

COVID-19 Management Overview

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Outline of Presentation

- Introduction
- The Outbreak and time-lines
- Epidemiology
- What we now know about the virus, pathogenesis and immune responses
- Spectrum of Clinical Presentation
- Patient triage and case definition
- Severity of illness
- Admission Criteria
- Approach to Management
 - Oxygen therapy
 - Dexamethasone
 - Anticoagulation
 - Proning
- Anti-SARS-CoV-2 Treatments
- Discharge Criteria
- Therapeutics – What works
- Prevention – What works
- Conclusion

Introduction

- In December of 2019, several cases of pneumonia of unknown aetiology were reported in Wuhan, Hubei province, China
- Most patients worked at or lived around the local Huanan seafood wholesale market, where live animals were also on sale
- In the early stages of this pneumonia, severe acute respiratory infection symptoms occurred, with some patients rapidly developing acute respiratory distress syndrome (ARDS), acute respiratory failure, and other serious complications
- The following respiratory viruses were examined with real-time RT-PCR and found not to be the cause of the severe pneumonia:
 - Influenza A virus (H1N1, H3N2, H7N9)
 - Influenza B virus
 - Respiratory syncytial virus
 - Parainfluenza virus
 - Adenovirus
 - SARS coronavirus (SARS-CoV)
 - MERS coronavirus (MERS-CoV)
- A new viral pathogen was suspected and finally was identified as SARS-CoV 2

Timeline of the key events of the COVID-19 outbreak.

Nature Reviews Microbiology 19, 141–154(2021)



**Total Cases
=171658**

**Male = 104178
Female = 67480**

**Deaths
=3223**

1.1 Epidemiology

Since 13 March 2020 when the first case was confirmed in Kenya, a total of **171658** confirmed cases and **3223** deaths giving a case fatality rate of **1.9%** have been line listed. Of these, 165684 cases (97%) were local transmissions and 5973 (3%) are imported cases. Figure 1 below shows trends of cases.

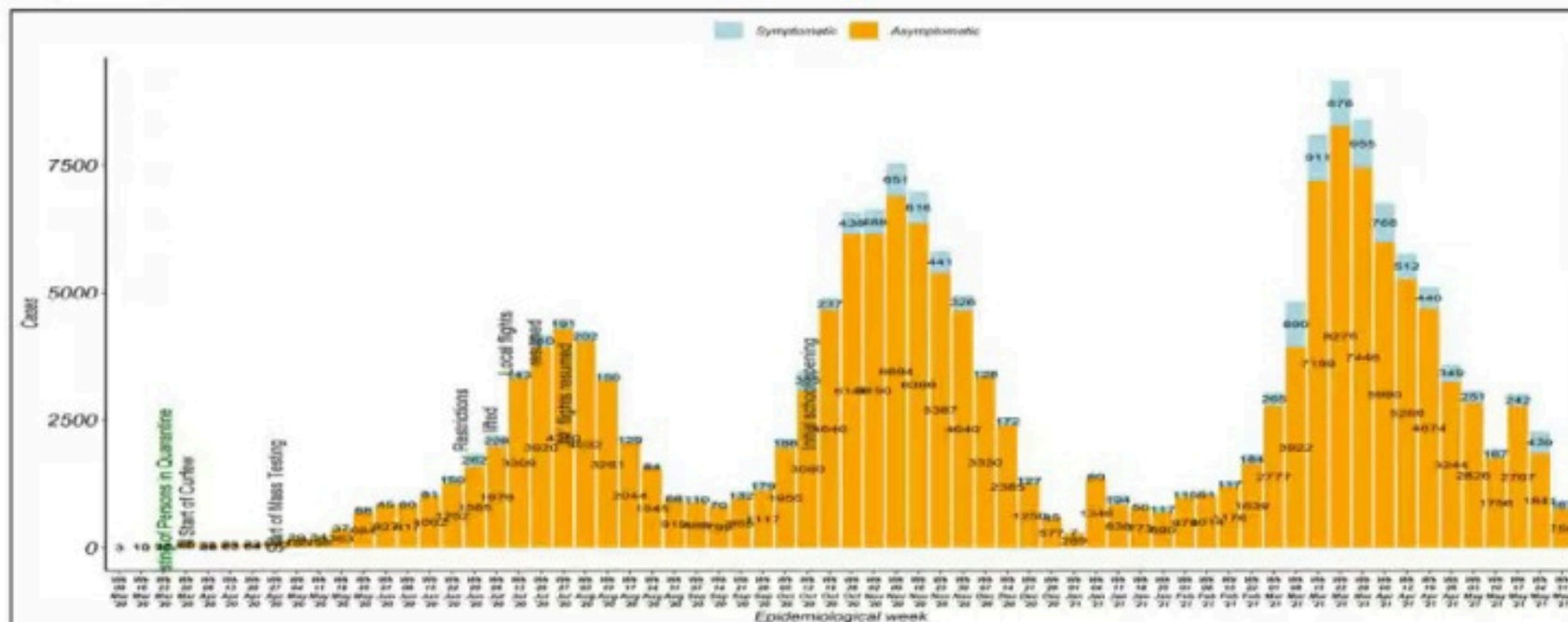


Figure 1: Trends of COVID-19 Outbreak Kenya

Pathogenic coronaviruses in recent history

Front. Immunol. 11:570927.

Alphacoronaviruses and related

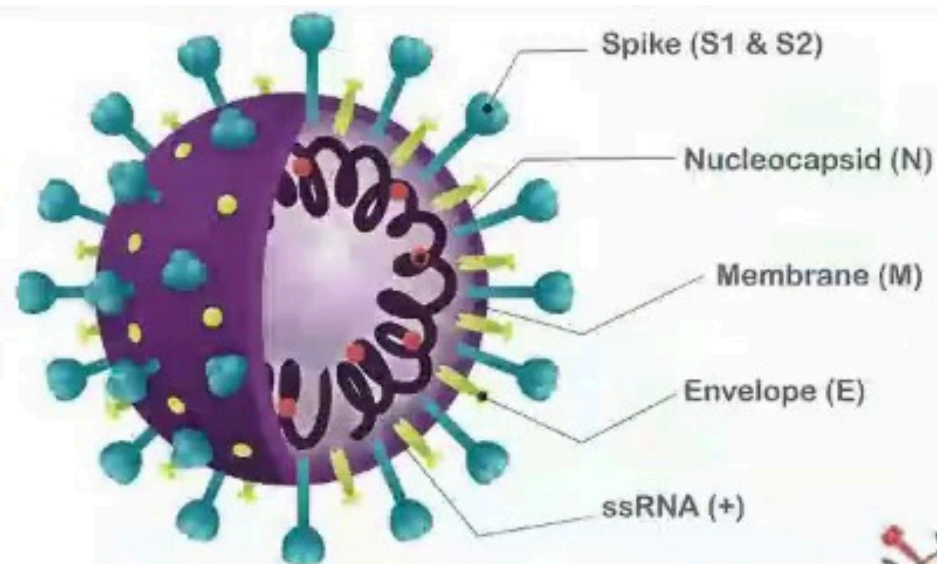
Human coronavirus 229E	HCoV-229E (1, 2)	Mid-1960's—5–30% of upper respiratory tract infections
Human coronavirus NL63	HCoV-NL63 (3)	Early 2000's—community-acquired pneumonia of the lower respiratory tract

Betacoronaviruses

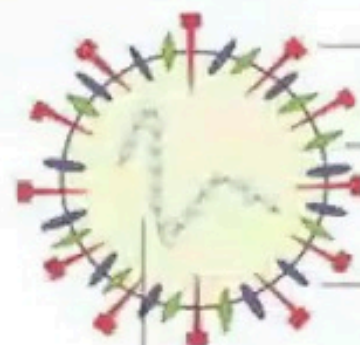
Human coronavirus OC43	HCoV-OC43 (1, 2)	Mid-1960's—5–30% of upper respiratory tract infections
Human coronavirus HKU1	HCoV-HKU1 (3)	Early 2000's—community-acquired pneumonia of the lower respiratory tract
Severe acute respiratory syndrome coronavirus	SARS-CoV (4)	2002–2003, China
Middle East respiratory syndrome coronavirus	MERS-CoV (4)	2013, Saudi Arabia
COVID-19	SARS-CoV-2	2019, Wuhan, China



	<i>Middle East respiratory syndrome-related coronavirus</i>	<i>Severe acute respiratory syndrome-related coronavirus</i>	
Virus species			
Individuum	MERS-CoV	SARS-CoV	SARS-CoV-2
First reported	Saudi-Arabia (2012)	China (2002)	China (2019)
Current status	Active	No reports since 2004	Active
Infections	2521+	8098	3,500,000+
Fatality rate	34%	10%	~1%
Preventive/curative treatment	None	None	None



SARS-CoV-2



S protein: Bind to the host receptor ACE2
 S1: vital function to regulates the virus-host
 S2: mediate membrane fusion and viral entry

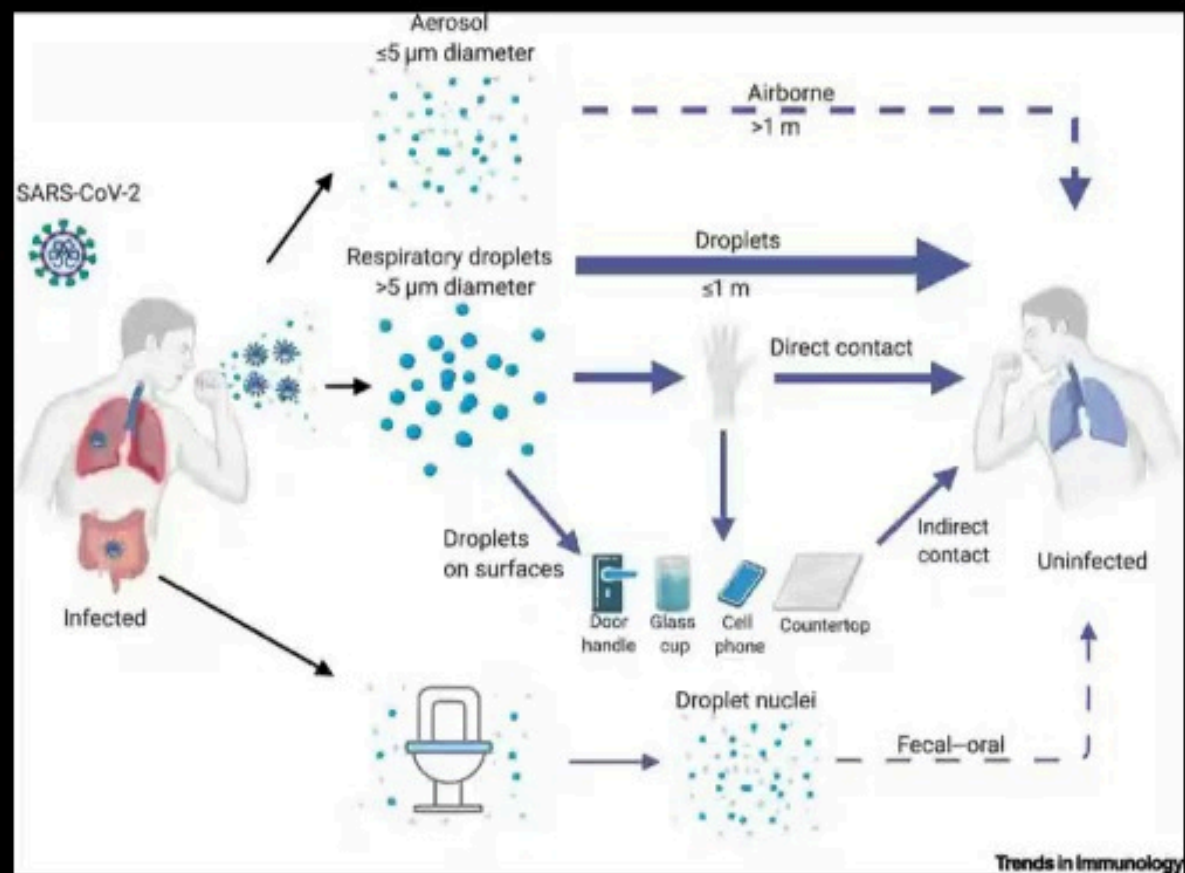
M protein: involved in
 viral integration

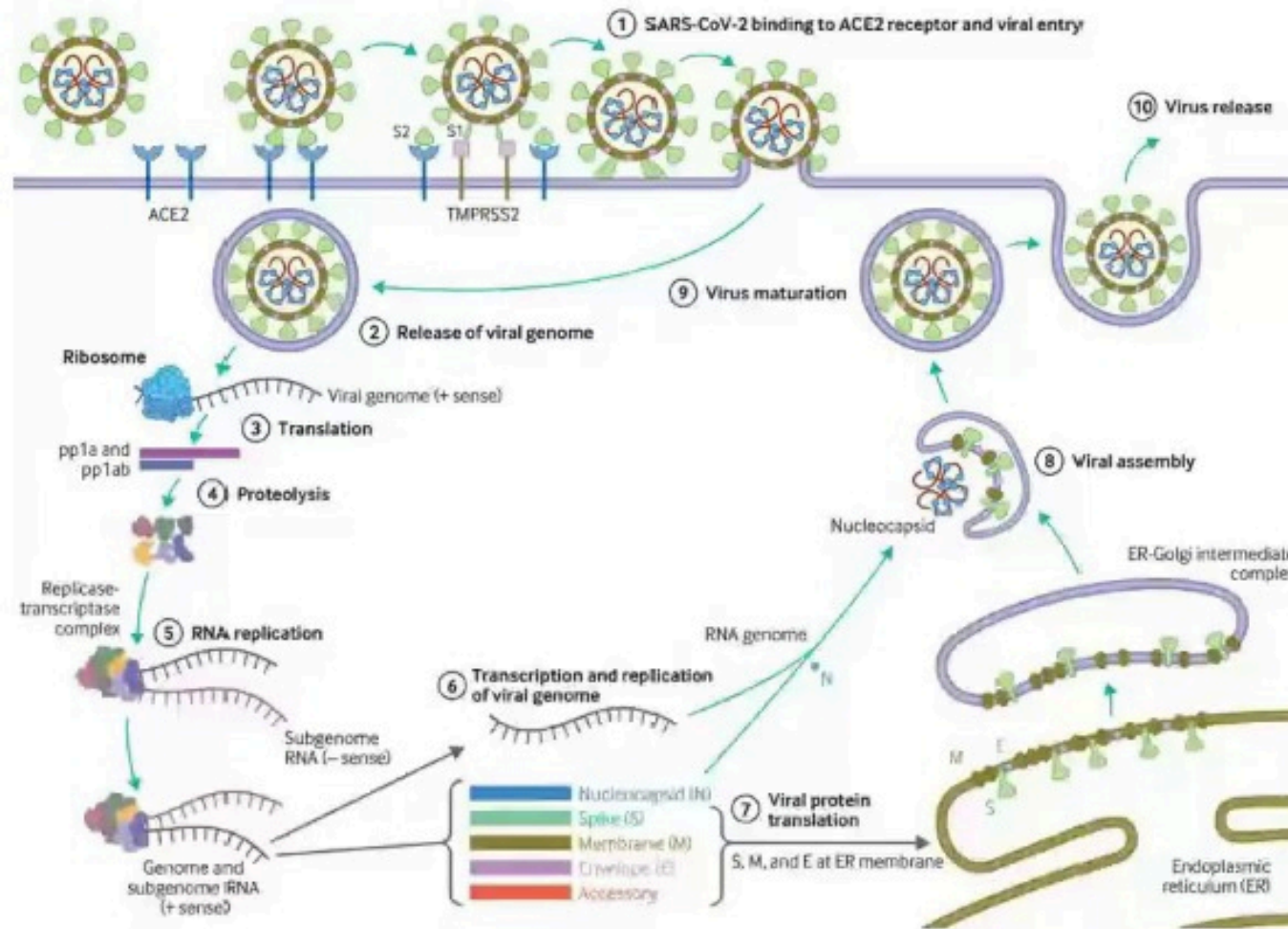
E protein: facilitates assembly,
 envelope formation, and
 budding

N protein: critical role
 in encapsidated genome
 packaging into virions
 and effective in viral
 replication



Figure 2





STEPS IN SARS-COV 2 REPLICATION CYCLE

1. Receptor binding and viral entry
2. Release of viral genome
3. Translation
4. Proteolysis
5. RNA replication
6. Transcription and replication of viral genome
7. Viral protein translation
8. Viral assembly
9. Virus maturation
10. Virus release

Distribution of ACE2 in Human Tissues by Immunohistochemistry (IHC)

LifeSpan BioSciences, Inc.

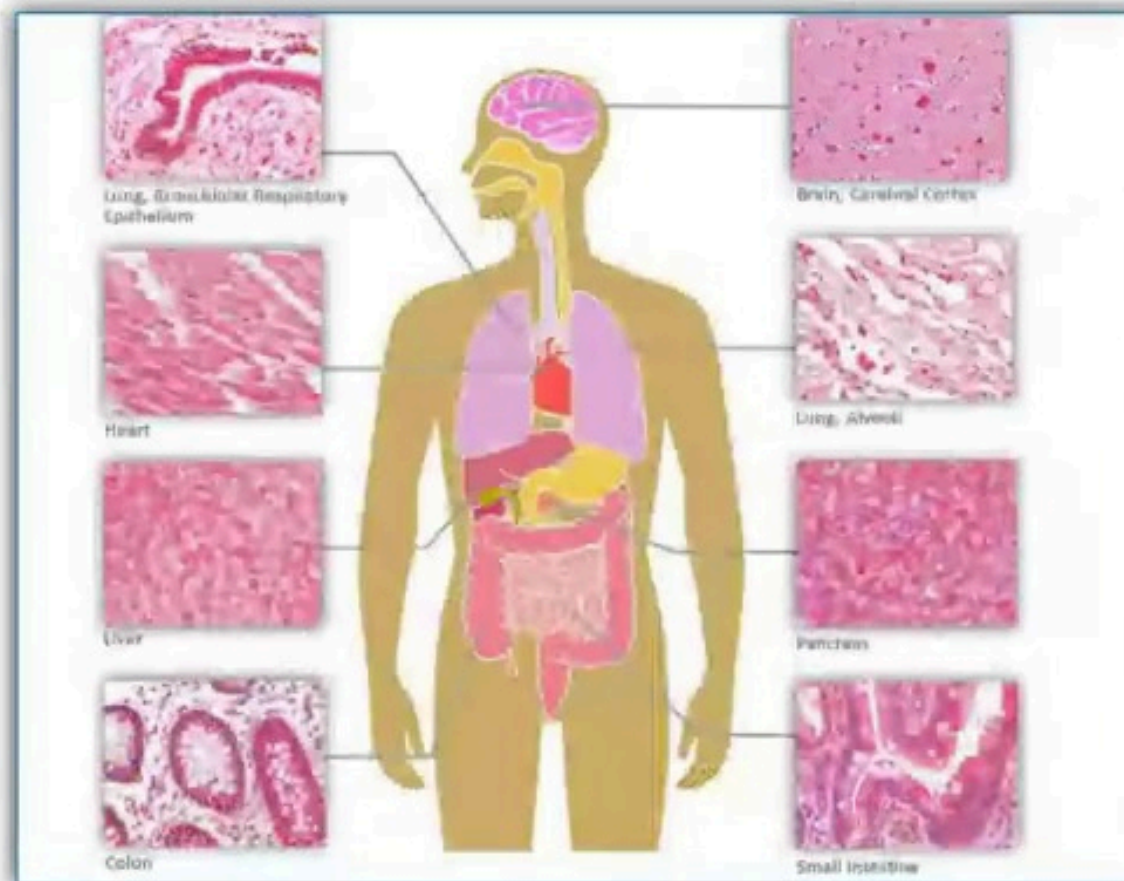
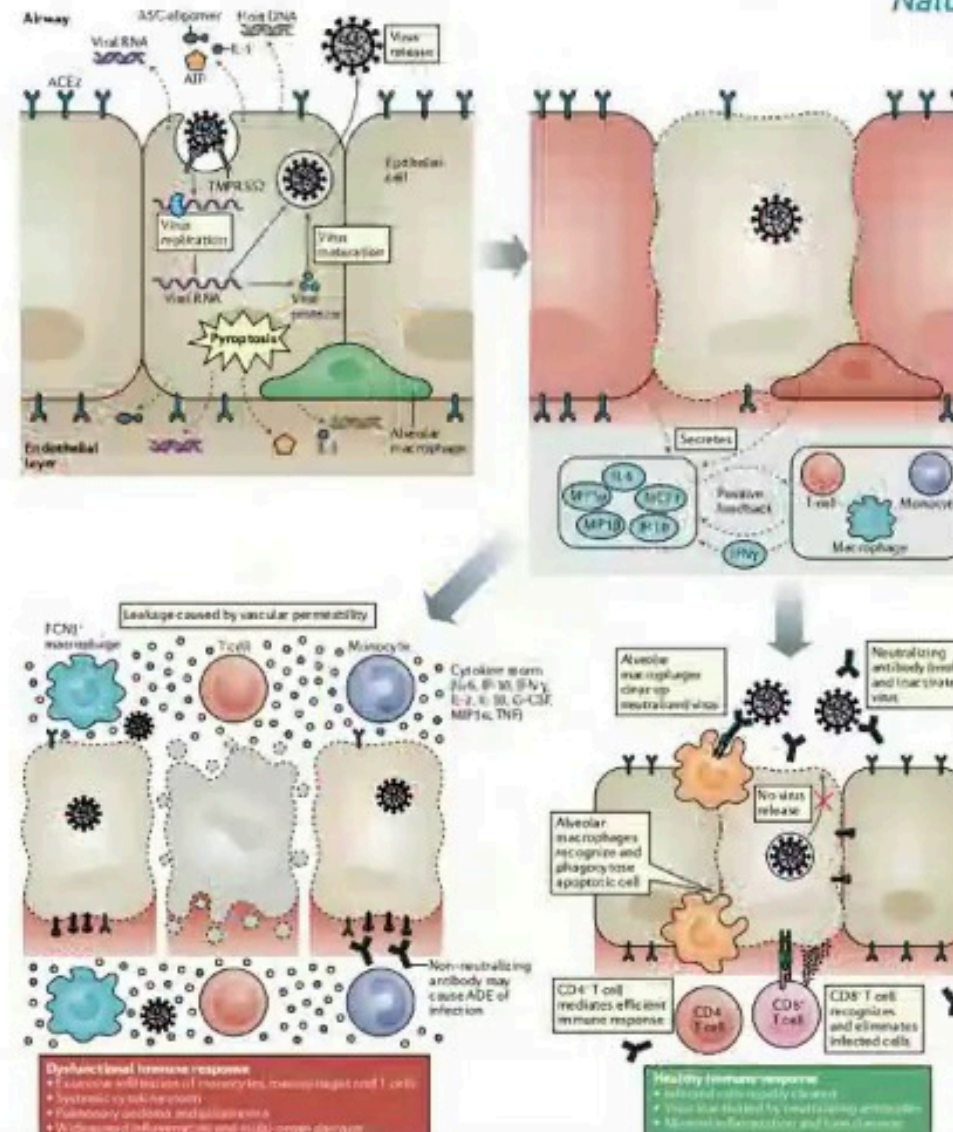


Figure 2 by Mark Burner

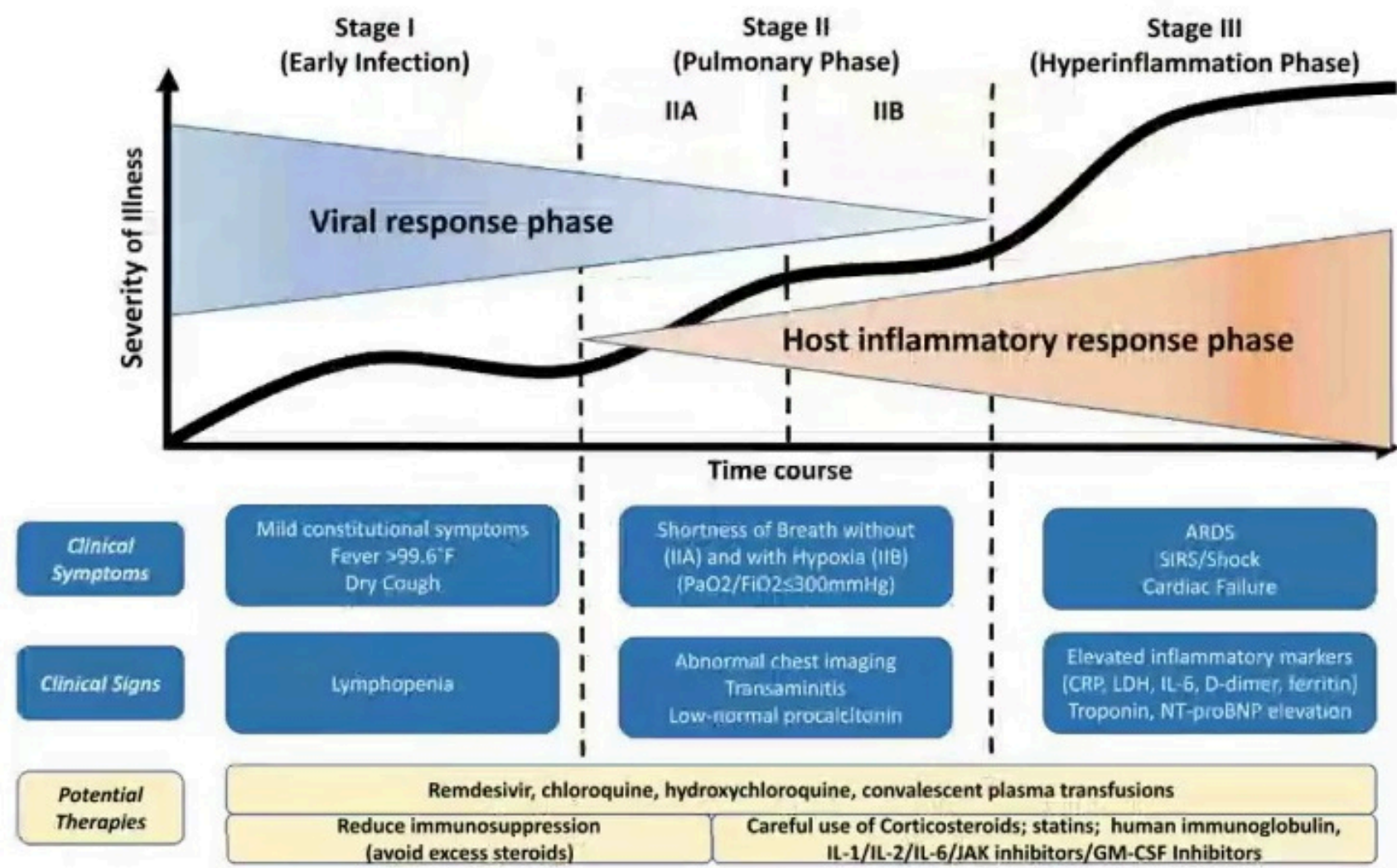
Chronology of events during SARS-CoV-2 infection

Nature Reviews Immunology 20, 363–374(2020)



Classification of COVID-19 disease states and potential therapeutic targets

The Journal of Heart and Lung Transplantation, Vol 39, No 5, May 2020



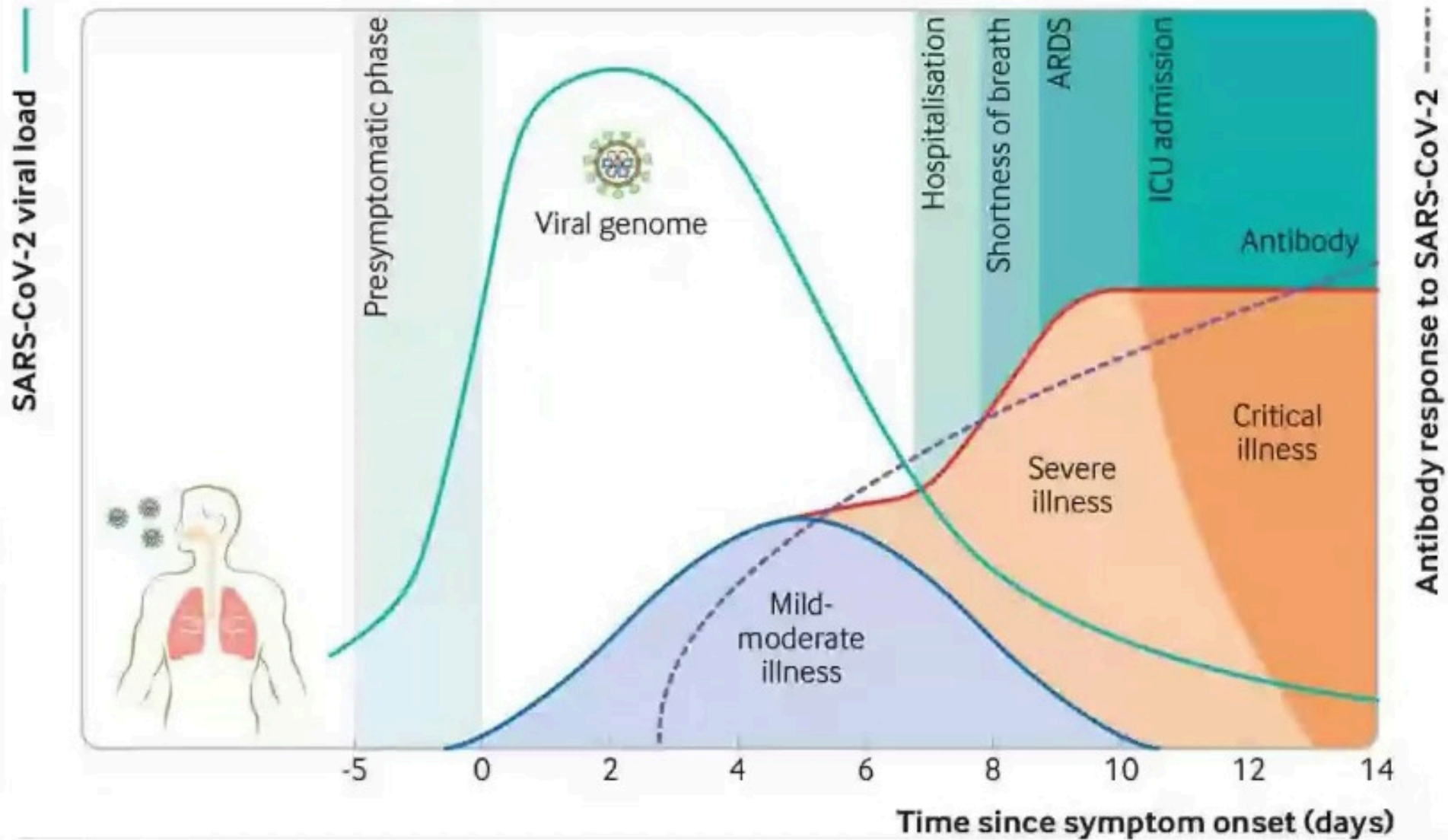


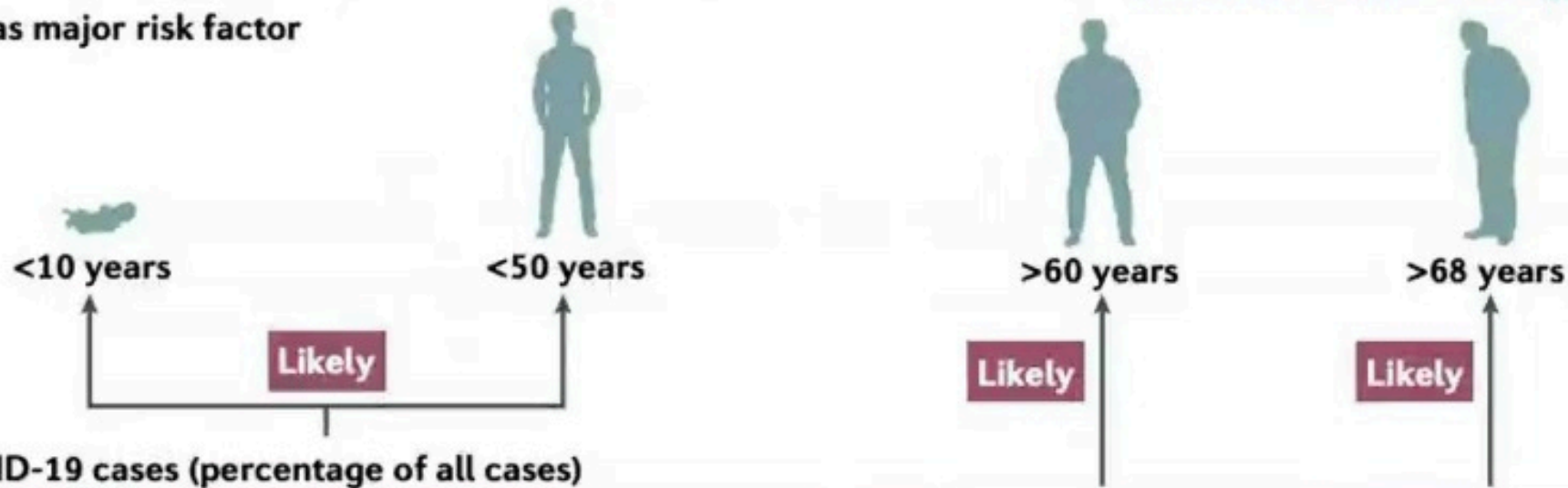
Table 1 Clinical spectrum of COVID-19 disease^{1 36–41}

Severity of disease	Presentation
Asymptomatic	▶ No clinical symptoms ▶ Positive nasal swab test ▶ Normal chest X-ray
Mild illness	▶ Fever, sore throat, dry cough, malaise and body aches or ▶ Nausea, vomiting, abdominal pain, loose stools
Moderate illness	▶ Symptoms of pneumonia (persistent fever and cough) without hypoxemia ▶ Significant lesions on high-resolution CT chest
Severe illness	▶ Pneumonia with hypoxemia ($\text{SpO}_2 < 92\%$)
Critical state	▶ Acute respiratory distress syndrome, along with shock, coagulation defects, encephalopathy, heart failure and acute kidney injury

Clinical features of COVID-19

Nature Reviews Microbiology 19, 141–154(2021)

Age as major risk factor



COVID-19 cases (percentage of all cases)

Asymptomatic...	and mild disease (81%)	Severe (14%)	Critical and deceased (5%)
Incubation period	• Fever, fatigue and dry cough • Ground-glass opacities • Pneumonia	• Dyspnea • Coexisting illness • ICU needed	• ARDS • Acute cardiac injury • Multi-organ failure
~5 days (1–14)	~8 days (7–14)		~16 days (12–20)

Disease onset

Box 1: Risk factors associated with the development of severe disease, admission to intensive care unit, and mortality

Underlying condition

- Older age
- Hypertension
- Cardiovascular disease
- Chronic obstructive pulmonary disease
- Diabetes
- Obesity
- Malignancy

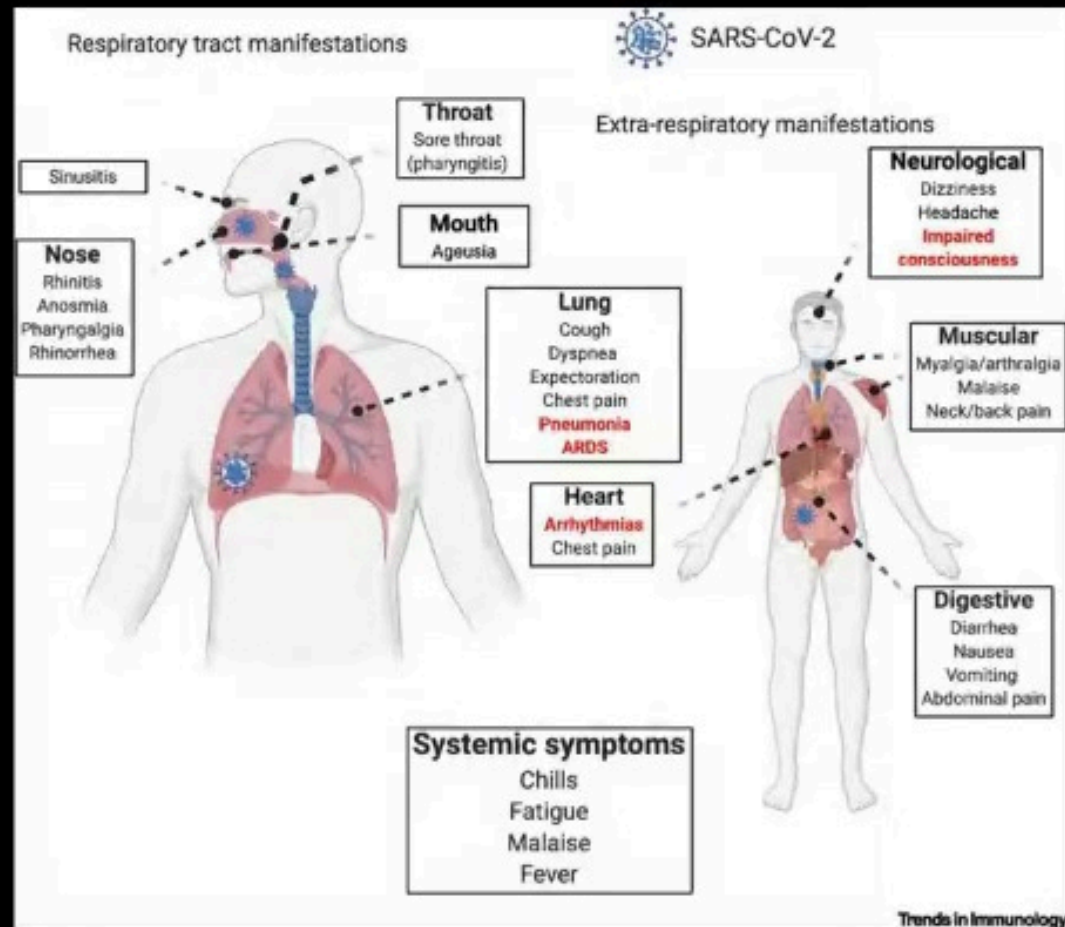
Presentation

- Higher fever ($\geq 39^{\circ}\text{C}$ on admission)
- Dyspnoea on admission
- Higher qSOFA score

Laboratory markers

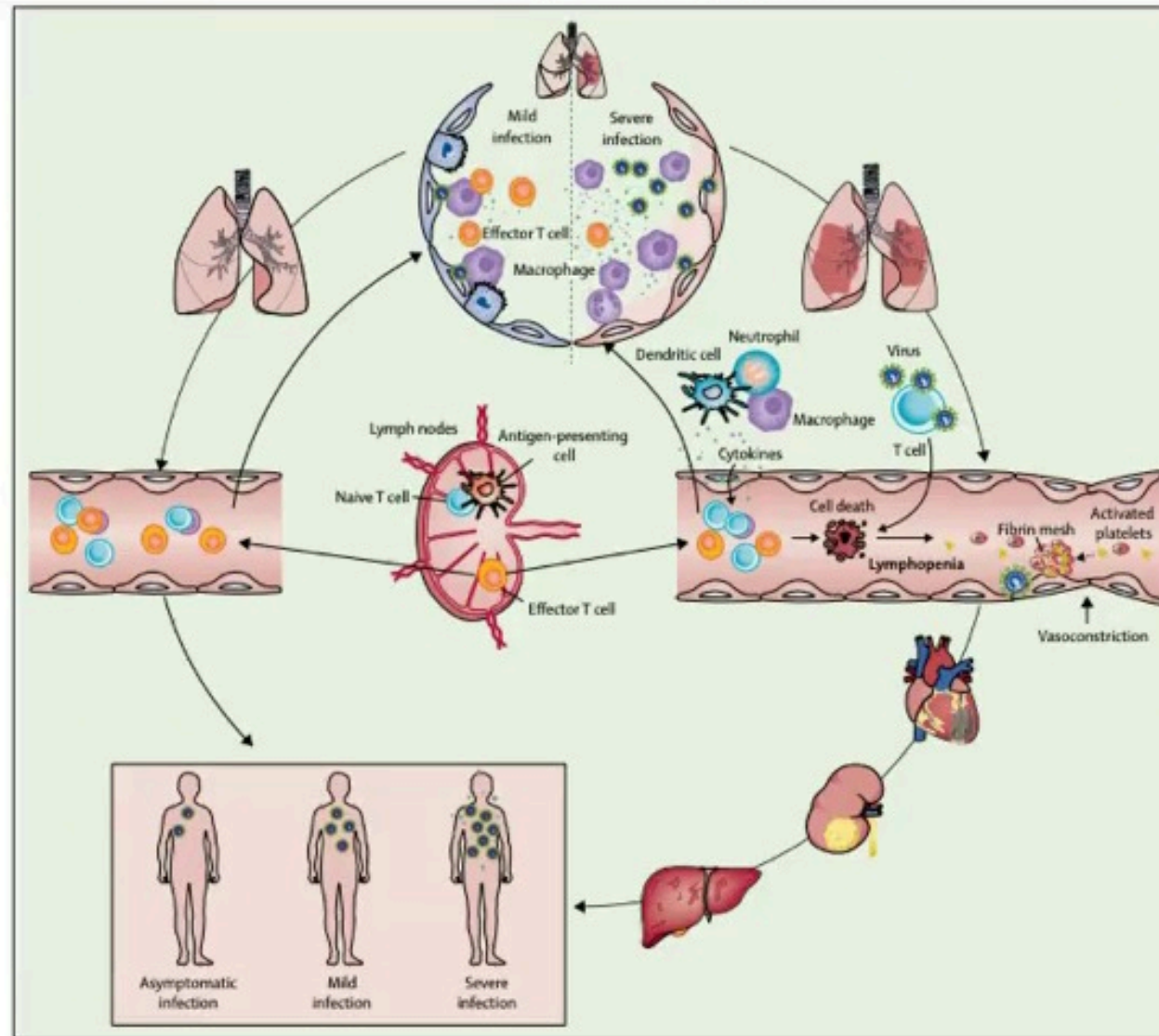
- Neutrophilia/lymphopenia
- Raised lactate and lactate dehydrogenase
- Raised C reactive protein
- Raised ferritin
- Raised IL-6
- Raised ACE2
- D-dimer $> 1 \mu\text{g/mL}$

Figure 3



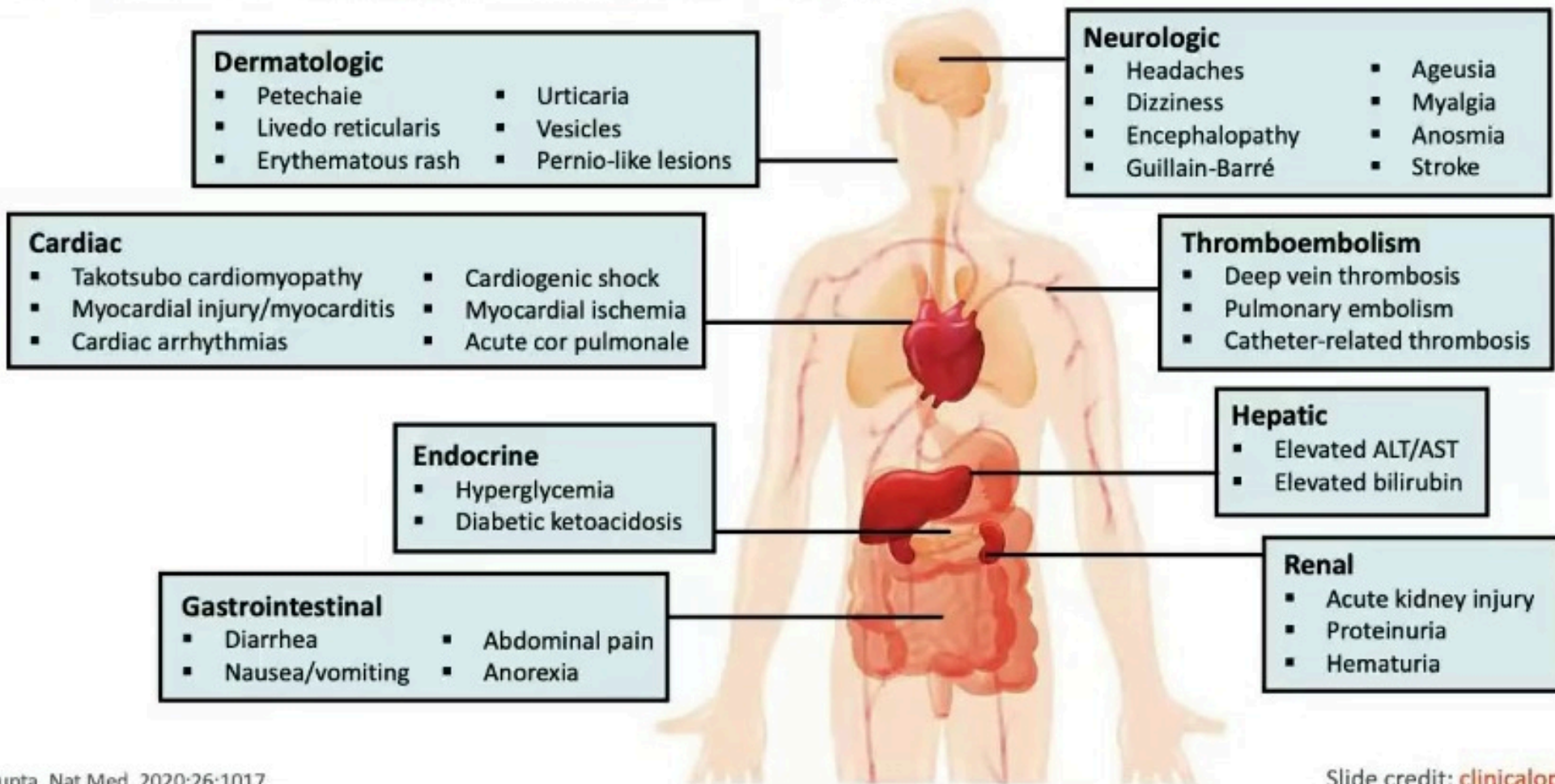
Occurrence and outcome of severe acute respiratory syndrome coronavirus 2 viral sepsis

Lancet 2020; 395: 1517–20



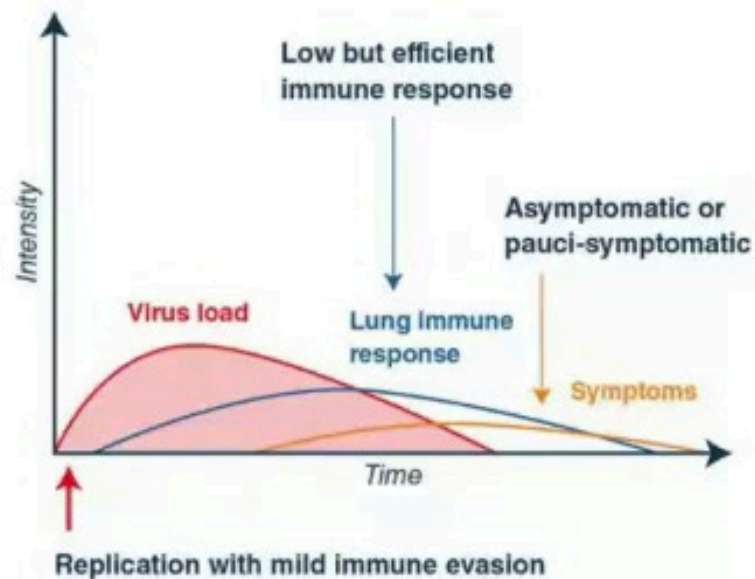
Extrapulmonary Manifestations of COVID-19:

Which of These Return or Last?

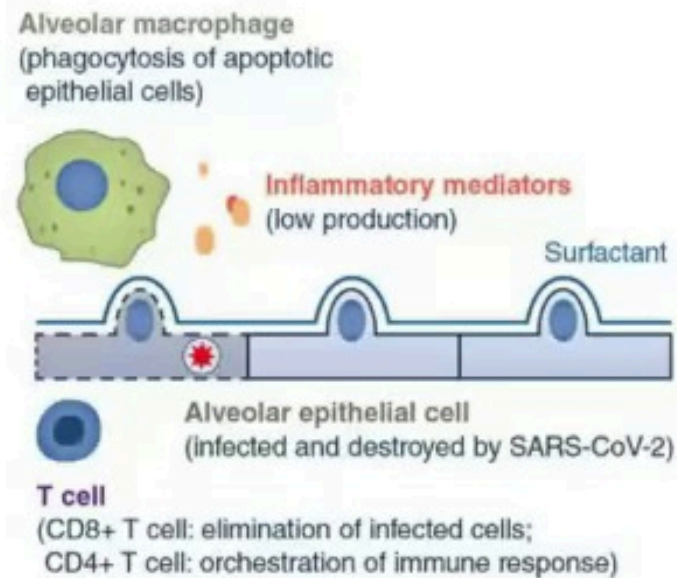


No disease/mild disease

Lung chronology of events



Host/SARS-CoV-2 interaction in lungs



Immunosuppressive therapy

may prevent the worsening of the symptoms

and/or

may facilitate viral replicator

Table 2 Complications seen in patients with COVID-19⁴²

Frequency	Complication
Commonly seen	▶ Acute respiratory distress syndrome ▶ Acute respiratory failure ▶ Sepsis ▶ Disseminated intravascular coagulation ▶ Acute liver and kidney injury ▶ Pulmonary embolism
Rare	▶ Rhabdomyolysis ▶ Multisystem inflammatory syndrome ▶ Aspergillosis ▶ Pancreatitis ▶ Autoimmune haemolytic anaemia ▶ Neurological complications

SARS-COV 2 Diagnosis with Rt-PCR

Clin Chem Lab Med 2020; 58(7): 1070–1076

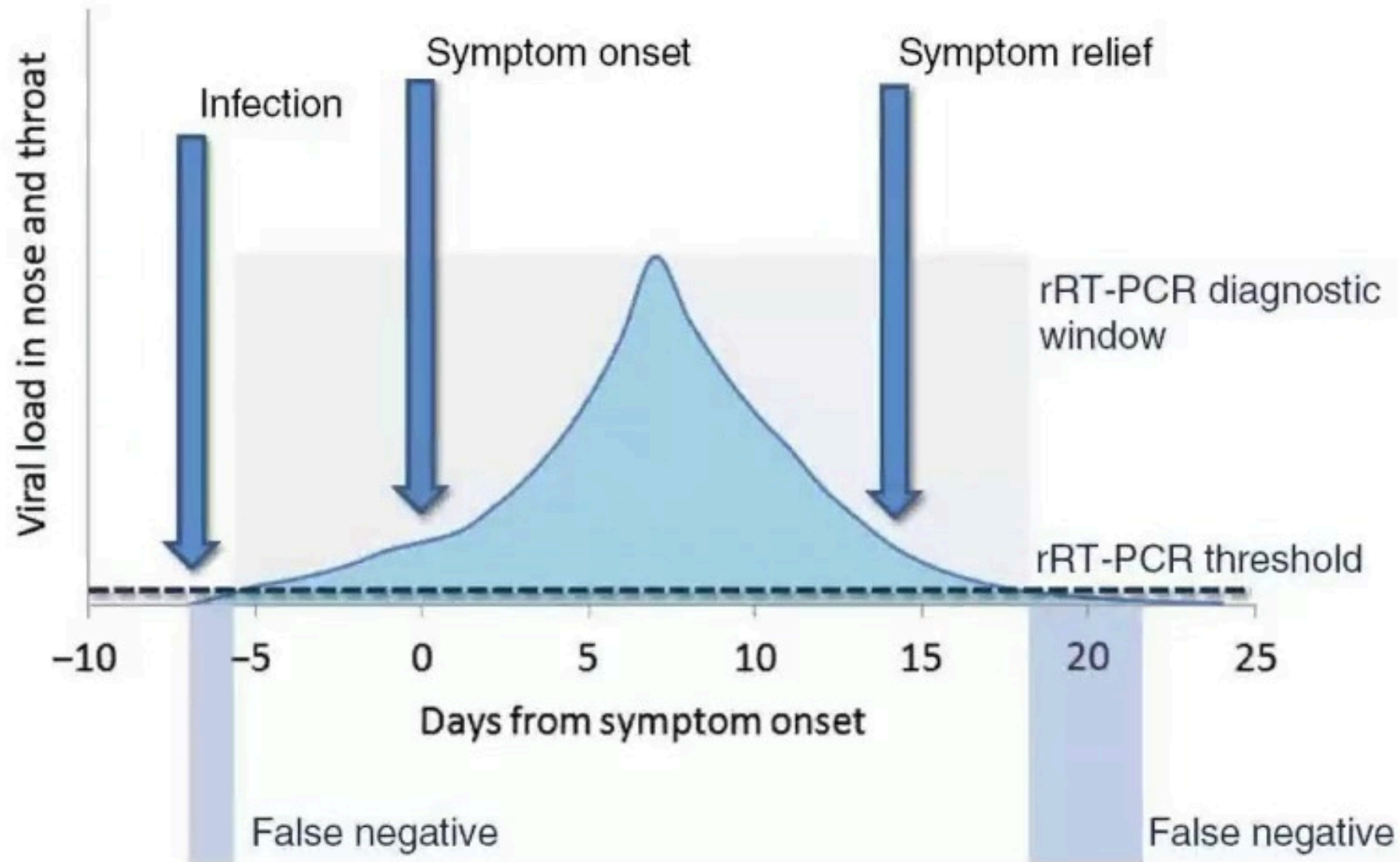
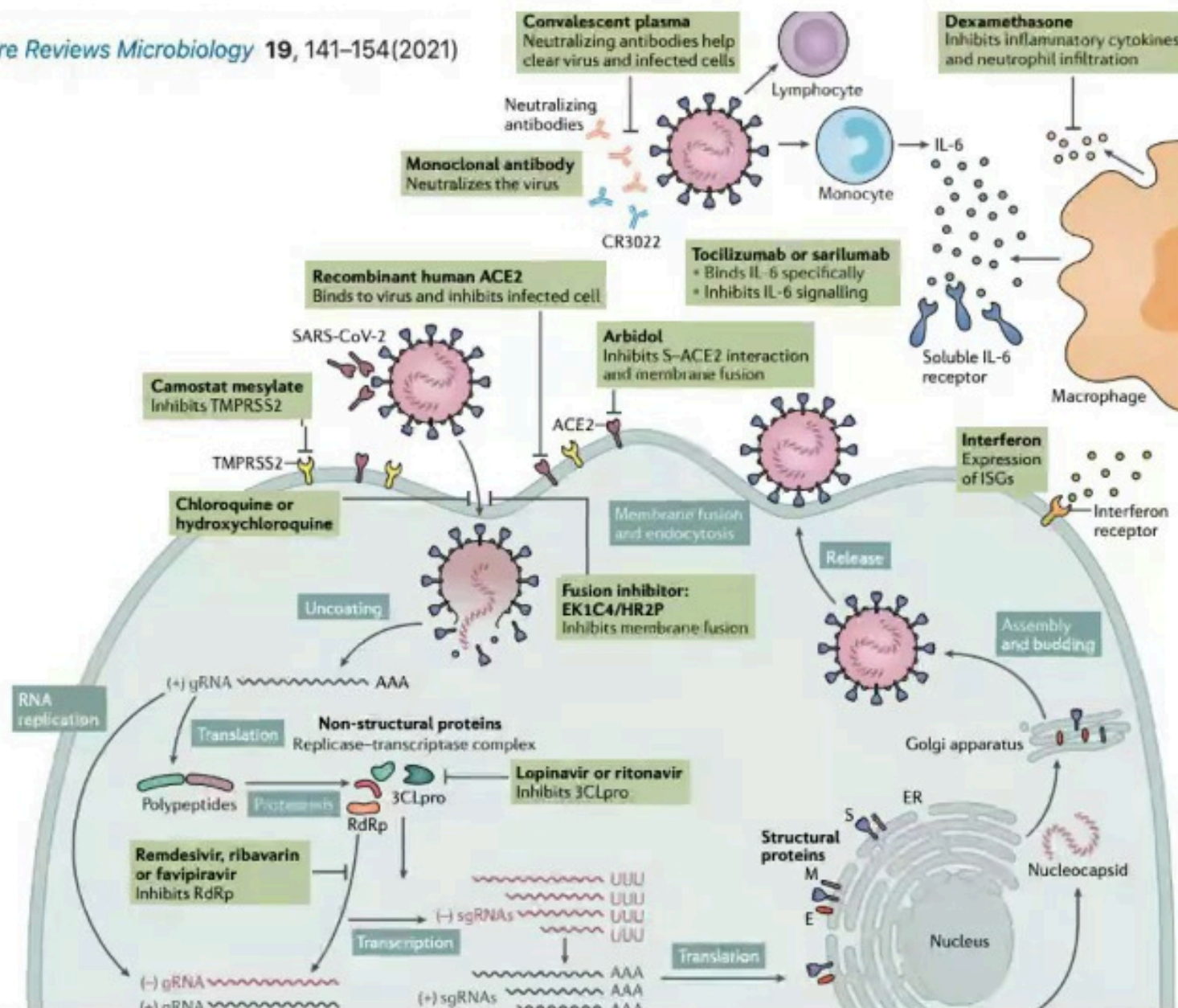
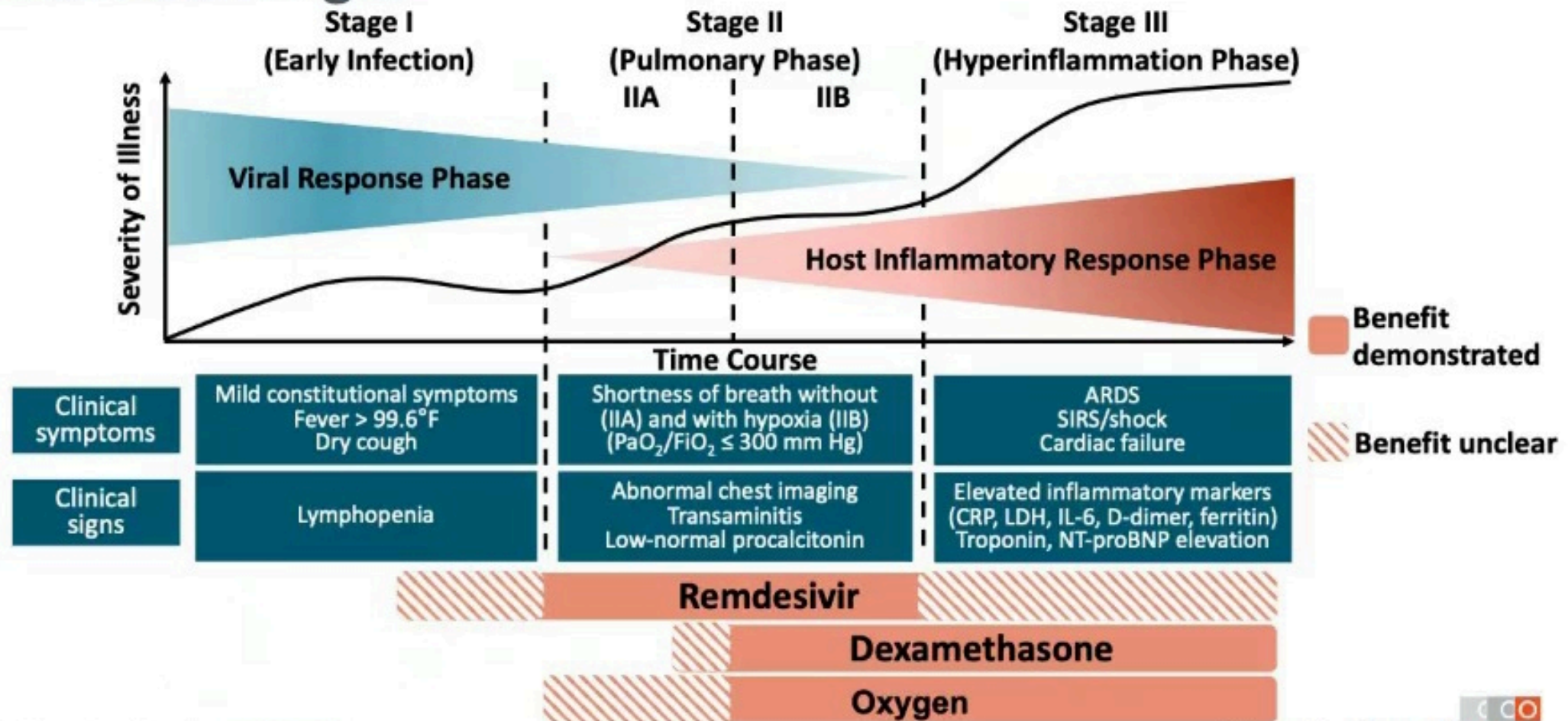


Table 3 Investigations for COVID-19

Investigation	Remarks
Basic blood work	▶ Decreased WBC count as well as lymphopenia ▶ Increased levels of AST and ALT, LDH and CRP ▶ Increased D-dimer ▶ Increased PT/INR
Molecular testing via RT-PCR	▶ Techniques employed are RT-PCR and rRT-PCR which amplify viral genetic material obtained via nasal swab ▶ Poor sensitivity ▶ Repeat testing required for verification of viral clearance
Chest X-ray	▶ No significant findings early in the disease ▶ Bilateral patchy opacities in advanced disease
HRCT chest	▶ Multifocal bilateral 'ground or ground-glass' areas associated with consolidation areas with patchy distribution ▶ 'Reverse halo' sign ▶ Cavitation, calcification and lymphadenopathy ▶ High sensitivity for COVID-19 diagnosis
Serology/antibody testing	▶ Further research still required for a proper/sensitive antibody test

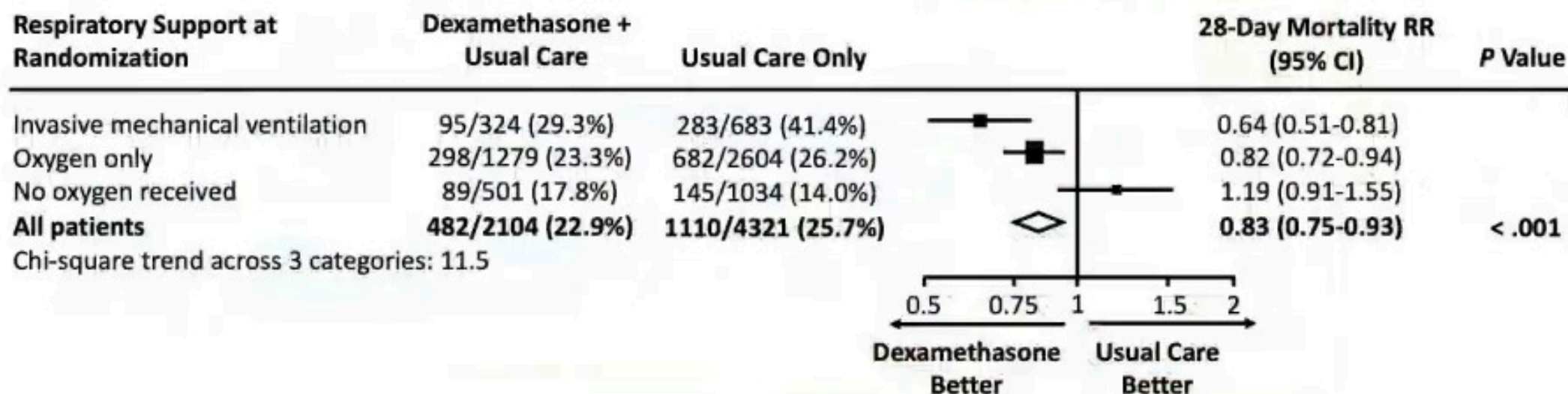


COVID-19 Therapies Predicted to Provide Benefit at Different Stages



RECOVERY Trial: Mortality at Day 28 (Primary Outcome)

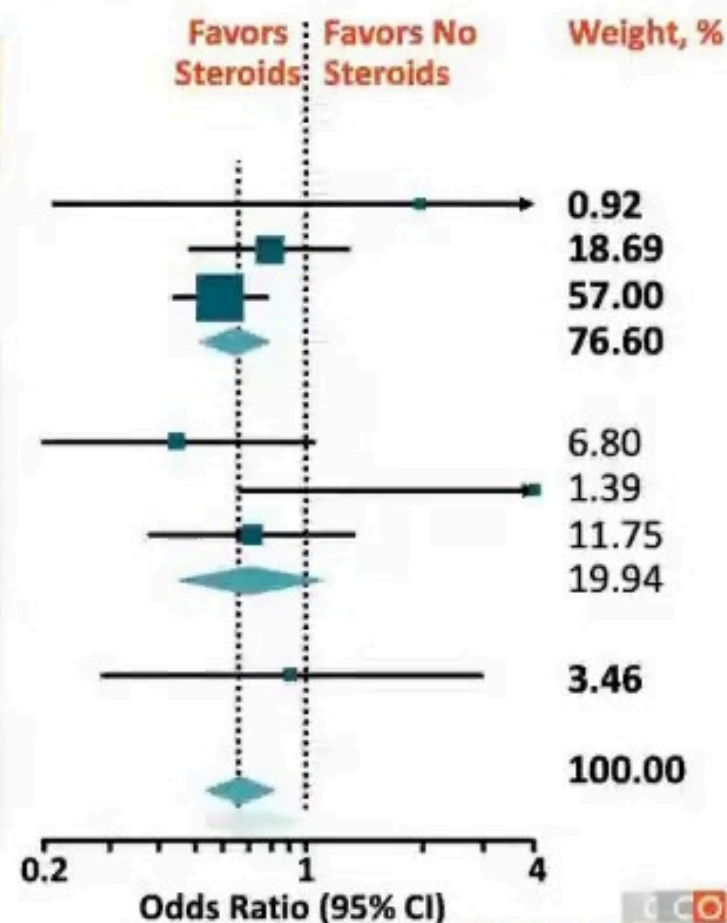
- Addition of dexamethasone to usual care associated with **lower mortality** among subsets receiving invasive mechanical ventilation or oxygen alone but not in those receiving no baseline respiratory support



Systemic Corticosteroids and 28-Day All-Cause Mortality in Critically Ill Patients With COVID-19

Drug/Trial	Initial Dose	Deaths/n		Odds Ratio (95% CI)	P Value
		Steroids	No Steroids		
Dexamethasone					
DEXA-COVID 19	High: 20 mg/day IV	2/7	2/12	2.00 (0.21-18.69)	
CoDEX	High: 20 mg/day IV	69/128	76/128	0.80 (0.49-1.31)	
RECOVERY	Low: 6 mg/day PO or IV	95/324	283/683	0.59 (0.44-0.78)	
Subgroup fixed effect		166/459	361/823	0.64 (0.50-0.82)	< .001
Hydrocortisone					
CAPE COVID	Low: 200 mg/day IV	11/75	20/73		
COVID STEROID	Low: 200 mg/day IV	6/15	2/14		
REMAP-COVID	Low: 50 mg every 6 hrs IV	26/105	29/92		
Subgroup fixed effect		43/195	51/179	0.69 (0.43-1.12)	.13
Methylprednisolone					
Steroids-SARI	High: 40 mg every 12 hrs IV	13/24	13/23	0.91 (0.29-2.87)	.87
Overall*					
Overall (fixed effects)		222/678	425/1025	0.66 (0.53-0.82)	< .001
Overall (random effects)		222/678	425/1025	0.70 (0.48-1.01)	.053

*P = .31 for heterogeneity; I² = 15.6%.



Case Management Guidelines Update

- Patient triage and case definition
- Severity of illness
- Admission Criteria
- Approach to Management
 - Oxygen therapy
 - Dexamethasone
 - Anticoagulation
 - Proning
- Anti-SARS-CoV-2 Treatments
- Discharge Criteria

Patient Triage and Case Definition

Suspected case of SARS-CoV-2 infection

A A person who meets the clinical **AND** epidemiological criteria:

Clinical Criteria:

- Acute onset of fever AND cough; OR
- Acute onset of **ANY THREE OR MORE** of the following signs or symptoms: Fever, cough, general weakness/fatigue¹, headache, myalgia, sore throat, coryza, dyspnoea, anorexia/nausea/vomiting¹, diarrhoea, altered mental status.

AND

Epidemiological Criteria:

- Residing or working in an **area with high risk of transmission of virus**: closed residential settings, humanitarian settings such as camp and camp-like settings for displaced persons; anytime within the 14 days prior to symptom onset; or
- Residing or travel to an **area with community transmission** anytime within the 14 days prior to symptom onset; or
- Working in **any health care setting**, including within health facilities or within the community; any time within the 14 days prior of symptom onset.

Case Definition II

- B** A patient with **severe acute respiratory illness**:
(SARI: acute respiratory infection with history of fever or measured fever of ≥ 38 C°; and cough; with onset within the last 10 days; and requires hospitalization).
- C** Asymptomatic person not meeting epidemiologic criteria with a **positive SARS-CoV-2 Antigen-RDT²**

Confirmed case of SARS-CoV-2 infection

- A** A person with a positive **Nucleic Acid Amplification Test (NAAT)**
- B** A person with a **positive SARS-CoV-2 Antigen-RDT AND** meeting either the **probable case definition or suspect criteria A OR B**
- C** An **asymptomatic person with a positive SARS-CoV-2 Antigen-RDT** who is a **contact of a probable or confirmed case**

³ A group of symptomatic individuals linked by time, geographic location and common exposures, containing at least **one NAAT-confirmed** case or at least **two** epidemiologically linked, symptomatic (meeting clinical criteria of Suspect case definition A or B) persons with **positive Ag-RDTs** (based on $\geq 97\%$ specificity of test and desired $>99.9\%$ probability of at least one positive result being a true positive)

⁴ Typical chest imaging findings suggestive of COVID-19 include the following:

- **Chest radiography:** hazy opacities, often rounded in morphology, with peripheral and lower lung distribution
- **Chest CT:** multiple bilateral ground glass opacities, often rounded in morphology, with peripheral and lower lung distribution
- **Lung ultrasound:** thickened pleural lines, B lines (multifocal, discrete, or confluent), consolidative patterns with or without air bronchograms.

Probable case of SARS-CoV-2 infection

- A** A patient who meets **clinical criteria** above **AND** is a **contact of a probable or confirmed case**, or linked to a **COVID-19 cluster**³
- B** A **suspect case with chest imaging** showing findings suggestive of COVID-19 disease⁴
- C** A person with recent onset of **anosmia** (loss of smell) or **ageusia** (loss of taste) in the absence of any other identified cause.
- D** **Death**, not otherwise explained, in an adult with **respiratory distress** preceding death **AND was a contact of a probable or confirmed case** or linked to a **COVID-19 cluster**³

Severity of illness I

- **Asymptomatic or Presymptomatic Infection:** Individuals who test positive for SARS-CoV-2 by virologic testing using a molecular diagnostic (e.g., polymerase chain reaction) or antigen test, but have no symptoms.
- **Mild Illness:** Individuals who have any of the various signs and symptoms of COVID 19 (e.g., Fever, cough, sore throat, malaise, headache, muscle pain) **without shortness of breath, dyspnea, or abnormal chest imaging.**

Severity of illness II

- **Moderate Illness:** Individuals who have evidence of lower respiratory disease by clinical assessment or imaging and a saturation of **oxygen (SpO₂) $\geq 94\%$** on room air at sea level.
- **Severe Illness:** Individuals who have **respiratory rate >30 breaths** per minute, **SpO₂ $<94\%$ on room air** at sea level, ratio of arterial partial pressure of oxygen to **fraction of inspired oxygen (PaO₂/FiO₂) <300 mmHg**, or **lung infiltrates $>50\%$** .
- **Critical Illness:** Individuals who have respiratory failure(ARDS), septic shock, and/or multiple organ dysfunction.

Admission Criteria

- Moderate illness with risk of disease progression to severe disease (Age and co-morbidities)
- Severe disease
- Critical disease

Risk Factors for Poor Outcomes

- Underlying noncommunicable diseases (NCDs):
 - diabetes,
 - hypertension,
 - cardiac disease,
 - chronic lung disease,
 - cerebrovascular disease,
 - chronic kidney disease,
 - immunosuppression and
 - cancer have been associated with higher mortality
- Age more than 60 years (increasing with age).
- Smoking
- Obesity

Approach to Management

- Oxygen therapy
- Dexamethasone
- Anti-coagulation
- Prone Positioning

Prone Positioning

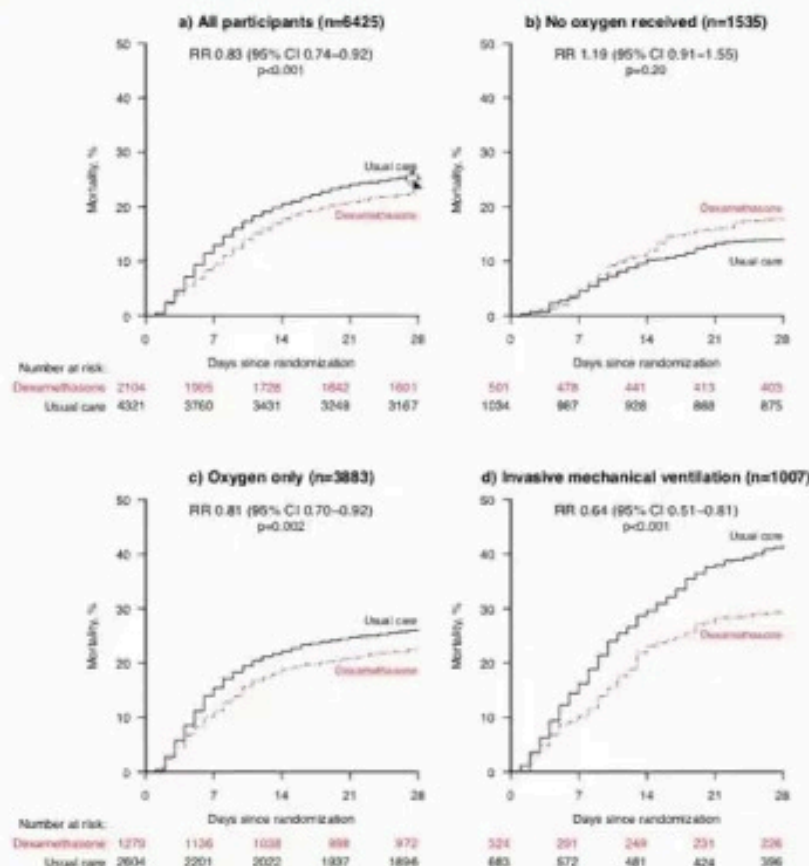


A prone-positioned patient on a ventilator. The new study will see if "proning" is effective for COVID-19 patients who do not need ventilation. Image from the Intensive Care Society's *Guidance For: Prone Positioning in Adult Critical Care*, 2019.

		PTP	Blood flow
Supine position			
		+ + + - - -	
Prone position			
		+ -	

Q.S.J.

28-day mortality in all patients (panel a) and separately according to level of respiratory support received at randomization (panels b–d)

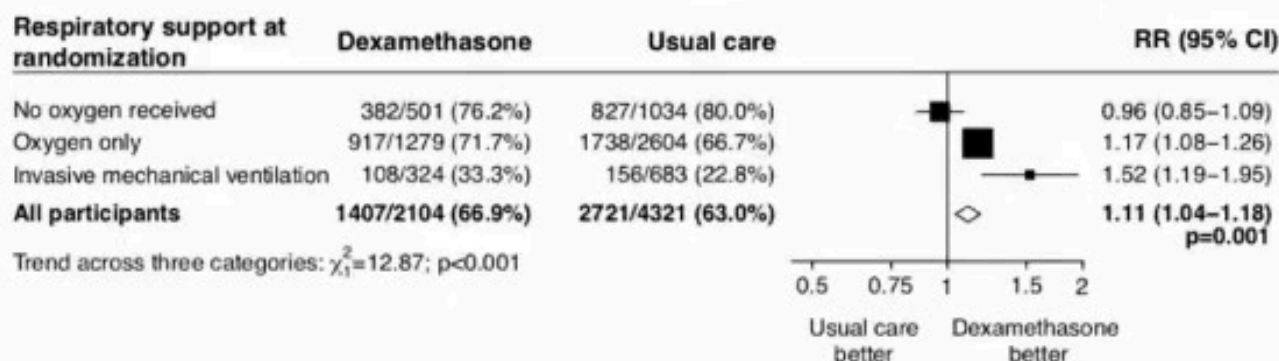


Dexamethasone

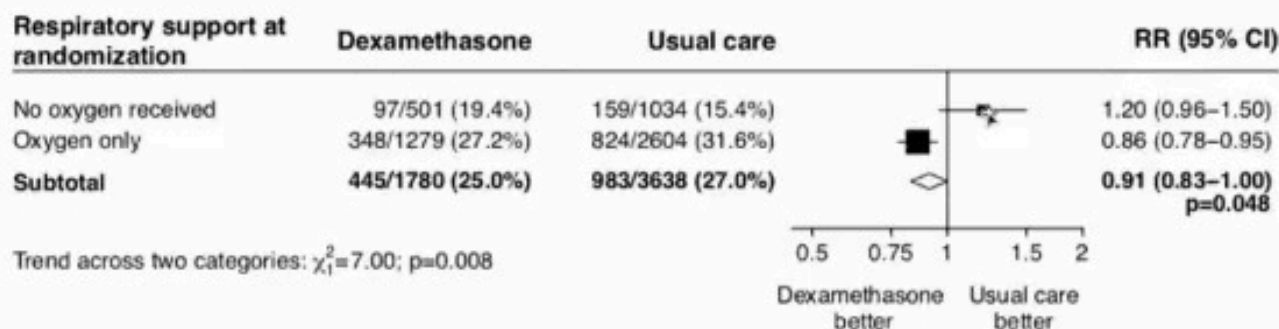
- Reduced deaths by one-third in patients receiving invasive mechanical ventilation (29.0% vs. 40.7%).
- Reduced deaths one-fifth in patients receiving oxygen without invasive mechanical ventilation (21.5% vs. 25.0%).
- Did not reduce mortality in patients not receiving respiratory support at randomization (17.0% vs. 13.2%).

Effect of allocation to dexamethasone on: a) discharge from hospital within 28 days; and b) invasive mechanical ventilation or death, by level of respiratory support received at randomization

a) Discharge from hospital within 28 days



b) Invasive mechanical ventilation or death (among those not on invasive mechanical ventilation at randomization)



Thromboembolism

Coagulopathy is common in patients with severe COVID-19, and both venous and arterial thromboembolism have been reported

- In patients (adults and adolescents) hospitalized with COVID-19, **use pharmacological prophylaxis, such as low molecular weight heparin (such as enoxaparin)**, according to local and international standards, to prevent venous thromboembolism, when not contraindicated
- For those **with contraindications, use mechanical prophylaxis (intermittent pneumatic compression devices)**
- Monitor patients with COVID-19, for signs or symptoms suggestive of thromboembolism, such as stroke, deep venous thrombosis, pulmonary embolism or acute coronary syndrome. If these are clinically suspected, proceed immediately with appropriate diagnostic and management pathways

Guidance on Thromboprophylaxis

Recommending Organization*

NIH ^[1]	ASH ^[2] New
■ Hospitalized adults with COVID-19 should receive VTE prophylaxis per the SoC for other hospitalized adults ■ Anticoagulant or antiplatelet therapy should not be used to prevent arterial thrombosis outside of the usual SoC for patients without COVID-19 ■ Currently insufficient data to recommend for or against the use of thrombolytics or increasing anticoagulant doses for VTE prophylaxis in hospitalized COVID-19 patients outside of clinical trial ■ Hospitalized patients should not be routinely discharged on VTE prophylaxis (extended VTE prophylaxis can be considered in patients with low bleeding risk and high VTE risk)	■ All hospitalized adults with COVID-19 should receive thromboprophylaxis with low-molecular-weight heparin over unfractionated heparin, unless bleeding risk outweighs thrombosis risk ■ Fondaparinux is recommended in the setting of heparin-induced thrombocytopenia ■ In patients in whom anticoagulants are contraindicated or unavailable, use mechanical thromboprophylaxis (eg, pneumatic compression devices) ■ Encourage participation on clinical trials rather than empiric use of therapeutic-dose heparin in COVID-19 patients with no other indication for therapeutic dose anticoagulation

*Additional recommendations available from the International Society on Thrombosis and Haemostasis^[3], and CHEST.^[4]

1. NIH. COVID-19 Treatment Guidelines. Updated: May 12, 2020. 2. American Society of Hematology. COVID-19 and VTE/ Anticoagulation: Frequently Asked Questions. 3. Spyropoulos. J Thromb Haemost. 2020;18:1859. 4. Moores. Chest. 2020;158:1143.

IDSA Recommendations FOR Treatment of Patients With COVID-19



- Overarching goal: recruit patients into ongoing trials to provide needed evidence regarding efficacy and safety of potential therapies

IDSA Guidance	Patient Population	Treatment
Recommends	Hospitalized with critical* COVID-19	Dexamethasone[†] vs none
Suggests	- Hospitalized with severe[‡] COVID-19 - Hospitalized with progressive severe[‡] or critical* COVID-19, elevated markers of inflammation - Hospitalized with severe^{*‡} COVID-19 - Ambulatory at high risk for severe disease - Hospitalized with severe[‡] COVID-19 and corticosteroids contraindicated	- Dexamethasone[†] vs none - Tocilizumab + SoC (ie, steroids) vs SoC alone - Remdesivir[§] vs no antiviral - Bamlanivimab/etesevimab vs none - Baricitinib + remdesivir vs remdesivir alone
Recommends only in clinical trial	- Hospitalized with COVID-19 - Hospitalized with COVID-19	- Convalescent plasma - Baricitinib + remdesivir + steroids

*Mechanical ventilation or ECMO. Includes end organ dysfunction (eg, ARDS). [†]If unavailable, methylprednisolone and prednisone acceptable at equivalent total daily doses. [‡]SpO₂ ≤ 94% on room air, including those on supplemental oxygen. [§]For patients on supplemental oxygen, 5 days suggested; for patients on mechanical ventilation or ECMO, 10 days.

Anti-SARS-CoV-2 Treatments

Re-purposed drugs

- Lopinavir/Ritonavir
- Hydroxychloroquine
- Interferon

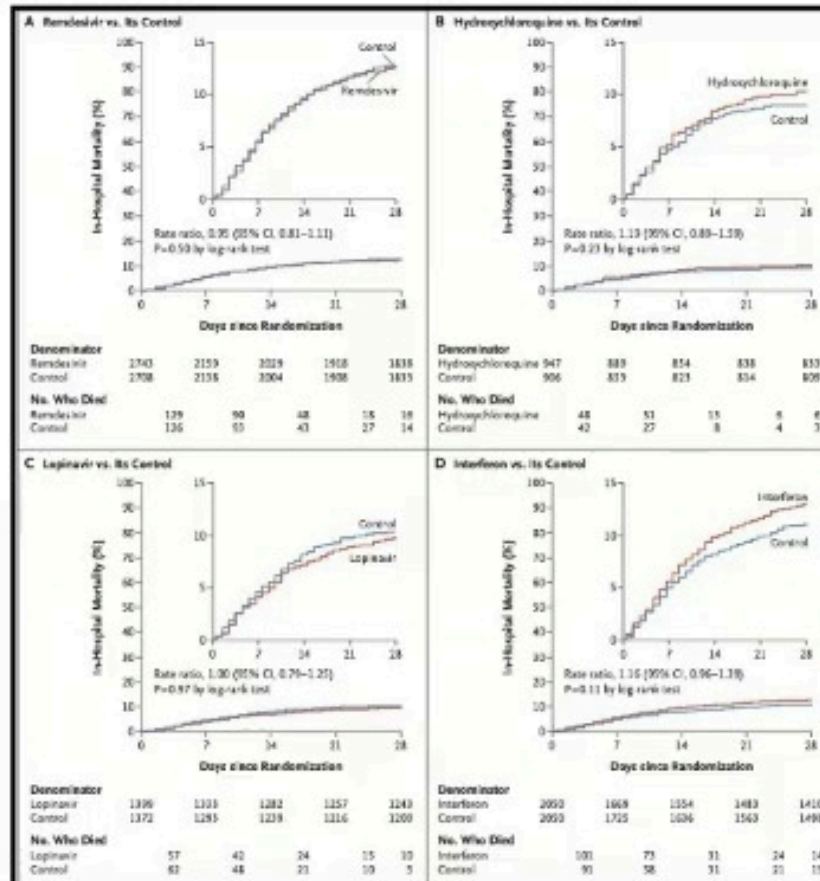
Insufficient evidence

- Ivermectin

ORIGINAL ARTICLE

Repurposed Antiviral Drugs for Covid-19 — Interim WHO Solidarity Trial Results

WHO Solidarity Trial Consortium*



Other Treatments

- Avoid empiric antibiotics unless there is a clear indication
- All other antiviral therapies to be used in the context of clinical trials
- IF for whatever reason you use other agents - should report to PPB

What has no Clear Evidence but no Harm

- Vitamin C
- Zinc
- Vitamin D

What does not Work and Should not be Used

- Hydroxychloroquine
- Azithromycin

Discharge Criteria

- Criteria for discharging patients from isolation (i.e., discontinuing transmission-based precautions) without requiring retesting:
 - For symptomatic patients: 10 days after symptom onset, plus at least 3 additional days without symptoms (including without fever and without respiratory symptoms)
 - For asymptomatic cases: 10 days after positive test for SARS-CoV-2

CDC: Discontinuation of Transmission-Based Precautions for Patients With Confirmed SARS-CoV-2

Updated

Symptom-Based Strategy*

≥ 24 hrs since resolution
of fever, last antipyretics

And

Improvement in symptoms
(eg, cough, shortness of breath)

And

≥ 10 days since symptom onset
for mild to moderate illness,
10-20 days for severe to critical illness
or those severely immunocompromised

Test-Based Strategy

Not generally recommended because
*“in the majority of cases, it results in
prolonged isolation of patients who
continue to shed detectable SARS-CoV-2
RNA but are no longer infectious”*

*If patient is asymptomatic, not severely immunocompromised, precautions may be discontinued ≥ 10 days after positive viral test.

Conclusion

- Reviewed the overview of COVID-19 management
 - What we now know about the virus, pathogenesis and immune responses
 - Spectrum of Clinical Presentation
 - Patient triage and Severity of illness
 - Approach to Management
 - Admission and Discharge Criteria
 - Therapeutics – What works

-
- Thank you