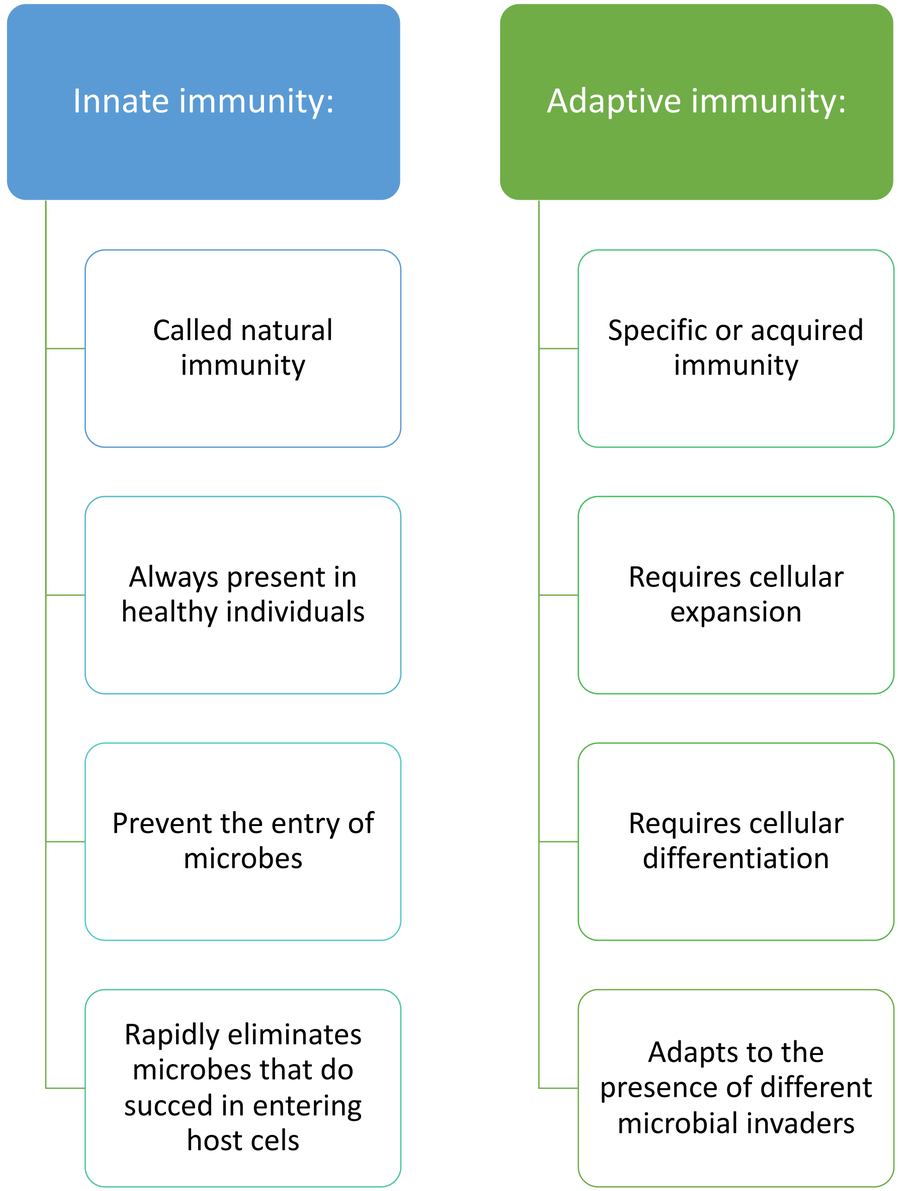
C. Hyperinflammation

van de Veerdonk F. 2020

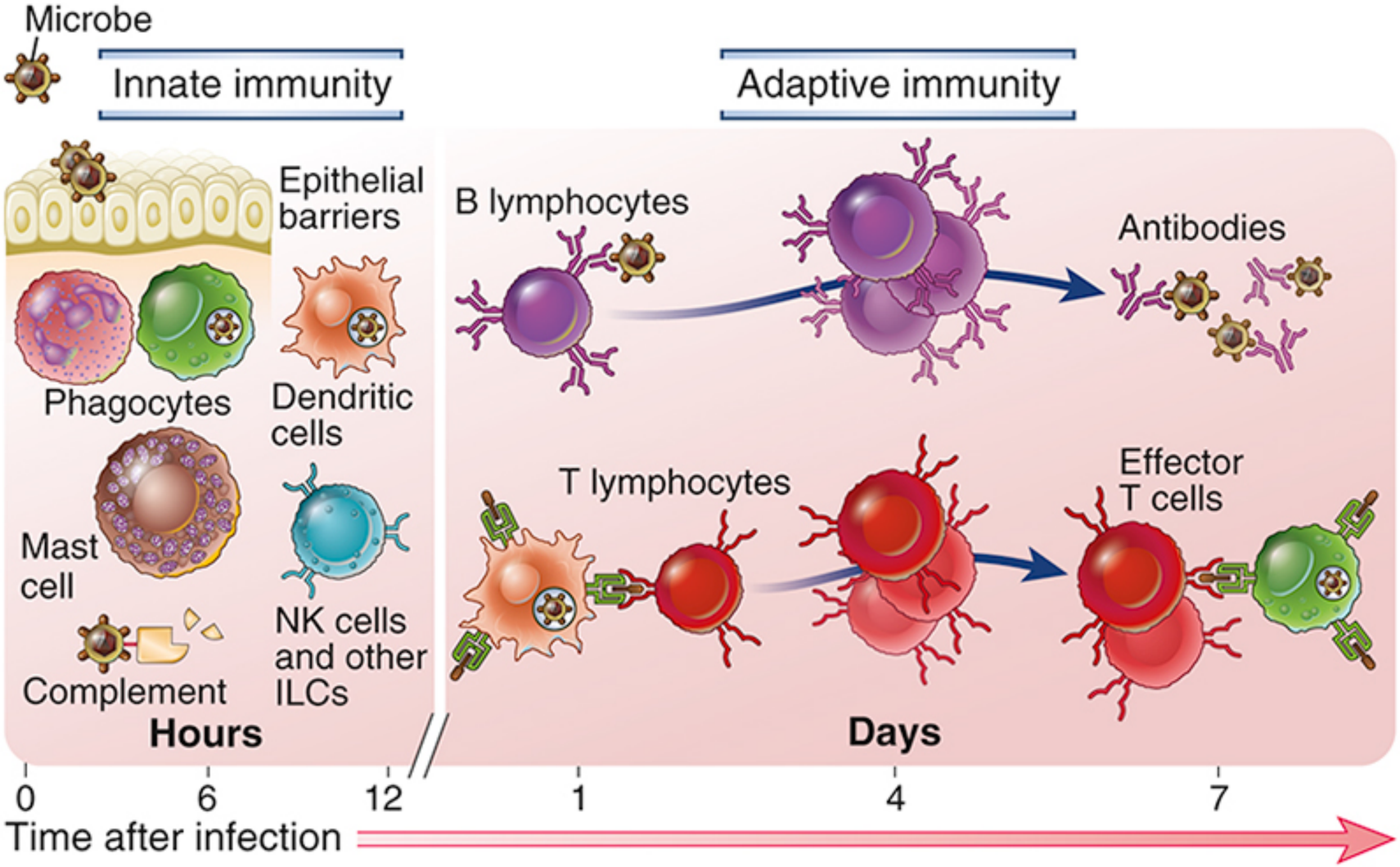
The big picture of the immune response

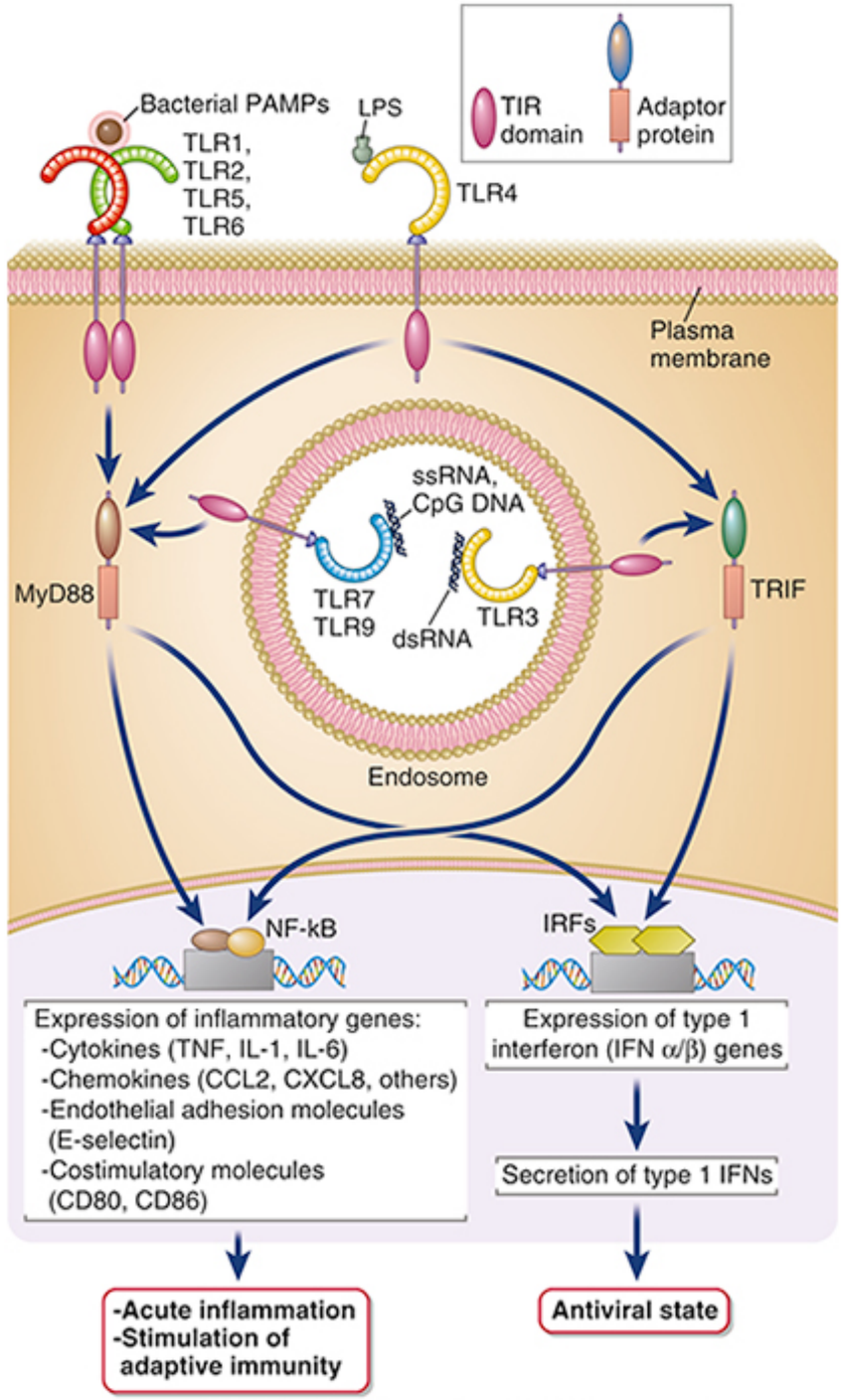
- Immune responses are essential to control and eliminate viral infections
- Excessive or prolonged immune responses can lead to immunopathology
- Immunopathology in the lungs can impaire pulmonary gas exchange
- Gaining a better understanding of the interaction between CoV-2 and the immune system to:
  - Recognize subjects at higher risk to develop severe disease (improve diagnosis)
  - Reduce the inflammatory response in lungs during COVID-19 (targeted treatment)
  - Prevent the infection (vaccine development)

Overview of the immune response



Types of immune responses



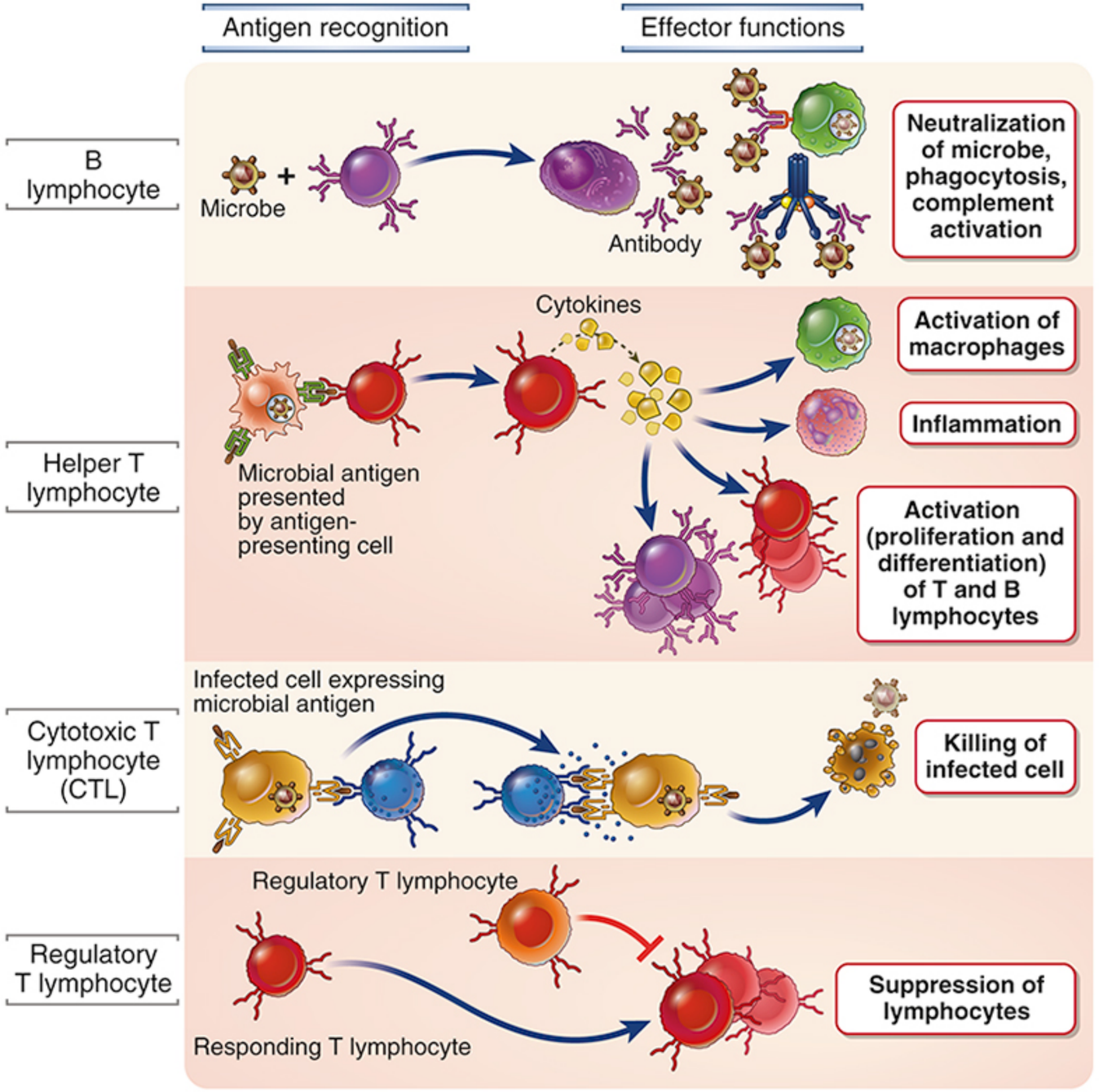


Innate Immune Response in COVID-19

- Innate immune cells recognize pathogen associated molecular patterns (PAMPs) by pattern recognition receptors (PRR)
- **TLR 7**, TLR 9, RIG-1, MDA-5
- An early burst in Type I INFs is associated with protective stage, while delay in this mechanism is associated with increased viral replication
- SARS-CoV-1 produce 8 viral antagonists that modulate the antiviral state: allowing viral replication to continue
- Once activated, cells can elicit the activation of T cells through antigen presentation (HLA-I and HLA-II)

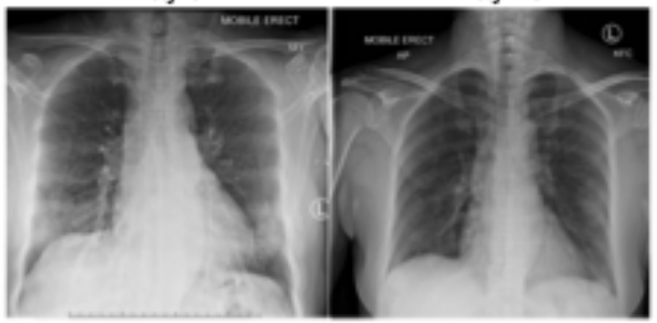
Adaptive Immune response

- Once primed, CTL become competent to kill virally infected cells
- HTL produce cytokines to help B cells (antibody responses) as well as enhance CTL function and activation of other types of cells
- B cells can undergo Isotype switch and affinity maturation (memory antibodies)
- Once the antigen is cleared, cells dye by apoptosis and we are left immune (memory cells & antibodies IgG)



Immune Responose in a recovery patient

b



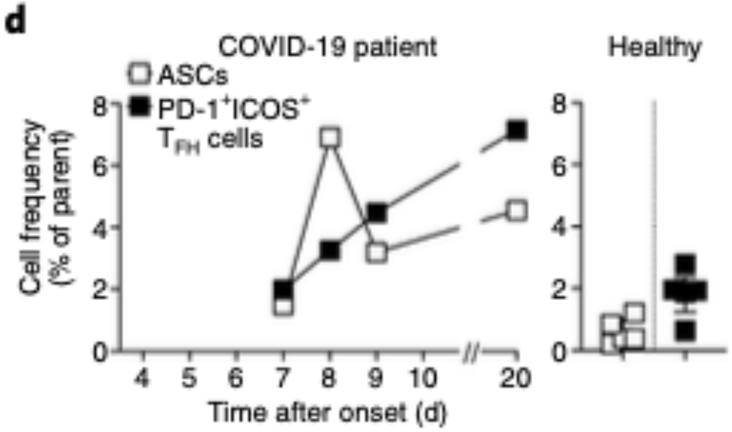
c

	Negative patient	COVID-19 patient d7	d8	d9	d20
Anti-IgG	0	1+	2+	3+	3+
Anti-IgM	0	+/–	+/–	2+	3+

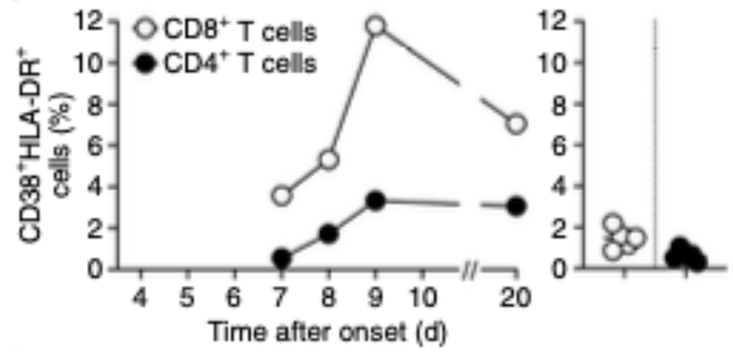
- Antibody secreting cells and T $_{FH}$ cells start appearing in peripheral blood at the time of viral clearence (7-8 days), an persisted until recovery (day 20)
- HTL and CTL rapidly increased from day 7-9 and then decreased
- Monocytes and NK were low
- Antibodies against S and N protein

Thevarajan I, 2020; Qin, 2020

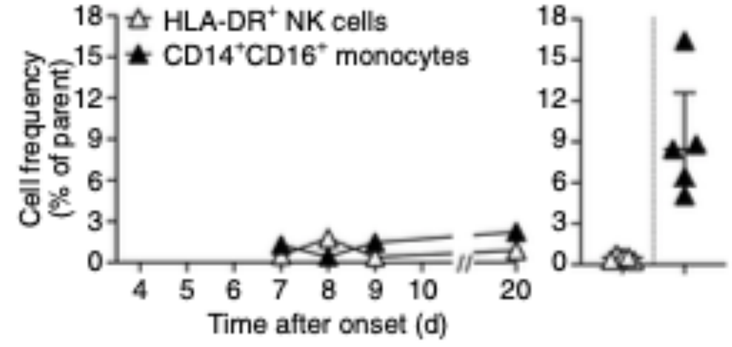
d



e

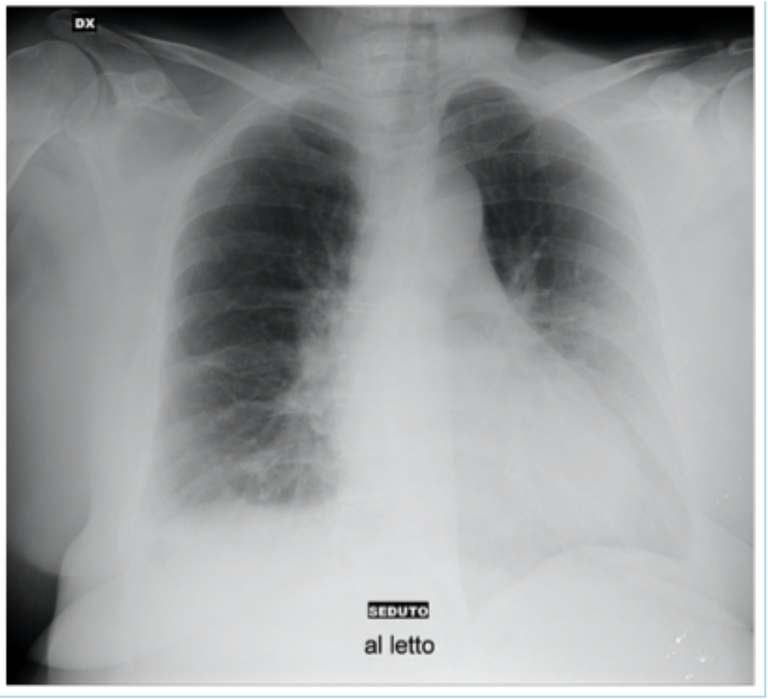


f

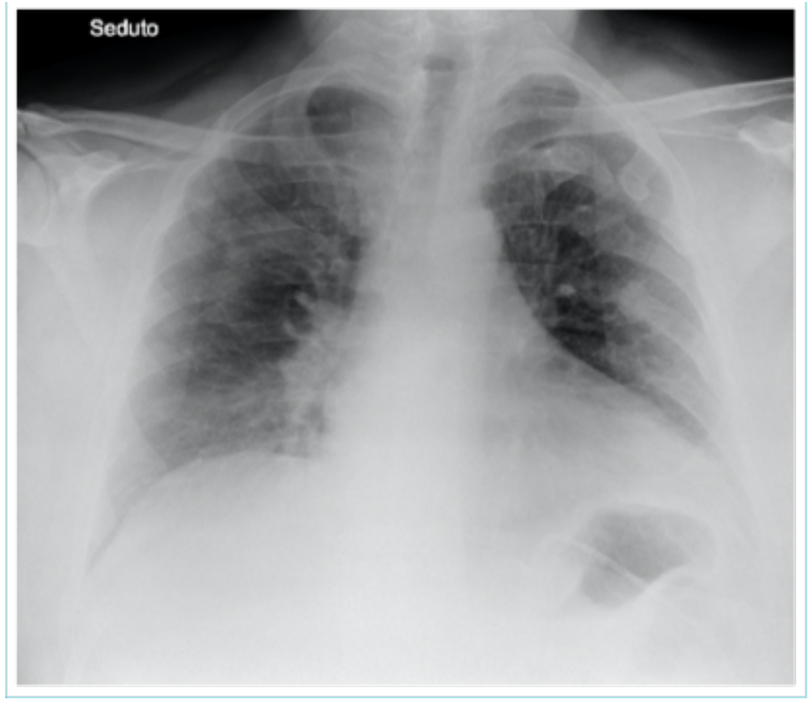


Immunocompromised patients with COVID-19

- Case report of a couple of two 60 year old: patient 1 a breast cancer female survivor with previous chemotherapy administration (immunosupressed), and patient 2 a hypertensive (immunocompetent) male



Patient 1 recovered in 6 days



Patient 2 recovered in 22 days, after ICU management

Spezanni V, 2020

Immunopathology in COVID-19

- HTL (CD 4+) → secrete cytokines for cell recruitment & inflammation (IL-1, IL-17, IL-6, MCP1, GCSF, IP-10), to hellp B cells (IL-10, IL-4), and to activate other cells (INF-g, IL-2)
- Innate immune cells effectively activated produce: TNF-a, IL-1 and IL-6
- ICU patients have a singificant increase of MCP1, GSCF, IP-10, IL-1, IL-6, TNF-a, IL-10 and IL-4: CYTOKINE STORM SYNDROME & LYMPHOPENIA
- Immunosenescence: immune changes associated to age and chronic inflammation; decreased naïve T and B cells → inhability to coordinate immune responses to new pathogens with misscommunication between innate and adaptive and failure to produce protective antibodies, and inflammaging

*Monocyte chemoatractant protein

Qin, 2020; Nikolich-Zugich, 2020

Considerations for treatment of severe cases

- Management is mostly supportive and under research
- Immunosupressive drugs (corticosteroids, anti-IL1, anti-IL6, choloroquine and hydroxicloroquine (2 RCT), azythromicin (4 RCT) anti-TNF, JAK inhibition)
- Intravenous immunoglobulin from recovered patients (15 days after) (2 case series)
- Antivirals: Oseltamivir, Remdesivir, Lopinavir/Ritonavir
- Interferon-a and Interferon-b
- Icatibant (Bradikinin receptor blocker)

van de Veerdonk, 2020; Bhimraj A, 2020

Considerations for prevention

- Currently, no vaccine is available
- Several vaccination strategies including live- attenuated virus, viral vectors, inactivated virus, subunit vaccines, recombinant DNA, and proteins vaccines
- Studies are in progress, but it requires months to years to develop the vaccines for SARS-CoV-2
- Stop the chain of transmission: Strict quarantine of suspected people and their close contacts

https://clinicaltrials.gov.

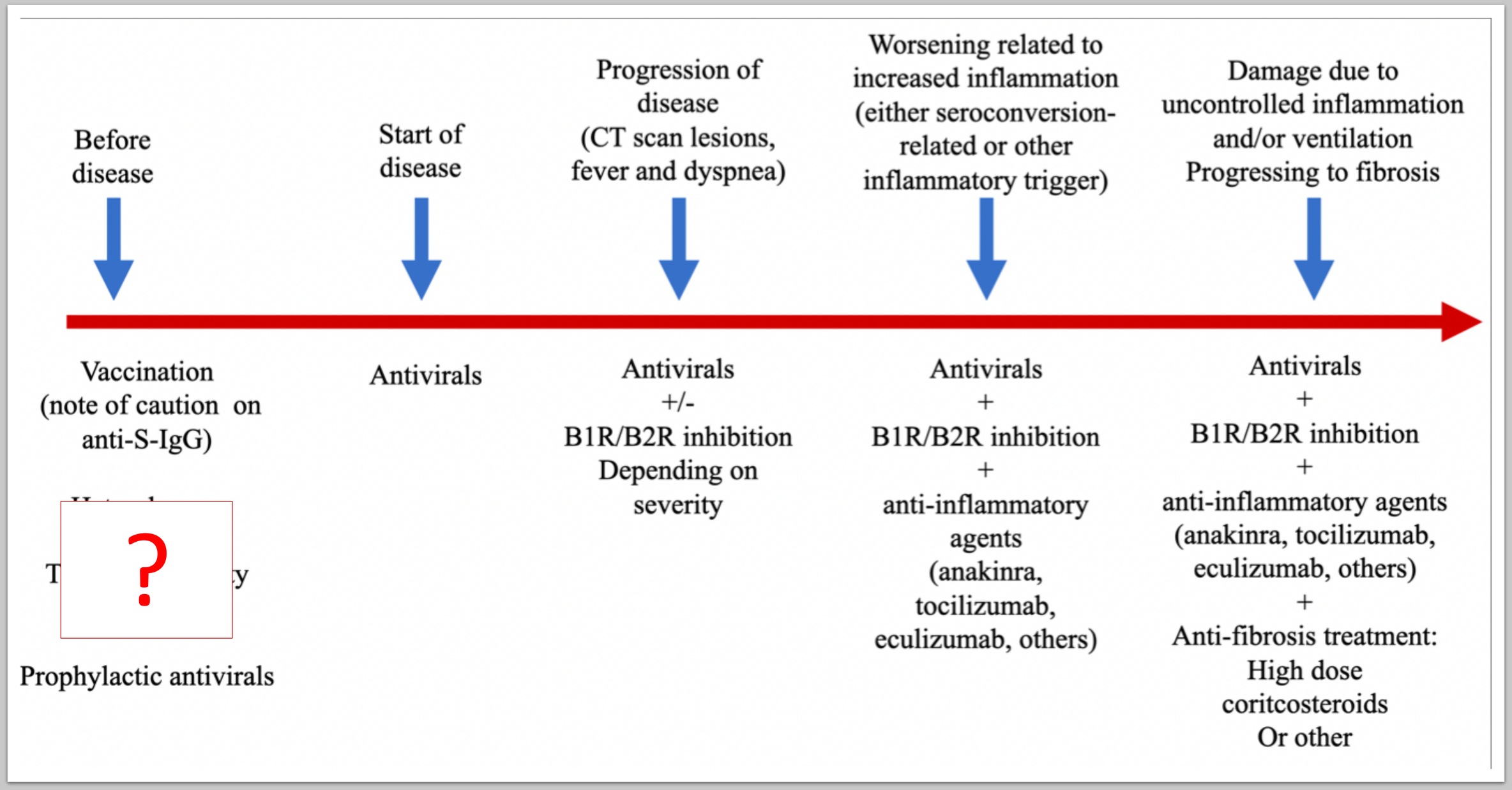
Download | Subscribe to RSS

Showing: 1-10 of **283** studies 10 studies per page

Show/Hide Columns

Row	Saved	Status	Study Title	Conditions	Interventions	Locations
1	☐	Not yet recruiting NEW	Study of TJ003234 (Anti-GM-CSF Monoclonal Antibody) in Subjects With Severe **Coronavirus** Disease 2019 (**COVID-19**)	• **Coronavirus** Disease 2019 **COVID-19**	• Drug: TJ003234 • Drug: Placebo	• OSF Healthcare Saint Francis Medical Center Peoria, Illinois, United States • Indiana University Health Indianapolis, Indiana, United States • Oschner Medical Center New Orleans, Louisiana, United States
2	☐	Not yet recruiting NEW	Bone Marrow-Derived Mesenchymal Stem Cell Treatment for Se (COVI	• **Coronavirus** Disease 2019 (**COVID-19**)	• Biological: BM-MSCs • Biological: Placebo	• Guangzhou Institute of Respiratory Health, The First Affiliated Hospital of Guangzhou Medical University Guangzhou, Guangdong, China
3	☐	Recruiting	Fingolimod in **COVID-19**	• **Coronavirus** Disease (**COVID-19**)	• Drug: Fingolimod 0.5 mg	• Wan-Jin Chen Fuzhou, China
4	☐	Not yet recruiting NEW	Hydroxychloroquine Post Exposure Prophylaxis for **Coronavirus** Disease (**COVID-19**)	• **COVID-19** • **Corona Virus Infection**	• Drug: Hydroxychloroquine • Drug: Placebo oral tablet	• Columbia University Irving Medical Center New York, New York, United States
5	☐	Not yet recruiting NEW	Treatment of Moderate to Severe **Coronavirus** Disease (**COVID-19**) in Hospitalized Patients	• **COVID-19**	• Drug: Lopinavir/ritonavir • Drug: Hydroxychloroquine sulfate • Drug: Baricitinib (janus kinase inhibitor) • Drug: Sarilumab (anti-IL-6 receptor)	• Nova Scotia Health Authority Halifax, Nova Scotia, Canada
6	☐	Recruiting	Treatment With Mesenchymal Stem Cells for Severe **Corona Virus** Disease 2019(**COVID-19**)	• **Corona Virus** Disease 2019(**COVID-19**)	• Biological: MSCs • Biological: Saline containing 1% Human serum albumin （solution of MSC)	• Maternal and Child Hospital of Hubei Province Wuhan, Hubei, China • Wuhan Huoshenshan Hospital Wuhan, Hubei, China

Show study NCT04346368: Bone Marrow-Derived Mesenchymal Stem Cell Treatment for Severe Patients With Coronavirus Disease 2019 (COVID-19)



van de Veerdonk F. 2020

The BCG hypothesis

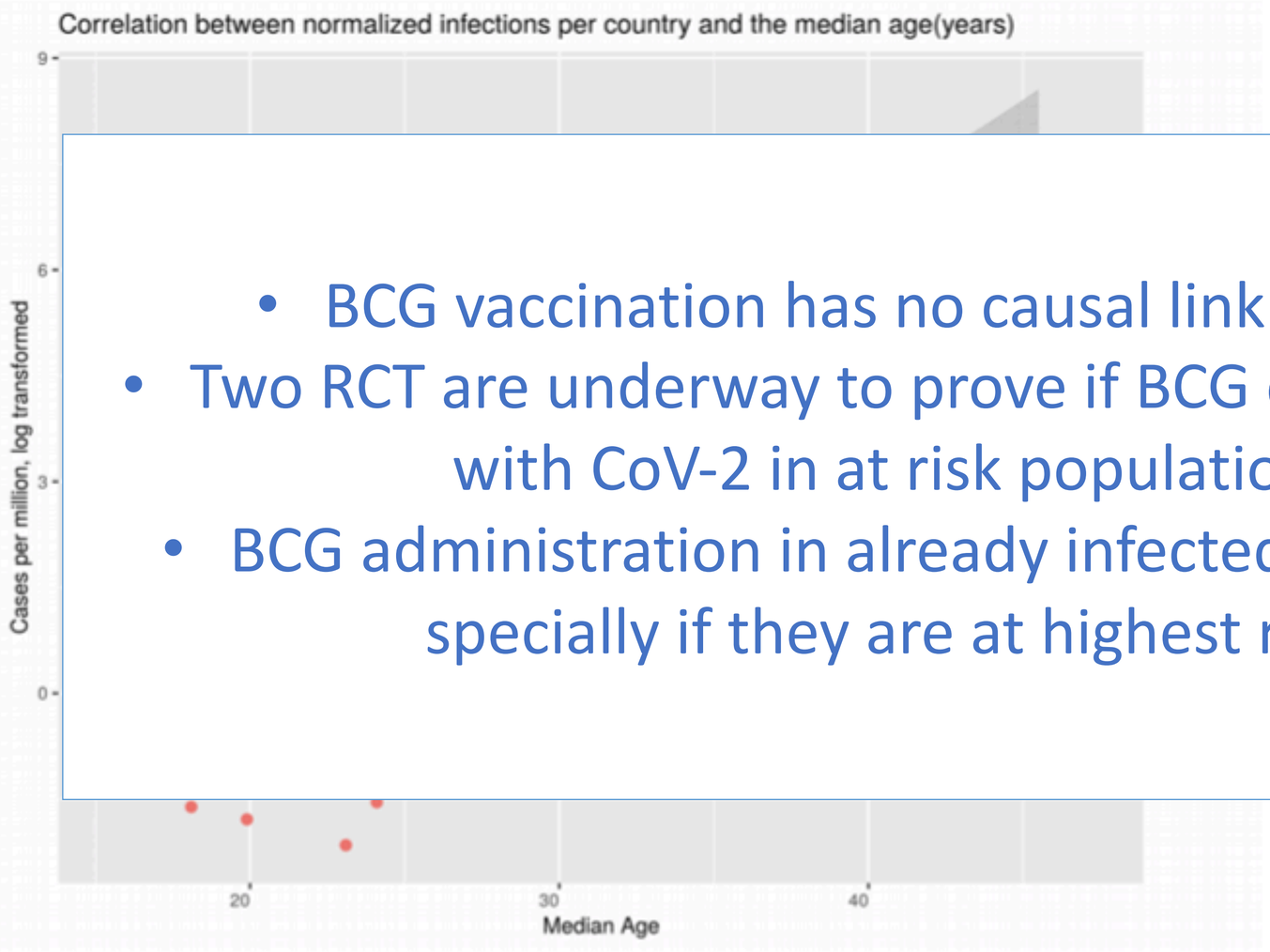
- Publications (without peer review) looked at the association between COVID-19 mortality on one hand and countries' policies with respect to BCG vaccination on the other
- Hypothesis: differences in rates of infection in countries where BCG vaccination is mandatory compared to countries without it
- The "known immunological benefits" of BCG vaccination may be behind the biological mechanism of such observation
- Results from two studies: Booster to improve influenza vaccine responses and increased viral clearance in yellow fever vaccine associated viremia (innate immune memory or priming)
- IIM or priming is short-lived, not enough for an effective immune response to develop, and could result in the opposite (tolerance)

Is there a true causal relationship?

- No biological mechanism to explain a protection against CoV-2
- Other potential confounders: ethnicity, rates of chronic diseases, time from community spread start date, major public policy decisions (underreport of cases), and income levels
- A study used data on average population age per country and number of infections (Wikipedia) and BCG immunization rates (WHO website)
- Kirov found that population age is a very significant confounding factor that explains the rates of infections much better and has a solid biology mechanism which explains this correlation

Kirov, 2020

Factors associated to mortality across countries



- After linear regression, the most significant factor was income level,

- BCG vaccination has no causal link to COVID-19 infection rates
- Two RCT are underway to prove if BCG can boost the IR before infection with CoV-2 in at risk population (healthcare workers)
- BCG administration in already infected persons might be deleterious, specially if they are at highest risk for a serious disease

Kirov, 2020

CONCLUSIONS

- SARS-2 has emerged as an exceptionally hardy and contagious virus
- Fever and pulmunary symptoms predominate
- CoV are recognized by TLR7, RIG-I/MDA and result in early IFN-I response, necessary fro appropiate control of infection
- Neutralizing antiodies agains S and N protein are likely key to protection
- Individuals for the highest burden of severe disease are older adults, and patients with chronic inflammatory conditions (immunosenescence)
- Patients with severe diasease my succumb to ARDS, supportive care is the mainstay of therapy
- Current successful anti-pandemic measures have included extensive testing, contact tracking, and strict quarantining
- Prevention is the most important strategy for older adults

References

- Li G, et al. Coronavirus infections and immune responses. J Med Virol (2020) DOI: 10.1002/jmv.25685
- Grifoni A, et al. A Sequence Homology and Bioinformatic Approach Can Predict Candidate Targets for Immune Responses to SARS-CoV-2. Cell Host & Microbe (2020) *27*, 671–680, April 8, 2020
- Harapan H, et al., Coronavirus disease 2019 (COVID-19): A literature review, *Journal of Infection and Public Health* (2020), doi: https://doi.org/10.1016/j.jiph.2020.03.019
- Spezzani V, et al. Benign COVID-19 in an immunocompromised cancer patient – the case of a married couple. Swiss Med Wkly (2020);150:w20246
- *Mehta P,* et al. COVID-19: consider cytokine storm syndromes and immunosuppression. The Lancet (2020). https://doi.org/10.1016/ S0140-6736(20)30628-0
- van de Veerdonk F., et al. Kinins and Cytokines in COVID-19: A Comprehensive Pathophysiological Approach. *Preprints* 2020, 2020040023 (doi: 10.20944/preprints202004.0023.v1)
- Qin Ch, et al. Dysregulation of immune response in patients with COVID-19 in Wuhan, China. *Clinical Infectious Diseases* (2020), ciaa248, https://doi.org/10.1093/cid/ciaa248
- Adarsh Bhimraj. Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19. https://www.idsociety.org/COVID19guidelines
- Thevarajan I. Breadth of concomitant immune responses prior to patient recovery: a case report of non-severe COVID-19. Nat Med (2020) VOL 26: 450–455, www.nature.com/naturemedicine
- Kirov S, Association Between BCG Policy is Significantly Confounded by Age and is Unlikely to Alter Infection or Mortality Rates. BMJ (2020) doi: https://doi.org/10.1101/2020.04.06.20055616
- Nikolich-Zugich J et al., SARS-CoV-2 and COVID-19 in older adults: what we may expect regarding pathogenesis, immune responses, and outcomes. Gero Science (2020) https://doi.org/10.1007/s11357-020-00186-0
- Liu et al. **The Science Underlying COVID-19: Implications for the Cardiovascular System.** 10.1161/CIRCULATIONAHA.120.047549