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VIRTUAL CONFERENCE

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Immunology Update: Cytokine Storm Syndrome

Amanda Mixon, PA-C
Colorado Center for Arthritis and Osteoporosis
Longmont, CO

Disclosure

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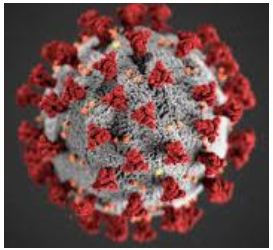
Faculty Disclosures

Amanda Mixon, PA-C

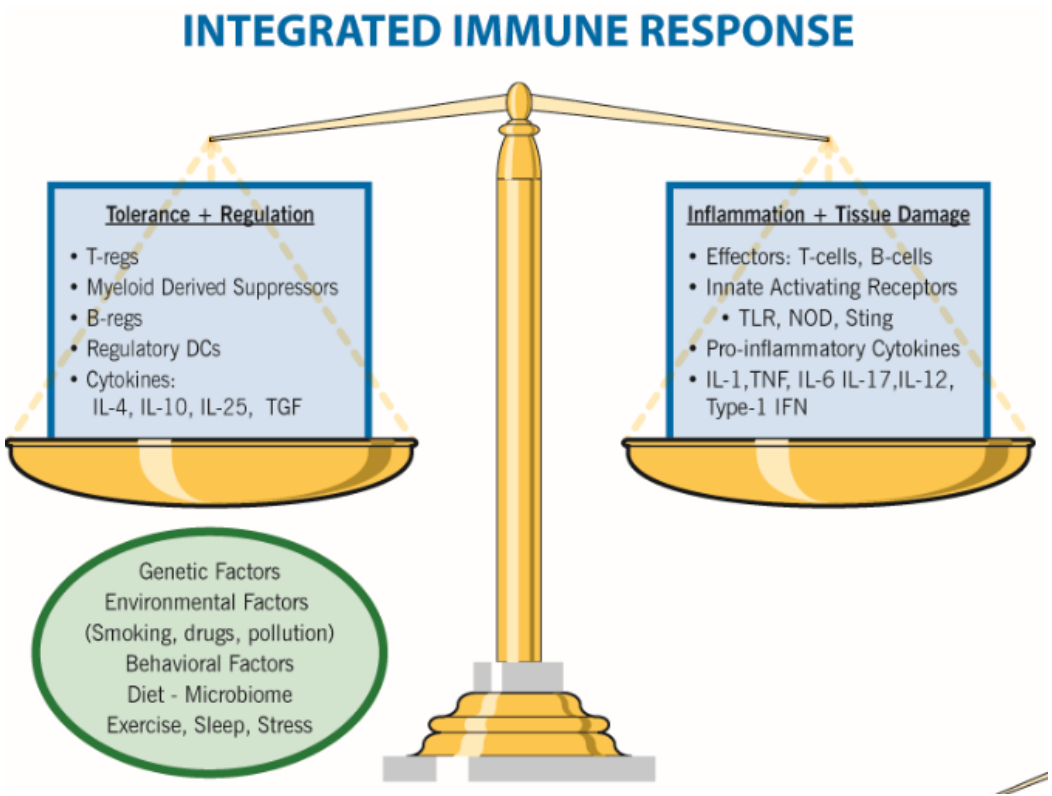
- There are no relevant relationships to disclose.

COVID-19

- Caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)
- Single-stranded enveloped RNA virus
- 7 human coronaviruses:
  - Severe disease: SARS-CoV, MERS-CoV, SARS-CoV-2
  - Mild symptoms: HKU1, NL63, OC43 and 229E
- Like SARS and MERS, SARS-CoV-2 believed to have moved from bats to an intermediate host – possibly Malayan Pangolin → humans

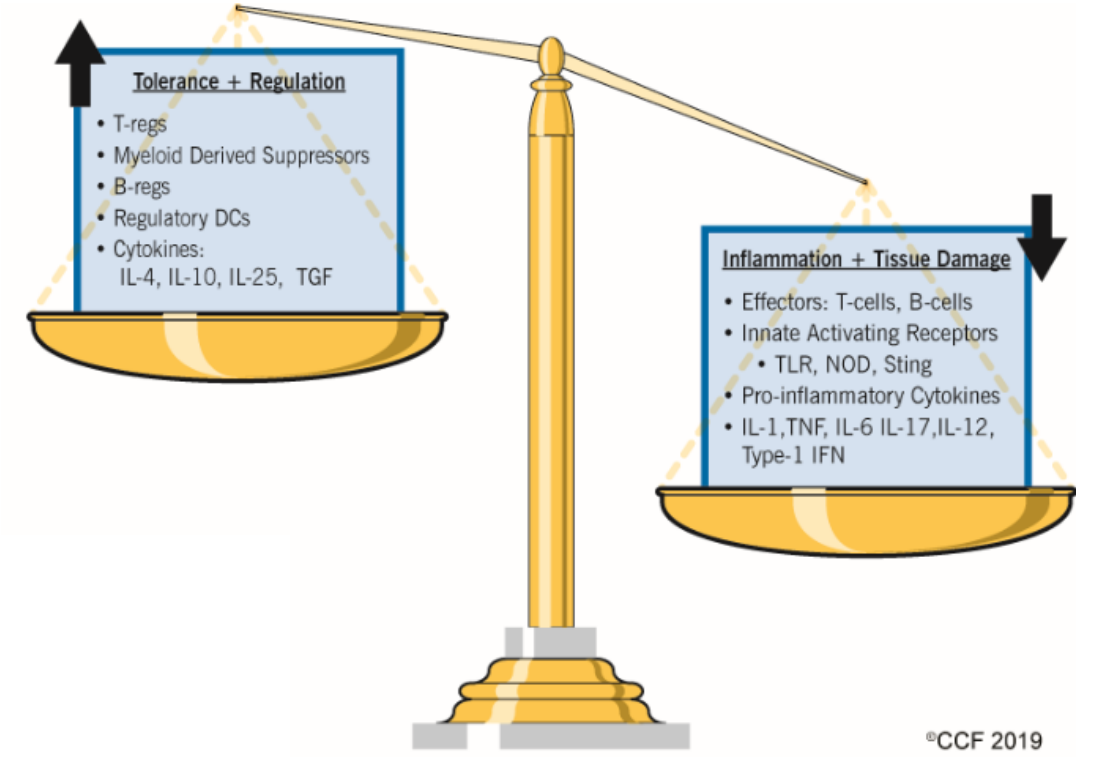


Balance



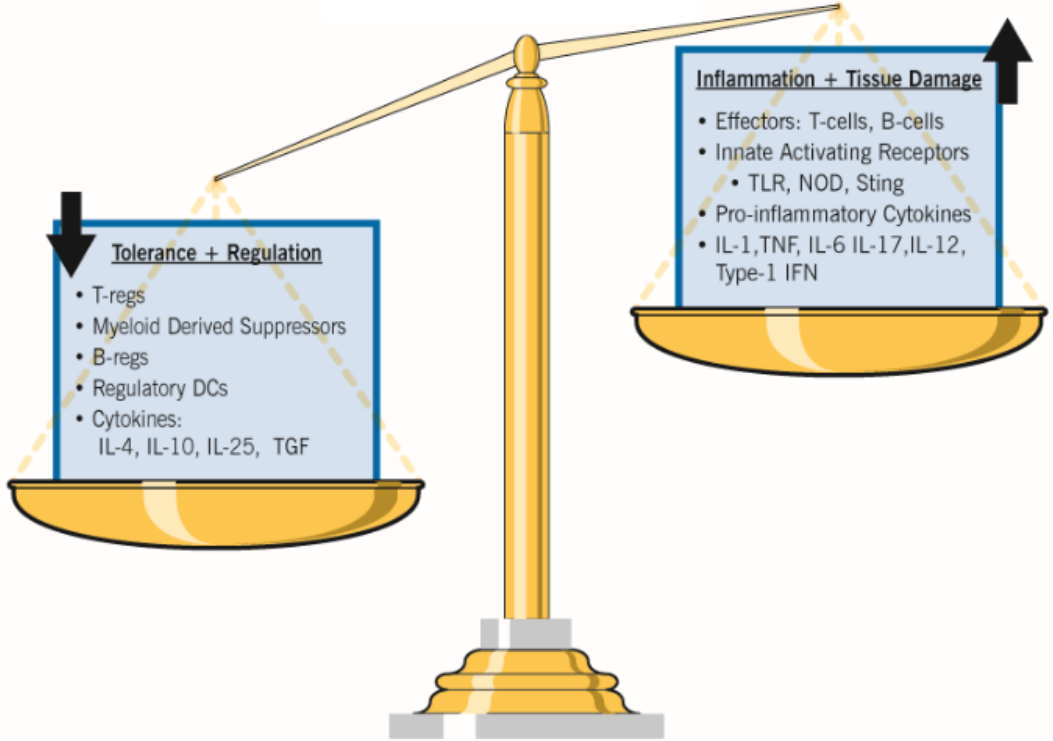
Calabrese LH, Marriot X. *Ann Rheum Dis*. Jan 2020.

Cancer-Infections



Calabrese LH, Marriot X. *Ann Rheum Dis*. Jan 2020.

COVID-19



Calabrese LH, Marriot X. *Ann Rheum Dis*. Jan 2020.

The COVID-19 Pandemic

- Most patients suffering from COVID-19 experience mild-to-moderate symptoms
- A subgroup of patients will become severely ill and suffer from:
  - Sepsis
  - Respiratory failure
  - Acute respiratory distress syndrome (ARDS)

Henderson LA, et al. *Arthritis Rheumatol*. 2020;72:1059-1063.

The COVID-19 Pandemic: ICU Admission and Death

Multiple factors are associated with ICU admission and death such as:

- Older age
- Comorbid conditions
- Elevated body mass index
- Lymphopenia
- Elevated blood levels of transaminases
- Lactate dehydrogenase (LDH)
- d-dimer
- Ferritin
- Soluble interleukin-2 receptor (sIL-2R) (1 – 4)

Henderson LA, et al. *Arthritis Rheumatol*. 2020;72:1059-1063.

The Cytokine Storm Syndrome

- The constellation of features associated with poor outcomes in COVID-19 is reminiscent of cytokine storm syndrome
- Defined as a family of features in which hyperinflammation and multiorgan disease arise through excessive cytokine release from uncontrolled immune activation
- Cytokine storm can be associated with infectious or non-infectious diseases

Henderson LA, et al. *Arthritis Rheumatol*. 2020;72:1059-1063.

Biomarkers of CRS and Status of COVID-19

Biomarker	Status in hyperinflammation	Status in COVID-19	Test availability
CBC	May be indicative of CRS (especially thrombocytopenia)	Associated with severity, ARDS	A
↑D-dimer, ↓fibrinogen	May be indicative of active CRS	Associated with severity, ARDS	A
LDH, AST, ALT	May be indicative of active CRS	Associated with severity, ARDS	A
Ferritin	Integral part of CRS diagnosis, predictive of sepsis mortality	Associated with severity, ARDS	A
Ferritin:ESR ration	Higher specificity than ferritin alone	Not assessed	A
CRP	Non-specific, useful for monitoring, blunted by IL-6 blockade	Associated with severity, ARDS	A
IL-6	Elevated, nonspecific	Associated with severity	S
IFN-γ	Elevated, but poor dynamic range	Elevated compared with healthy control	S,R
IL-1β	Elevated, but poor dynamic range	Variable elevated with severity	S,R
IL-18	Very high levels; may indicate MAS, not useful for monitoring	Not assessed	S

Henderson L, et al. A&R. MAY 2020.

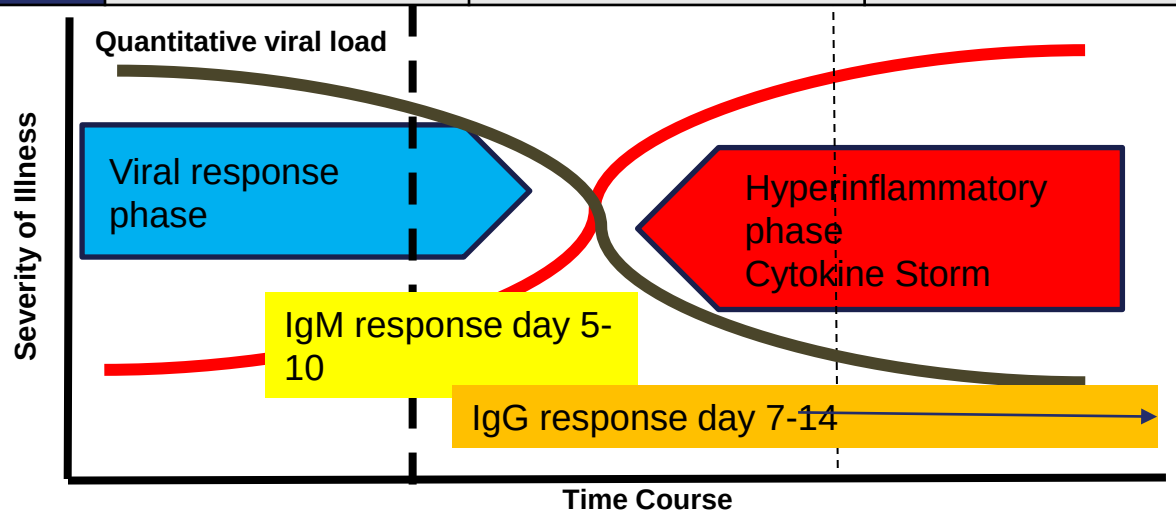
Explaining Cytokine Storm in Basic Terms

- A cytokine storm is often described as a hyperactive immune response
- On a basic level, it is like setting off a bomb in your house because you want to get rid of a few ants
- The real problem isn't just that the response is too strong
  - When everything is working as it should, pro-inflammatory cytokines and anti-inflammatory cytokines work together to kill off an invader and then settle down so the immune system isn't perpetually in attack mode
- The real problem is that the response keeps going when it shouldn't
  - When things go awry, however, your immune system stays on the attack and you can end up with a cytokine storm

Available at: https://creakyjoints.org/living-with-arthritis/coronavirus/managing-symptoms/cytokine-storm-covid-19-autoimmune-disease/. Accessed November 10, 2020.

Course of COVID-19 Infection – A Paradigm for Therapy

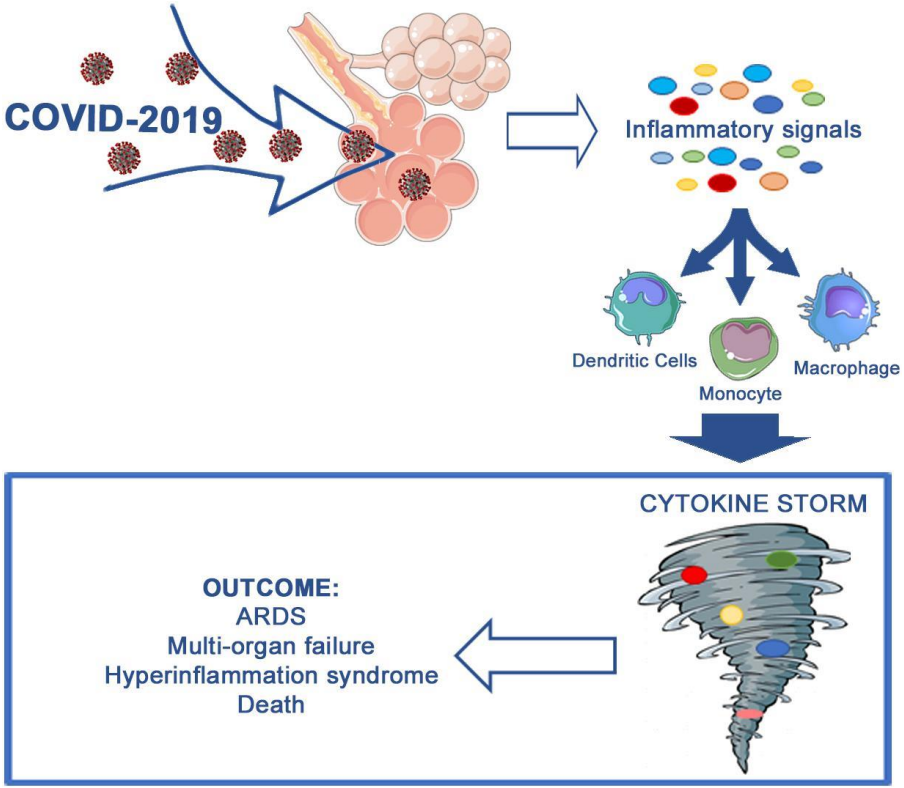
	ACT 1 Asymptomatic	ACT 2 Non-severe symptomatic	ACT 3 Severe respiratory
IMMUNE REPSONSE OVER TIME **Self limiting in 80%** **Severe in 15-20%** **Fatal 1-2%**	**INNATE IMMUNE ACTIVATION**	**ADAPTIVE IMMUNE ACTIVATION**	**CYTOKINE MEDIATED SYNDROME**
	Viral engagement of PAMPs Low Type 1 IFN	Generation of specific Abs and T cell response Release of DAMPS	IL-6, IL-1, TNF, GM-CSF, IFN, IFN Immuno-Coagulopathy



RISK FOR STAGE 3
AGE
RACE
DM / OBESITY
ASHD
Renal disease
HTN
Male sex
Other ABO

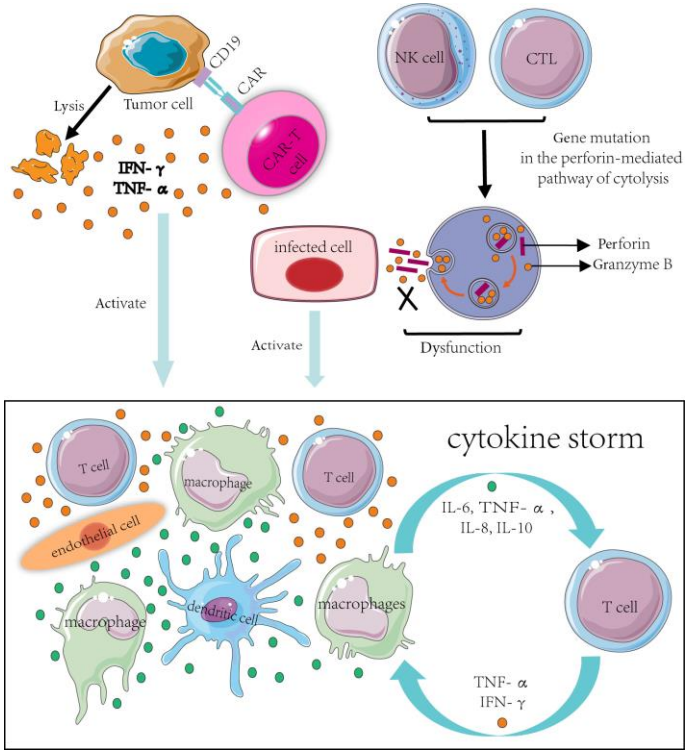
ASHD = arteriosclerotic heart disease; HTN = hypertension; PAMP = pathogen-associated molecular pattern;
DAMP = damage-associated molecular patterns; TNF = tumor necrosis factor; IL = Interleukin;
GM-CSF = Granulocyte-macrophage colony-stimulating factor; IFN = interferon

The Cytokine Storm in COVID-19



Castelli V, et al. *Front. Immunol*. 2020. https://doi.org/10.3389/fimmu.2020.02132.

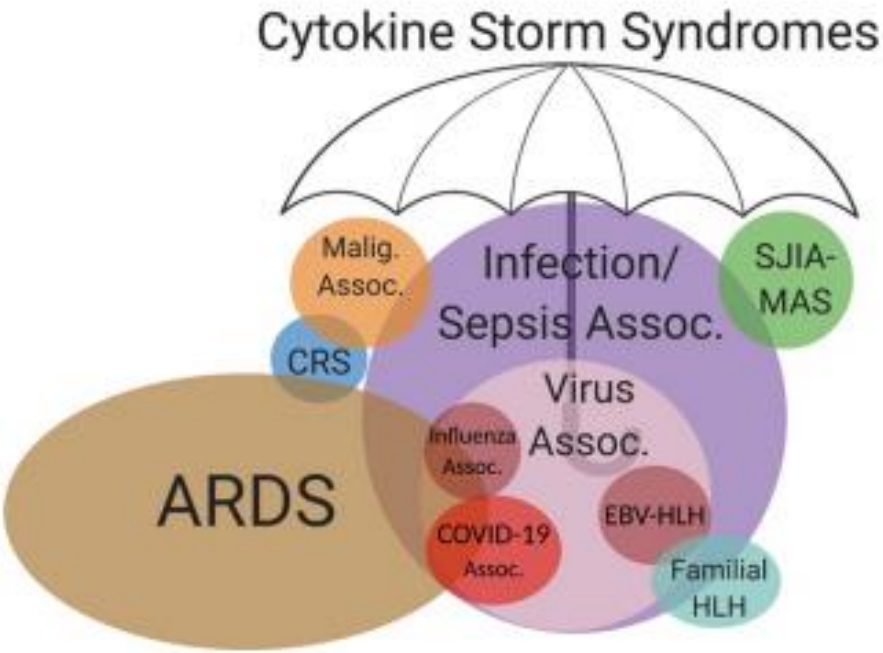
Proposed Pathogenesis of Cytokine Storm Syndrome



- CAR T cells and T cells become activated
- This causes a consecutive release of cytokines including IFN-γ or TNF-α
- These cytokines trigger a cascade reaction by activation of innate immune cells including macrophages, DCs and endothelial cells
- This results in further cytokine releasing, which finally leads to a cytokine storm

Gao YM, et al. *J Intern Med*. 2020 Jul 22:10.1111/joim.13144. doi: 10.1111/joim.13144.

The Family of Conditions Characterized by Cytokine Storm



Malig. = malignancy; Assoc. = associations; SJIA = systemic juvenile idiopathic arthritis; MAS = macrophage activation syndrome; CRS = cytokine release syndrome; ARDS = acute respiratory distress syndrome; EBV = Epstein-Barr virus; HLH = hemophagocytic lymphohistiocytosis.

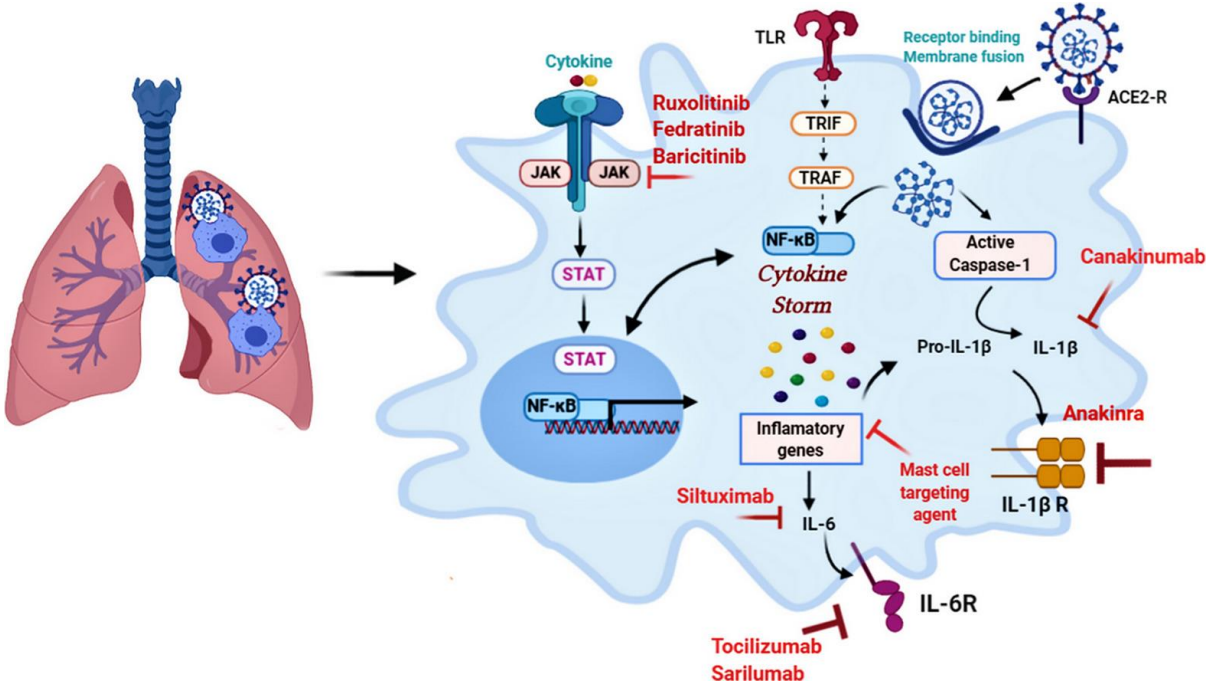
Henderson LA, et al. *Arthritis Rheumatol*. 2020;72:1059-1063.

Cytokine Storm Syndromes in Rheumatology

"Rheumatology practices face this foe regularly in systemic juvenile idiopathic arthritis (JIA), adult-onset Still's disease, and systemic lupus erythematosus, among other diseases"

Henderson LA, et al. *Arthritis Rheumatol*. 2020;72:1059-1063.

COVID-19 and Cytokine Storm Syndrome:
What Can We Learn From Rheumatology Experience?



Immunomodulatory agents used in rheumatology have a potential role in COVID-19

Abdin SM, et al. *Life Sci*. 2020;257:118054. doi: 10.1016/j.lfs.2020.118054.

Challenges in Immunobiology of COVID-19 and Clinical Trial Design and Interpretation

- Clinical Heterogeneity of advanced COVID-19 (MIS-C, MIS-A, ARDS)
- Immunologic heterogeneity of COVID-19
  - Early versus late antibody formation
  - High and low viral burdens
  - Heterogeneity of innate and adaptive immune responses
  - Lack of correlation between chronologic time of disease and biologic endotypes

Clinical Heterogeneity of Stage 3 COVID-19

MIS-C CDC defined

- Age < 21
- Fever >38
- Hyperinflammation
  - CRP, ferriten, D-dimer, LDH, cytopenias, etc
- Multisystem Disease
  - CVD
  - Respiratory
  - Renal
  - Coagulopathy
  - Neuro

MIS-A CDC preliminary

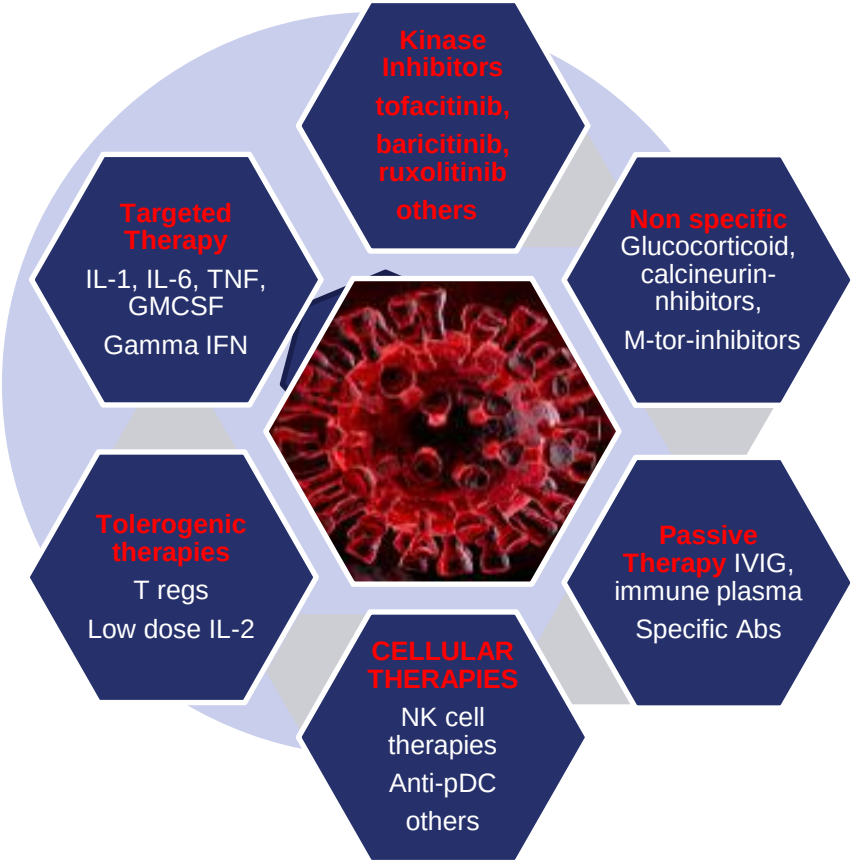
- Age > 21
- Fever
- Hyperinflammation
  - CRP, ferriten, D-dimer, LDH, cytopenias, etc
- Multisystem Disease
  - CVD
  - Renal
  - Coagulopathy
  - Neuro

NO ARDS or severe respiratory disease

Advanced Respiratory Disease

- No formal definition
- i.e. ARDS, secondary pneumonia (bacterial, opportunistic other)
- With or without hyperinflammation

Immunotherapeutic Strategies for COVID-19 Cytokine Release and Beyond



Treatments for Cytokine Storm Syndrome of Potential Utility in Severe COVID-19

Intervention	Biology	Experience in Hyperinflammation
Glucocorticoids (< 2 mg/kg/day)	Transcriptional regulation via glucocorticoid receptor	Mainstay of treatment
Glucocorticoids (> 250 mg/day)	Transcriptional regulation via glucocorticoid receptor	Commonly used during initiation
Cyclosporine, tacrolimus	Inhibit calcineurin-mediated lymphocyte activation	Case reports/small series in MAS, part of HLH treatment protoco
Anakinra	Block IL-1 signaling	Re-analysis of sepsis trials, large series in MAS and HLH
Sarilumab, tocilizumab	Block IL-6 signaling	CAR-T cytokine release syndrome, case reports, ongoing clinical trials¶
Emapalumab	Neutralize IFNγ	Refractory familial HLH, other case reports, ongoing trials
JAK inhibitors	Inhibit JAK/STAT pathway cytokines	Case reports, ongoing clinical trials

Henderson LA, et al. *Arthritis Rheumatol.* 2020;72:1059-1063.

Anti-IL6 and COVID-19

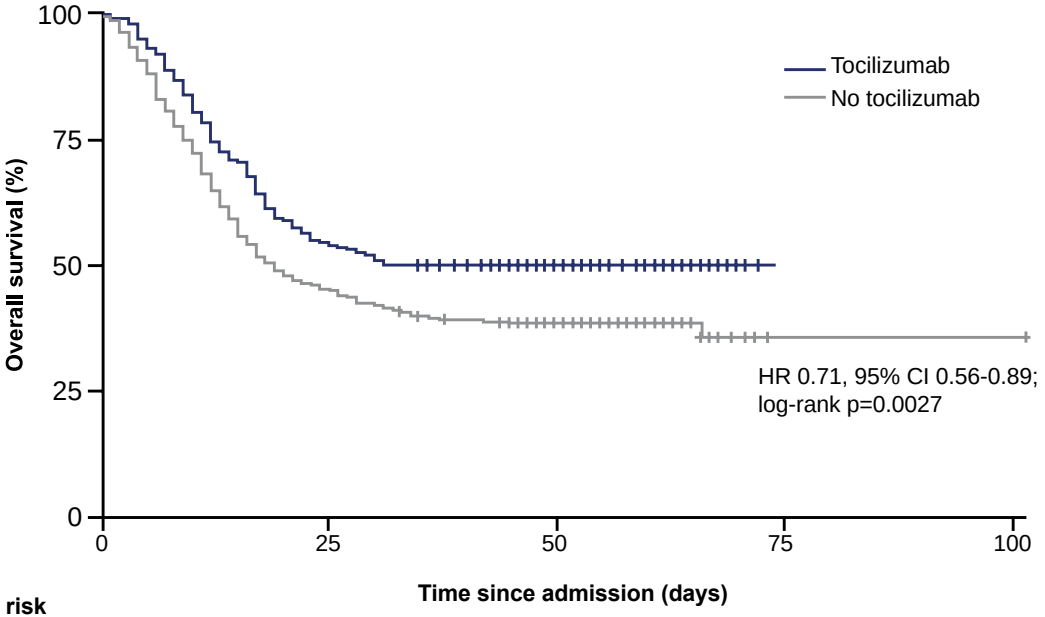
	Phase 1	Phase 2	Phase 3	Phase 4
Clazakinumab		NCT04348500		
Sarilumab	NCT04386239	NCT04359901 NCT04322773	NCT04315298	
Tocilizumab		NCT04333914 NCT04335071 NCT04315480 NCT04445272 NCT04370834 NCT04331808 NCT04322773	NCT04330638	NCT04377750

IL-6 Inhibition in COVID-19 Patients Requiring ICU Support

- Tocilizumab is a monoclonal antibody directed against the IL-6 receptor
- IL-6 inhibition has been proposed to mitigate the cytokine storm syndrome associated with severe COVID-19
- Investigators conducted a retrospective observational cohort study at 13 hospitals involving 764 patients with COVID-19 who required ICU support
  - 210 patients (27%) received tocilizumab
- Patients with COVID-19 requiring ICU support who received tocilizumab had reduced mortality
- Results of ongoing randomized controlled trials are awaited

Biran N, et al. *Lancet Rheumatol*. 2020;2:e603-e612. doi: 10.1016/S2665-9913(20)30277-0.

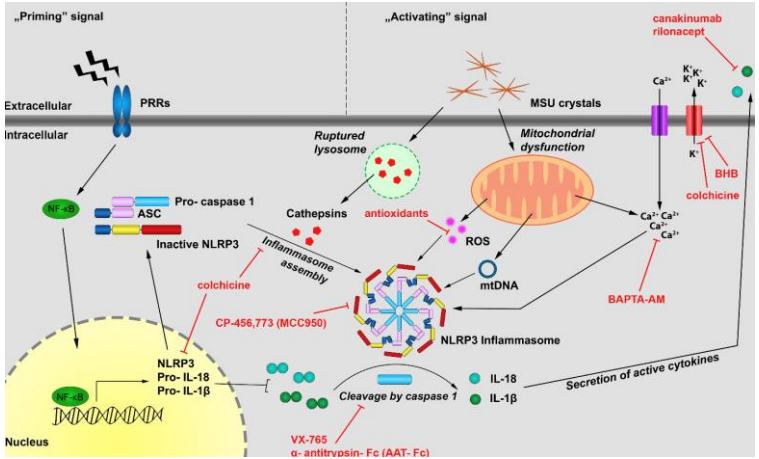
An Association Was Noted Between Receiving Tocilizumab and Decreased Hospital-Related Mortality



Number at risk (number censored)					
No tocilizumab	416 (0)	189 (0)	130 (35)	2 (158)	1 (159)
Tocilizumab	205 (0)	112 (0)	64 (42)	0 (103)	0 (103)

Biran N, et al. *Lancet Rheumatol.* 2020;2:e603-e612. doi: 10.1016/S2665-9913(20)30277-0.

IL-1



Product of inflammasome activation DAMPS

Table 1. Currently available IL-1 inhibitors

Agent	Mechanism of Action	Current FDA-approved indications and dosing	Contraindications and cautions
Anakinra (Kineret)	Recombinant human IL-1 receptor antagonist. Inhibits activity of IL-1-alpha and IL-1-beta	**Rheumatoid arthritis:** 100mg SC qDay **CAPS/NOMID:** 1-2mg/kg SC qDay; may increase by 0.5-1mg/kg increments, max dose of 8mg/kg Renal dosing – if CrCl < 30ml/min or ESRD, consider every other day dosing	**Use with caution** in patients with: • Concomitant TNG inhibitor use • Serious active infection • Neutropenia
Canakinumab (Ilaris)	Human monoclonal anti-IL-1-beta. Neutralizes IL-1 beta activity	**Systemic juvenile idiopathic arthritis:** 4mg/kg SC gMonth; not to exceed 300mg/dose (≥ 2 years and weight ≥ 7.5kg) **CAPS:** 15-40kg – 2mg/kg SC q8wk. ≥ 40kg – 150mg SC q8wk **FMF, TRAPS and HIDS/MVD:** ≤ 40kg – 2mg/kg SC q4wk; may increase to 4mg/kg q4wk. > 40kg – 150mg SC q4wk; may increase to 300mg q4wk	**Use with caution** in patients with: • Serious active infection
Rilonacept (Arcalyst(	Fusion protein of extracellular domains of IL-1-RAcP and IL-1-R1 fused to FC portion of human IgG1. Binds to IL-1 alpha and IL-1 beta to block IL-1 signaling	CAPS: adults – loading dose of 320mg SC followed by 160mg SC q1wk Prediatric (12-17 yrs) – loading dose of 4.4mg/kg (max dose 320mg) followed by 2.2mg/kg SC q1wk (max dose 160mg)	**Use with caution** in patients with: • Serious active infection

Slide from Dr. Calabrese.

Anakinra – 3: 52 Patients

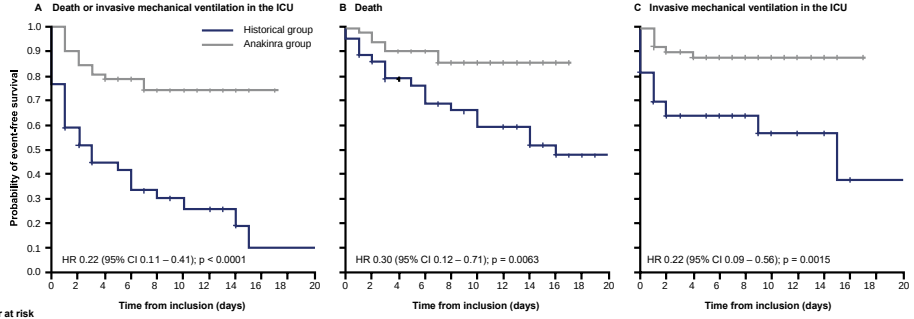
	Anakinra group (n=52)	Historical group (n=44)	p value
Age, years	71·0 (13·1)	71·1 (14·9)	0·97
Age category	--	--	0·80
<50 years	2 (4%)	1 (2%)	--
50–69 years	23 (44%)	22 (50%)	--
≥70 years	27 (52%)	21 (48%)	--
Sex	--	--	0·21
Male	36 (69%)	25 (57%)	--
Female	16 (31%)	19 (43%)	--
Body-mass index, kg/m²	25·5 (4·0)	29·0 (5·7)	0·0009
Comorbidities	--	--	--
Hypertension	31 (60%)	29 (66%)	0·53
Diabetes	14 (27%)	16 (36%)	0·32
Cardiopathy	9 (17%)	11 (25%)	0·36
Stroke	4 (8%)	7 (16%)	0·21
Pulmonary disease*	8 (15%)	12 (27%)	0·15
Number of comorbidities ≥2 vs 0–1	29 (56%)	20 (45%)	0·22
Not to be resuscitated	26 (50%)	20 (45%)	0·66
Positive swab RT-PCR†	36/41 (88%)	33/34 (97%)	0·14
Chest CT	--	--	0·55
Lung infiltrates <50%	31 (60%)	25/38 (66%)‡	--
Lung infiltrates ≥50%	21 (40%)	13/38 (34%)‡	--
Duration of symptoms before inclusion, days	8·4 (4·3)	6·2 (3·6)	0·0088
Clinical inclusion parameters	--	--	0·076
SpO_2 ≤93% under 6 L/min or more oxygen therapy	42 (81%)	41 (93%)	--
SpO_2 ≤93% under 3 L/min oxygen therapy with aggravation§	10 (19%)	3 (7%)	--
Oxygen saturation, %	91·6% (2·4)	92·1% (3·9)	0·53
Oxygen therapy, L/min	7·9 (3·6)	5·6 (3·7)	0·33
Low-flow oxygen therapy	32 (62%)	25 (57%)	0·22
High-flow oxygen therapy	20 (38%)	19 (43%)	--
Persistent fever >38°C	28 (54%)	28 (64%)	0·33

(Table 1 continues on next page)

Anakinra for severe forms of COVID-19: a cohort study

Thomas Huet, Hélène Beaussier, Olivier Voisin, Stéphane Jouveshomme, Gaëlle Dauriat, Isabelle Lazareth, Emmanuelle Sacco, Jean-Marc Naccache, Yvonnick Bézie, Sophie Laplanche, Alice Le Berre, Jérôme Le Pavec, Sergio Salmeron, Joseph Emmerich, Jean-Jacques Mourad, Gilles Chatellier, Gilles Hayem

- No patient on mechanical ventilation
- Anakinra: 200 mg SC /day 3 days and 100 mg SC /day 7 days
- Historical controls



Thelancet.com/rheumatology Published online May 29, 2020.

Glucocorticoids

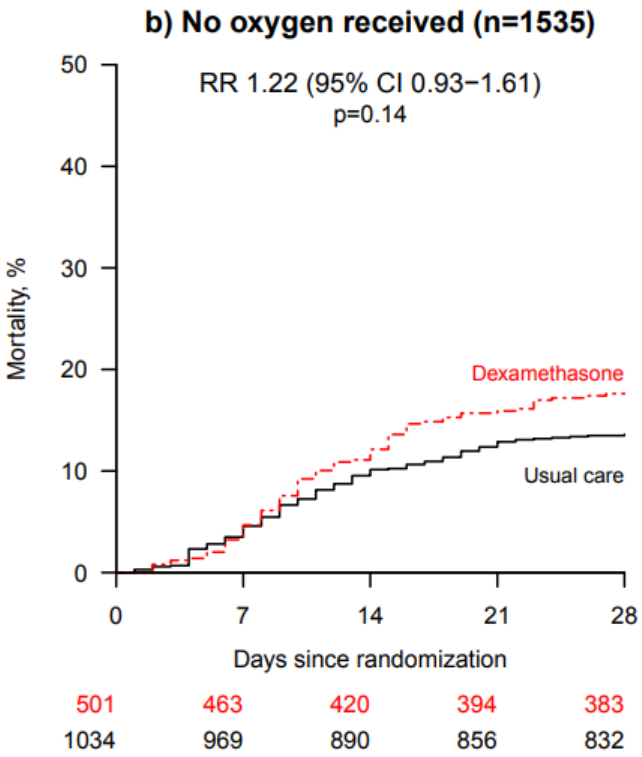
- Glucocorticoids are known to modulate the immune system since 1924
- Landmark work by Dale et al in the 1970's documented their immunosuppressive effects
- More recently, human immunome studies have demonstrated suppression of NF-kB, apoptosis and cell death differentially effecting T and B cells and NK cells in humans[1]
- Previous work in SARS, MERS and severe influenza mixed/underpowered and suffer from heterogeneity of agent/dose/duration
- Currently over 40 trials using glucocorticoids in COVID-19 on clinicaltrials.gov

1. Olnes M, et al. *Sci Reports*. 6:23002,16.

Steroids and COVID-19

Total = 40	Phase 2	Phase 3	Phase 4	Observational	Other
Dexamethasone n=12	NCT04360876	NCT04381936 NCT04452565 NCT04327401 NCT04347980 NCT04395105	NCT04325061	NCT04445506	NCT04344730 NCT04380818 NCT04402840 NCT04445337
Methylprednisolone n=14	NCT03852537 NCT04329650 NCT04343729 NCT04355247 NCT04377503	NCT04341038 NCT04345445 NCT04438980 NCT04244591 NCT04349410	NCT04263402	NCT04323592 NCT04374071	NCT04273321
Prednisone n=2	NCT04344288	NCT04451174			
Prednisone + Hydrocort n=1		NCT04359511			
Inhaled Ciclesonide n=4	NCT04330586 NCT04381364	NCT04377711 NCT04435795			
Inhaled Budesonide n=4	NCT04416399	NCT04193878 NCT04331470	NCT04355637		
Nasal Budesonide n=3	NCT04422275	NCT04361474	NCT04374474		

Dexamethasone COVI9-19



Effect of Dexamethasone in Hospitalized Patients with COVID-19 – Preliminary Report

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

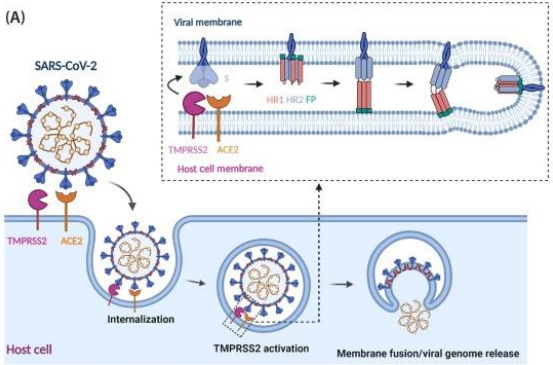
Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19
A Meta-analysis

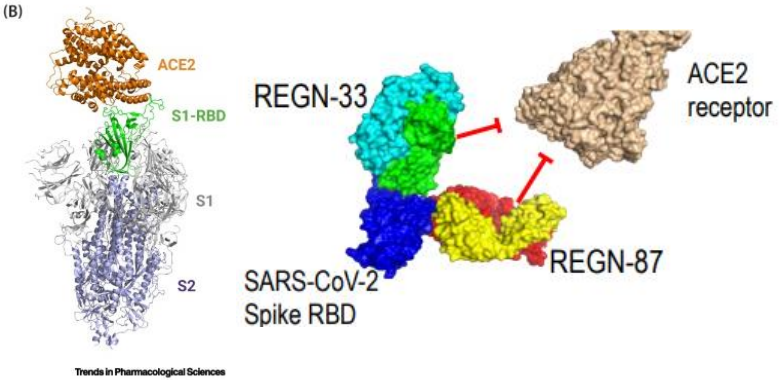
The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group

Correspondence to: Dr Peter W Horby and Dr Martin J Landray, RECOVERY Central Coordinating Office, Richard Doll Building, Old Road Campus, Roosevelt Drive, Oxford OX3

Dexamethasone reduced deaths by one-third in patients receiving invasive mechanical ventilation (29.0% vs. 40.7%, RR 0.65 [95% CI 0.51 to 0.82]; p
NNT=8 for mortality

STUDY 2067 Outpatient (IV): Seamless P1/2/3 – Symptomatic – Initial Data – Asymptomatic N=275

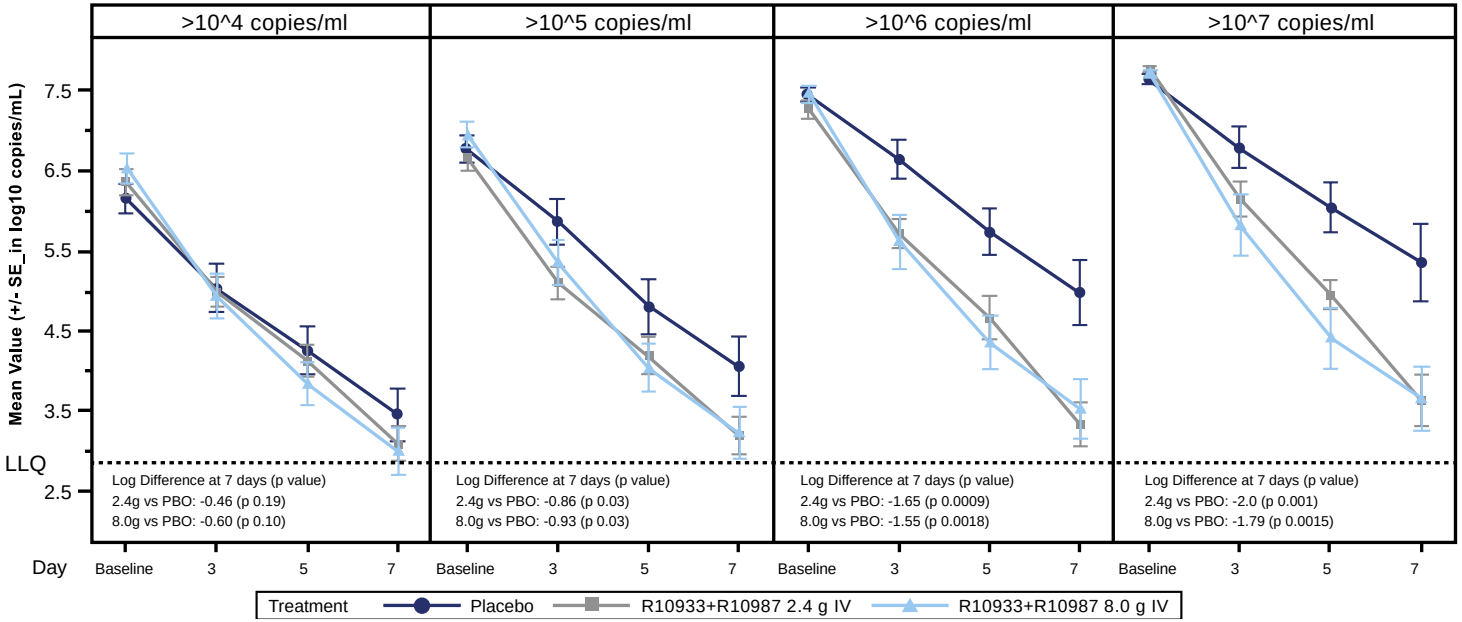




- The REGN-COV2 antibody cocktail reduces viral loads and symptoms vs. placebo in nonhospitalized patients who are infected with SARS-COV2
- Greatest improvements were observed in patients who had not mounted their own effective immune response prior to treatment (antibody seronegative and/or high viral loads at baseline)

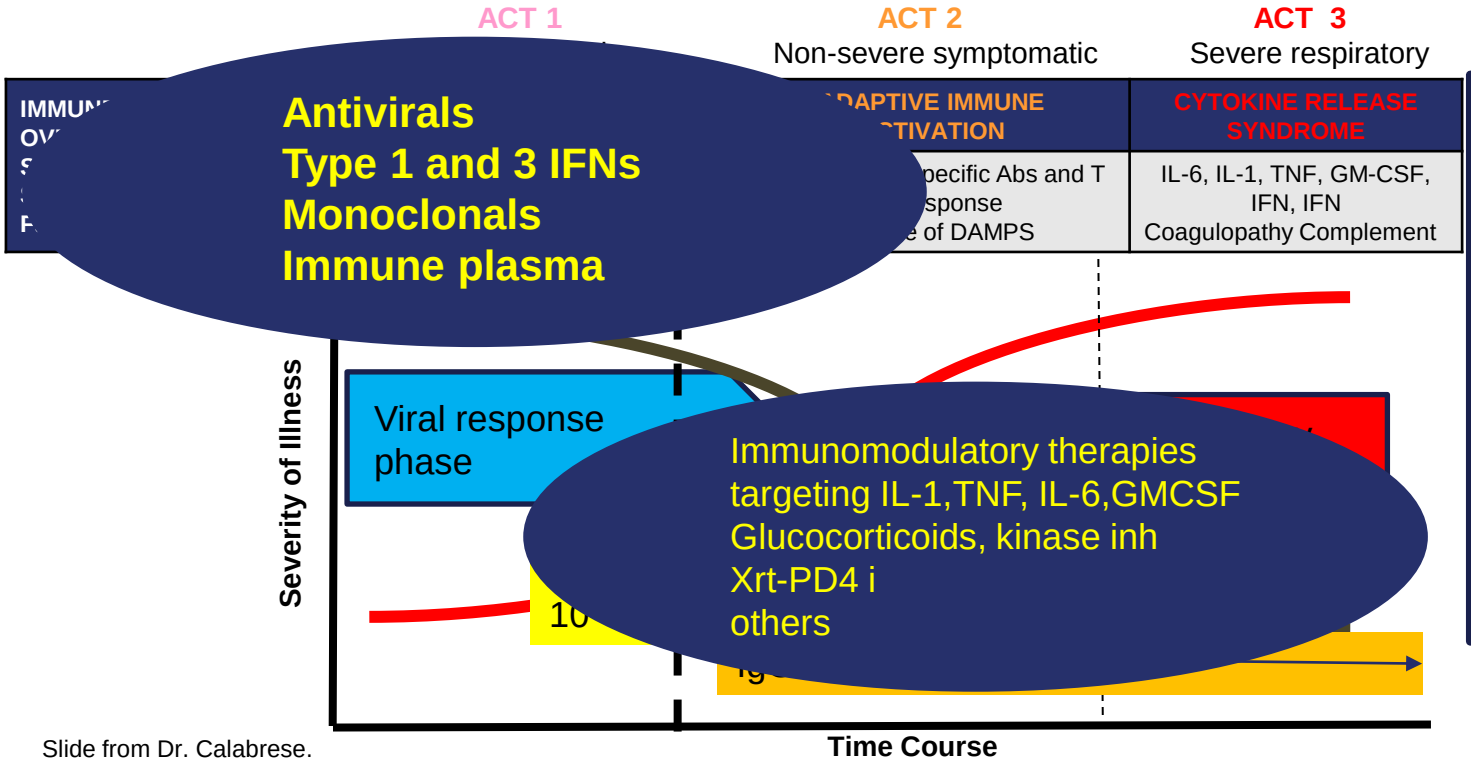
Regn-COV2 Provided Greater Reduction in Viral Load in Those With Higher Viral Load at Baseline

REGN-COV2 PROVIDED GREATER REDUCTION IN VIRAL LOAD IN THOSE WITH HIGHER VIRAL LOAD AT BASELINE



Regeneron Press Release, 10/20.

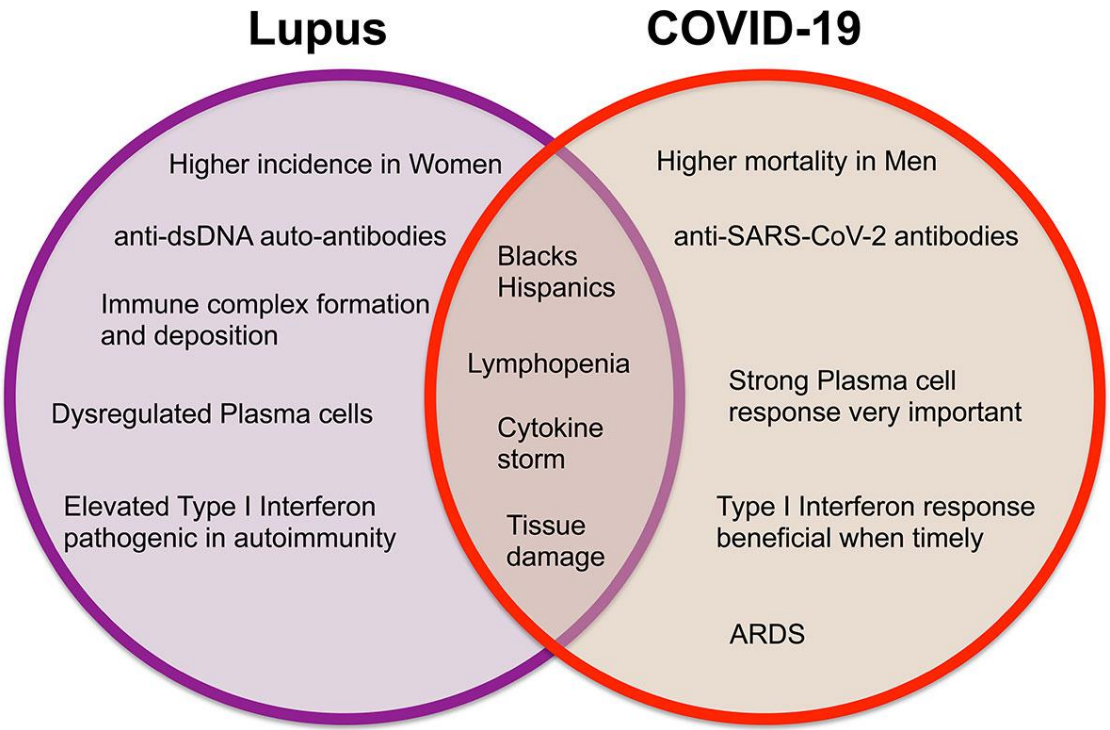
Course of COVID-19 Infection – A Paradigm for Therapy



RISK FOR STAGE 3
AGE
RACE
DM / OBESITY
ASHD
Renal disease
HTN
Male sex
Other ABO etc

Slide from Dr. Calabrese.
ASHD = arteriosclerotic heart disease; HTN = hypertension; PAMP = pathogen-associated molecular pattern; DAMP = damage-associated molecular patterns; TNF = tumor necrosis factor; IL = Interleukin; GM-CSF = Granulocyte-macrophage colony-stimulating factor; IFN = interferon.

Many Aspects of SLE and COVID-19 Overlap



Spihlman AP, et al. *Front. Immunol*. 2020. https://doi.org/10.3389/fimmu.2020.589474.

Conclusions

- Immunology is a big topic for 30 minutes!
- Always interesting stuff happening
- A better understanding of the underlying immune response and therapeutic strategies in rheumatology and COVID-19 is important to guide management of this deadly infectious disease

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Thank you