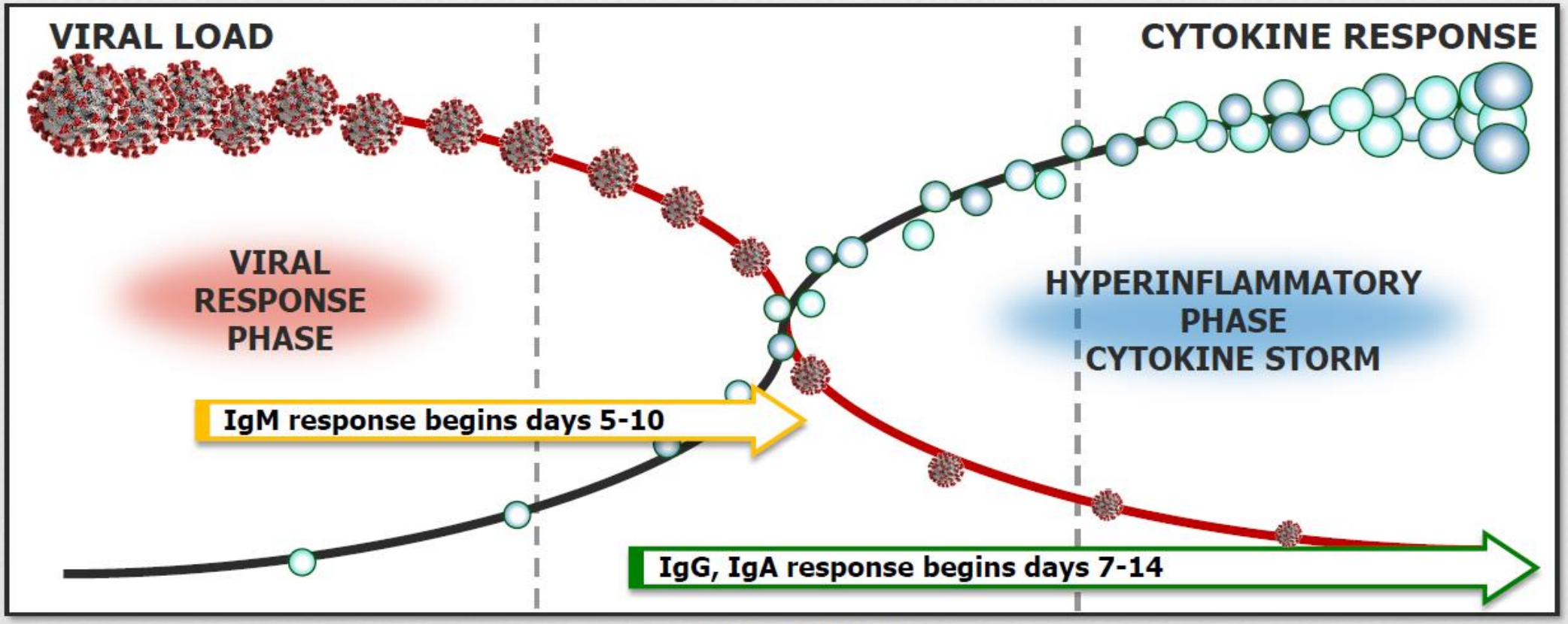
Covid 19

Course of COVID-19 Infection – A Paradigm for Therapy

Asymptomatic
Innate immune activation
STAGE 1

Nonsevere symptomatic
Adaptive immune activation
STAGE 2

Severe respiratory/inflammatory
Cytokine release syndrome
STAGE 3



Disease Course

- Self limiting in 80%
- Severe in 15%-20%
- Fatal in 1%-2%

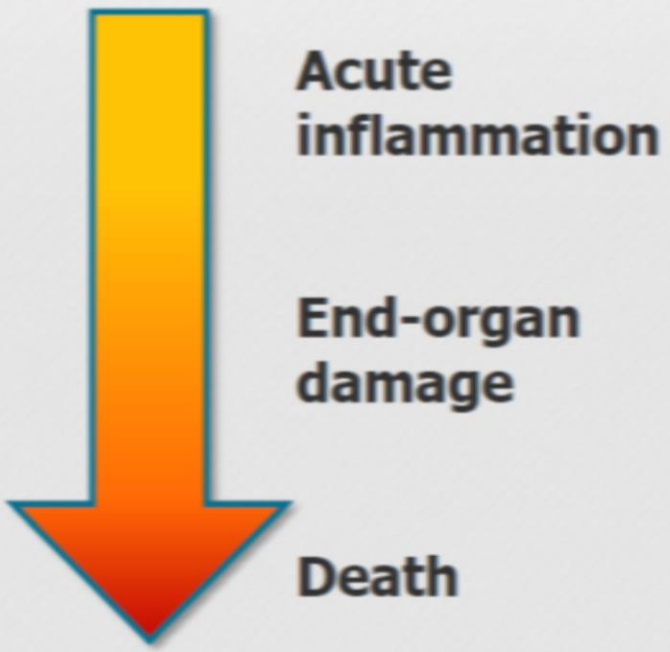
Risk Factors for Stage 3 Disease

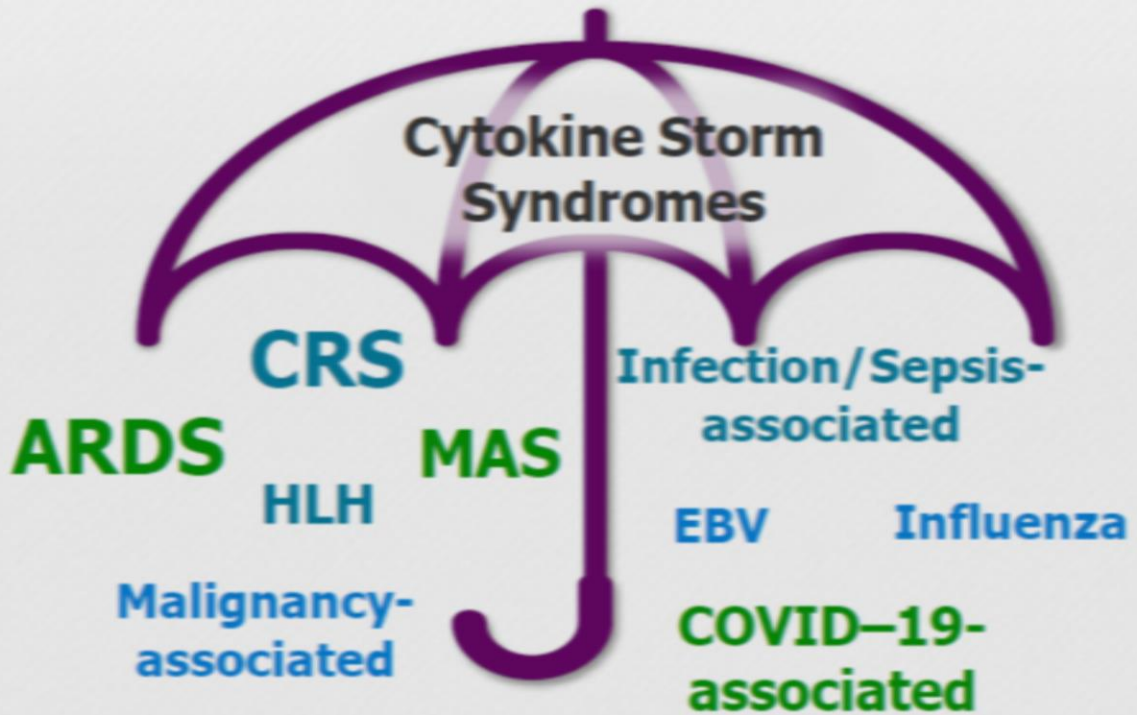
- Age
- Immunosuppressed states
- Diabetes
- ASHD
- Renal disease
- Hypertension
- Male sex
- Other

ASHD = arteriosclerotic heart disease; Ig = immunoglobulin.
Adapted from Calabrese LH. *Cleve Clin J Med*. 2020;87(7):389-393.

Secondary HLH/MAS – Lessons Learned

Cytokine storm/cytokine-release syndrome loosely applies to a wide variety of conditions driven by inflammatory cytokines and immune hyperactivation, triggered by such factors as genetic disorders, cancer, infections, and certain drugs





ARDS = acute respiratory distress syndrome; CRS = cytokine-release syndrome; EBV = Epstein-Barr virus; HLH = hemophagocytic lymphohistiocytosis; MAS = macrophage

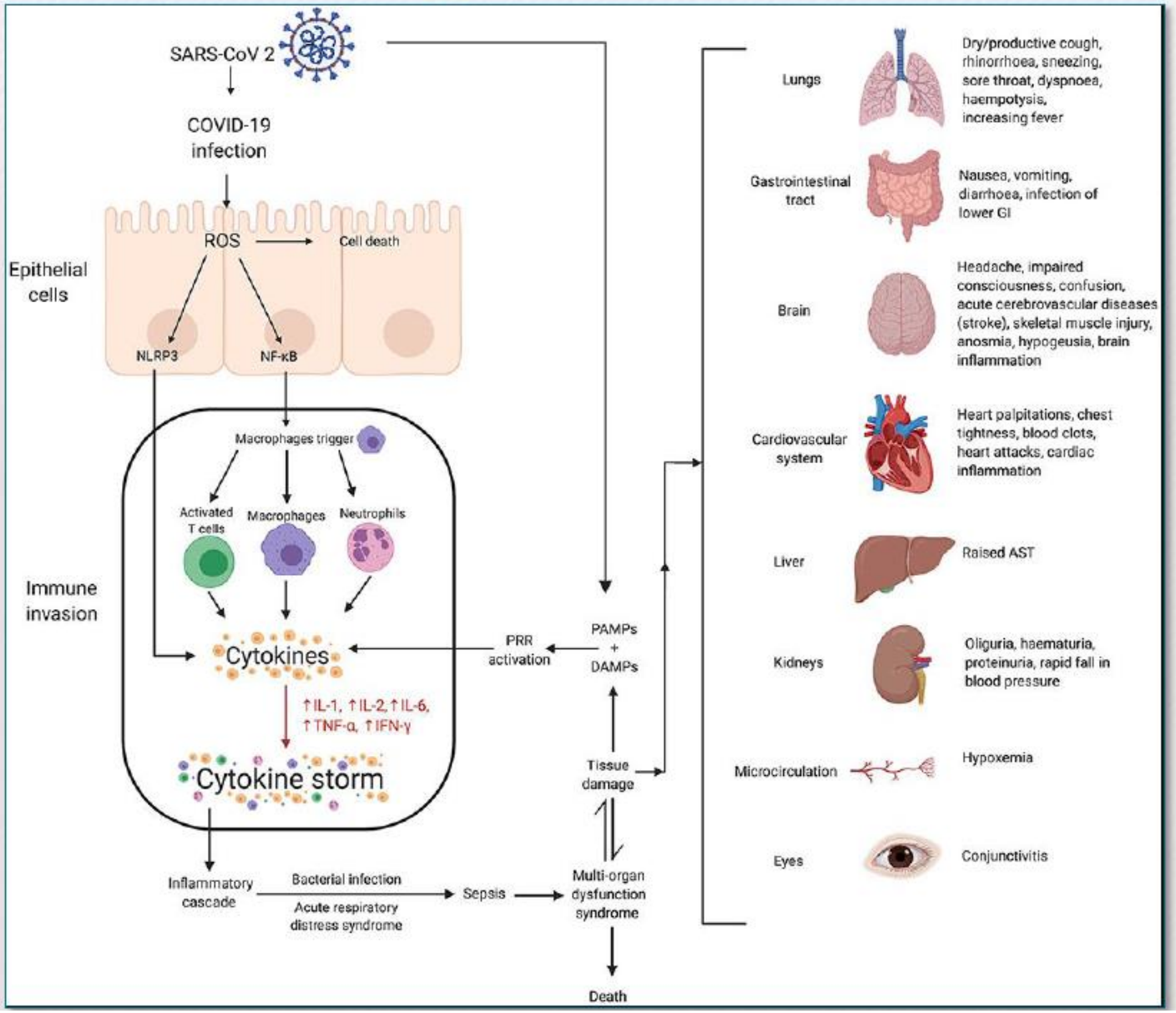
Clinical Presentation of Cytokine Storm

COVID-19 "cytokine storm"

- Typically single organ disease (ie, ARDS)
- Multiorgan disease less common
- Elevated cytokines/mediators
- Response to immunomodulatory therapies

Drivers are still unclear

- Virus
- DAMPS
- Genetics
- Comorbidities



DAMPS = damage-associated molecular patterns.
Fajgenbaum DC, et al. *N Engl J Med.* 2020;383(23):2255-2273.
Image from Bhaskar S, et al. *Front Immunol.* 2020;11:1648. Open access.

Biomarkers in COVID-19

Although inflammatory markers—such as C-reactive protein (CRP), D-dimer, and ferritin—are not routinely measured as part of standard care, results from such measurements may have prognostic value[2]

Biomarkers of CRS and Status in COVID-19[1]

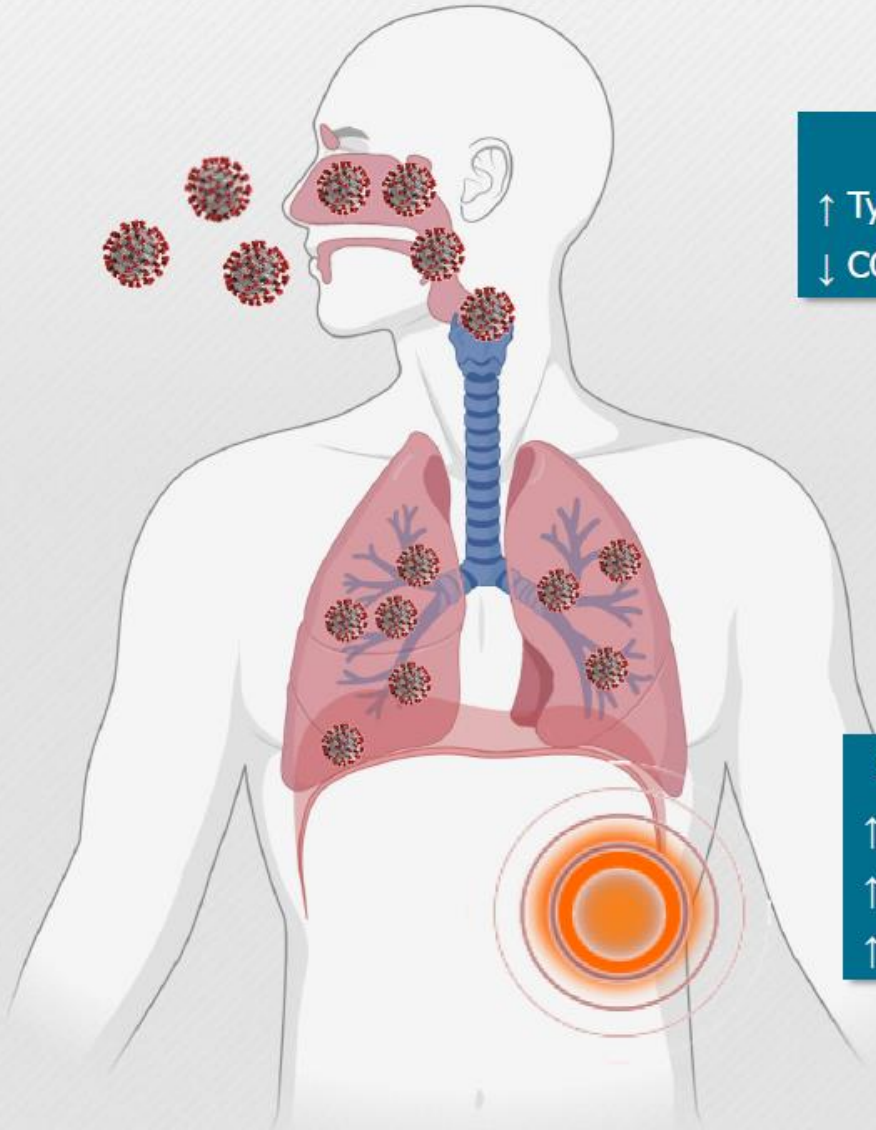
Biomarker	Status in hyperinflammation	Status in COVID-19
CBC	Lymphopenia, neutrophil/lymphocyte	Associated with severity, ARDS
↑ D-dimer, ↓ fibrinogen	May be indicative of active CRS	Associated with severity, ARDS
LDH, AST, ALT	May be indicative of active of CRS	Associated with severity, ARDS
Ferritin	Integral part of CRS diagnosis, predictive of sepsis mortality	Associated with severity, ARDS
Ferritin:ESR ratio	Higher specificity than ferritin alone	Not assessed
CRP	Nonspecific, useful for monitoring, blunted by IL-6 blockade	Associated with severity, ARDS
IL-6	Elevated, nonspecific	Associated with severity
IFN-γ	Elevated, but poor dynamic range	Elevated compared with healthy control
IL-1β	Elevated, but poor dynamic range	Variably elevated with severity
IL-18	Very high levels; may indicate MAS, not useful for monitoring	Not assessed

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CBC = complete blood count; ESR = erythrocyte sedimentation rate; LDH = lactate dehydrogenase.

1. Henderson LA, et al. *Arthritis Rheumatol.* 2020;72(7):1059-1063.
2. National Institutes of Health. Updated July 24, 2021. Accessed August 19, 2021. https://www.covid19treatmentguidelines.nih.gov/

Current Unresolved Issues in Immunopathogenesis of Severe COVID-19

- Interferon is important in host defense early, but can be deleterious later
- Both genetic and autoimmune factors may contribute to altered function
- Immunologic discordance anatomically (upper/lower respiratory tract) between tissue and blood
- Drivers of SEVERE inflammation may be viral, damage-associated, or both
- Lack of clinically predictive biomarkers or correlates with deep immunologic profiling to guide precision medicine



UPPER AIRWAYS
↑ Type 1/type 3 interferons
↓ COVID-19 severity

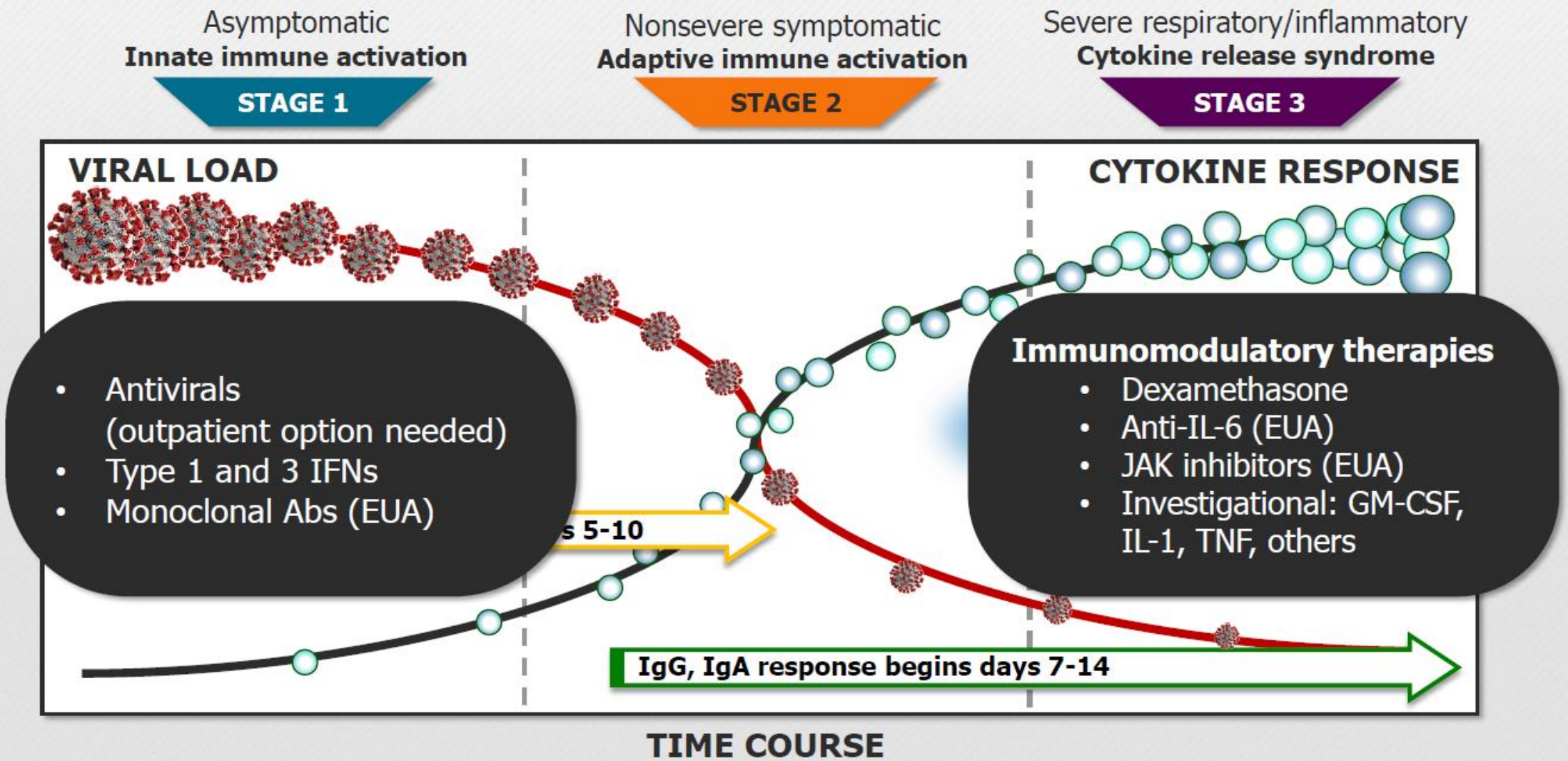
LOWER AIRWAYS
↑ Type 1/type 3 interferons
↑ Lung tissue damage

SYSTEMIC INFLAMMATION
↑ Delayed/prolonged interferons
↑ Severe COVID-19
↑ Distal tissue damage

Zanoni I. *Curr Opin Virol.* 2021;50:119-127.

Image created with BioRender.com

Course of COVID-19 Infection – A Paradigm for Therapy

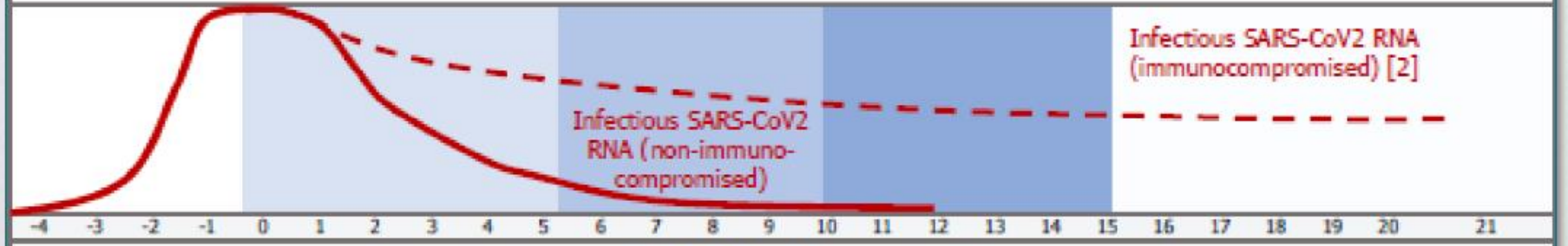


EUA = FDA emergency use authorization; GM-CSF = granulocyte colony-stimulating factor; IFN = interferon; IL = interleukin; JAK = Janus kinase; TNF = tumor necrosis

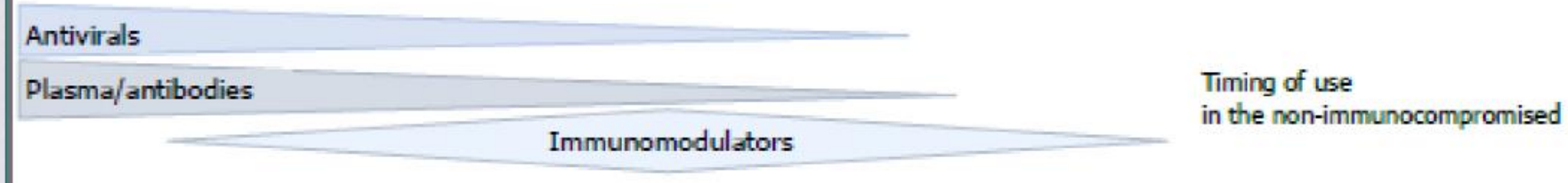
Severe COVID-19 Clinical Course

Figure. Schematic of Clinical Course of Severe COVID-19

Representation of SARS-CoV-2 RNA levels correlating with infectious replicating virus (shedding of non-infectious viral RNA may persist for a much longer time), common symptoms, and possible timing of therapeutics for the greatest benefit. Duration of symptoms and viral shedding may be prolonged in some patients who are substantially immunocompromised. Below, the red lines illustrate the typical trends for SARS-CoV2 RNA levels in individuals who are and are not immunocompromised. [1]



Symptoms	Fever, cough, myalgia, dyspnea, etc.	Hypoxia, respiratory failure, fever, hypotension	ARDS	Recovery



Notes:

1. Viral variants may have longer period of infectious virus, i.e., >10 days in normal hosts
2. In the immunocompromised, variable duration, especially in severely immunocompromised (longer)

Johns Hopkins Medicine. Accessed September 8, 2021. https://hopkinsinfectiousdiseases.jhmi.edu/wp-content/uploads/2021/06/6-9-21_Update_JHMI-Recommendations-for-COVID-19-Therapeutics.pdf

4 Out of 400 Drugs Studied for COVID-19 → Benefit (Endorsed by Professional Societies)

- Dexamethasone
- Remdesivir
- Tocilizumab
- Baricitinib

CORONA Registry

STORM Grades

Click treatment name to view RCT and Publication Data

Search	Grade	# Positive Trials/ Total Completed (Randomized Control Trials)	# Patients in Completed Trials (Randomized Control Trials)	# Trials Underway (Randomized Control Trials)	# Total Uses Recorded (Published Literature)
Baricitinib	A	1/1	1,033	10	181
Remdesivir	A	2/4	7,345	38	4,868
Dexamethasone	A	2/2	6,724	34	5,593
Tocilizumab	A	4/10	6,586	56	11,707
Interferon beta 1a (inhaled)	B	1/1	101	7	
Recombinant super-compound interfero..	B	1/1	94		
Novaferon	B	1/1	89	2	52
Interferon beta 1b	B	1/1	80		11,983
Interferon kappa + TFF2	B	1/1	80	1	40
Interferon alpha 2b + interferon gamma	B	1/1	63		
Lopinavir/ritonavir + ribavirin + interfer..	B	1/1	86		
Interferon beta 1a (SQ)	B	1/2	4,192	16	11,983
Peginterferon Lambda-1	B	1/2	150		
Colchicine	B	3/3	243	29	1,493

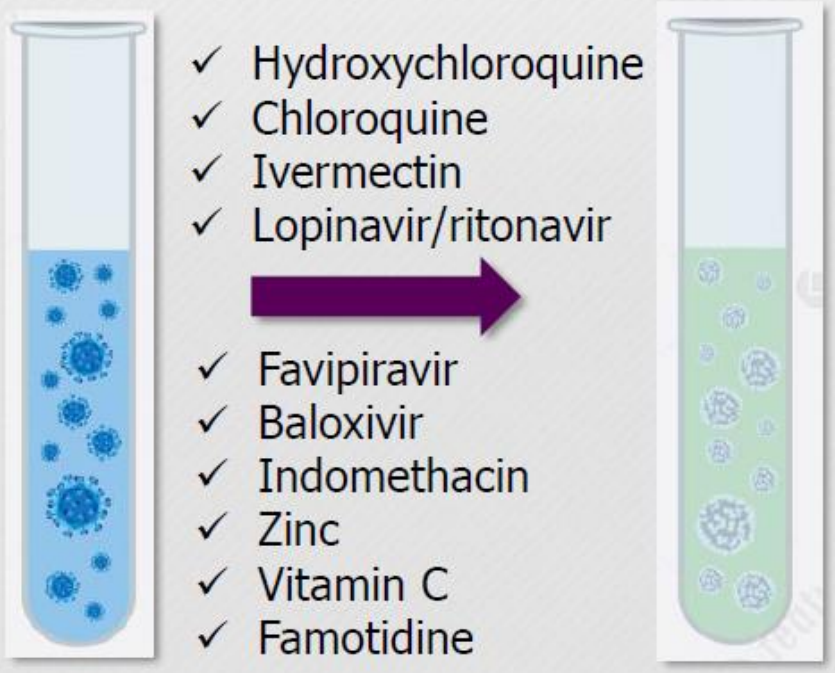
Note: Order of drugs with same grade does not indicate priority.

See Grading Methods

Castleman Disease Collaborative Network (CDCN). Accessed September 8, 2021. https://cdcn.org/corona-data-viewer/

Repurposed Drugs
So Much "Promise"… So Little to Show

SAR-CoV-2



- ✓ Hydroxychloroquine
- ✓ Chloroquine
- ✓ Ivermectin
- ✓ Lopinavir/ritonavir

- ✓ Favipiravir
- ✓ Baloxivir
- ✓ Indomethacin
- ✓ Zinc
- ✓ Vitamin C
- ✓ Famotidine

≠

Viral Tissue Culture Studies, *in vitro*

Human Studies, *in vivo*

Treatment of COVID-19 (as of October 2, 2021)

- Ambulatory: Monoclonal antibodies
- Hospitalized
  - Not on oxygen: Monoclonal antibodies (if not hospitalized for COVID-19)
  - Oxygen needed: Remdesivir + dexamethasone
  - High flow O_2 or NIV: Remdesivir + dexamethasone
    - Rapid worsening: Tocilizumab or baricitinib
  - IMV or ECMO: Dexamethasone
    - If first 24 hours in ICU: Tocilizumab

NIV = noninvasive ventilation.

Infectious Diseases Society of America. Accessed September 8, 2021. https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/; NIH. Updated August 25, 2021. Accessed October 2, 2021. https://www.covid19treatmentguidelines.nih.gov/

NIH Guidelines for Therapeutic Management of Hospitalized Patients

Hospitalized but Does Not Require Supplemental Oxygen	The Panel **recommends against** the use of **dexamethasone (AIIa)** or other **corticosteroids (AIII)**.[a] There is insufficient evidence to recommend either for or against the routine use of remdesivir. For patients who are at high risk of disease progression, the use of remdesivir may be appropriate.
Hospitalized and Requires Supplemental Oxygen	Use one of the following options: • **Remdesivir**[b,c] (e.g., for patients who require minimal supplemental oxygen) **(BIIa)** • **Dexamethasone**[d] **plus remdesivir**[b,c] (e.g., for patients who require increasing amounts of supplemental oxygen) **(BIII)** • **Dexamethasone**[d] (when combination therapy with remdesivir cannot be used or is not available) **(BI)**
Hospitalized and Requires Oxygen Delivery Through a High-Flow Device or Noninvasive Ventilation	Use one of the following options: • **Dexamethasone**[d] **(AI)** • **Dexamethasone**[d] **plus remdesivir**[b,c] **(BIII)** For patients who were recently hospitalized[e] with rapidly increasing oxygen needs and systemic inflammation: • Add either **baricitinib**[f,g] **(BIIa)** or **tocilizumab**[f,h] **(BIIa)** to one of the two options above
Hospitalized and Requires IMV or ECMO	For most patients: • **Dexamethasone**[d,i] **(AI)** For patients who are within 24 hours of admission to the ICU: • **Dexamethasone**[d,i] **plus tocilizumab**[f,h] **(BIIa)**

Last updated August 25, 2021.

Ritonavir-Boosted Nirmatrelvir (Paxlovid)

In the EPIC-HR trial, ritonavir-boosted nirmatrelvir (Paxlovid) reduced the risk of hospitalization or death by 88% compared to placebo in nonhospitalized adults with laboratory-confirmed SARS-CoV-2 infection.[8] This efficacy is comparable to the efficacies reported for sotrovimab (i.e., 85% relative reduction),[9] and remdesivir (i.e., 87% relative reduction)[10] and greater than the efficacy reported for molnupiravir (i.e., 30% relative reduction).[11]

Ritonavir-boosted nirmatrelvir (Paxlovid) is expected to be active against the Omicron VOC, although in vitro and in vivo data are currently limited.[12] Because of the potential for significant drug-drug interactions with concomitant medications, this regimen may not be a safe choice for all patients (see the Panel's statement on these drug-drug interactions for details).

PATIENT DISPOSITION	PANEL'S RECOMMENDATIONS
Not Requiring Hospitalization or Supplemental Oxygen, As Determined by a Health Care Provider During an ED, In-Person, or Telehealth Visit	Provide symptomatic management for patients who are not at high risk of disease progression. For patients who are at high risk of progressing to severe COVID-19 (treatments are listed in order of preference, based on efficacy and convenience of use): • **Ritonavir-boosted nirmatrelvir (Paxlovid)**; *or* • **Sotrovimab**; *or* • **Remdesivir**; *or* • **Molnupiravir** The Panel **recommends against** the use of **dexamethasone** or **other systemic glucocorticoids** in the absence of another indication **(AIII)**.[a]
Discharged From Hospital Inpatient Setting in Stable Condition and Does Not Require Supplemental Oxygen	The Panel **recommends against** continuing the use of **remdesivir (AIIa)**, **dexamethasone (AIIa)**, or **baricitinib (AIIa)** after hospital discharge.
Discharged From Hospital Inpatient Setting and Requires Supplemental Oxygen *For those who are stable enough for discharge but who still require oxygen*[b]	There is insufficient evidence to recommend either for or against the continued use of remdesivir, dexamethasone, and/or baricitinib. Review the text below when considering the use of any of these agents after hospital discharge.
Discharged From ED Despite New or Increasing Need for Supplemental Oxygen *When hospital resources are limited, inpatient admission is not possible, and close follow-up is ensured*[c]	The Panel recommends using **dexamethasone** 6 mg PO once daily for the duration of supplemental oxygen (dexamethasone use **should not** exceed 10 days) with careful monitoring for AEs **(BIII)**. There is insufficient evidence to recommend either for or against the use of remdesivir. When considering the use of remdesivir, review the text below for more information. The Panel **recommends against** the use of **baricitinib** in this setting, except in a clinical trial **(AIII)**.

Figure 2. Therapeutic Management of Hospitalized Adults With COVID-19 Based on Disease Severity

DISEASE SEVERITY	PANEL'S RECOMMENDATIONS
Hospitalized but Does Not Require Supplemental Oxygen	The Panel **recommends against** the use of **dexamethasone (AIIa)** or **other corticosteroids (AIII)**.[a] There is insufficient evidence to recommend either for or against the routine use of remdesivir. For patients at high risk of disease progression, remdesivir may be appropriate.
Hospitalized and Requires Supplemental Oxygen	Use 1 of the following options: • **Remdesivir**[b,c] (e.g., for patients who require minimal supplemental oxygen) **(BIIa)** • **Dexamethasone plus remdesivir**[b,c] **(BIIb)** • **Dexamethasone (BI)** For patients on dexamethasone with rapidly increasing oxygen needs and systemic inflammation, add a second immunomodulatory drug[d] (e.g., baricitinib[e] or tocilizumab[e]) **(CIIa)**.
Hospitalized and Requires Oxygen Through a High-Flow Device or NIV	Use 1 of the following options: • **Dexamethasone (AI)** • **Dexamethasone plus remdesivir**[b] **(BIII)** For patients with rapidly increasing oxygen needs and systemic inflammation, add either **baricitinib**[e] **(BIIa)** or **IV tocilizumab**[e] **(BIIa)** to 1 of the 2 options above.[d,f]
Hospitalized and Requires MV or ECMO	• **Dexamethasone (AI)**[g] For patients who are within 24 hours of admission to the ICU: • **Dexamethasone plus IV tocilizumab (BIIa)** If IV tocilizumab is not available or not feasible to use, IV **sarilumab** can be used **(BIIa)**.