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Science News

from research organizations

Researchers confirm speed, simplicity and sensitivity for new COVID-19 test

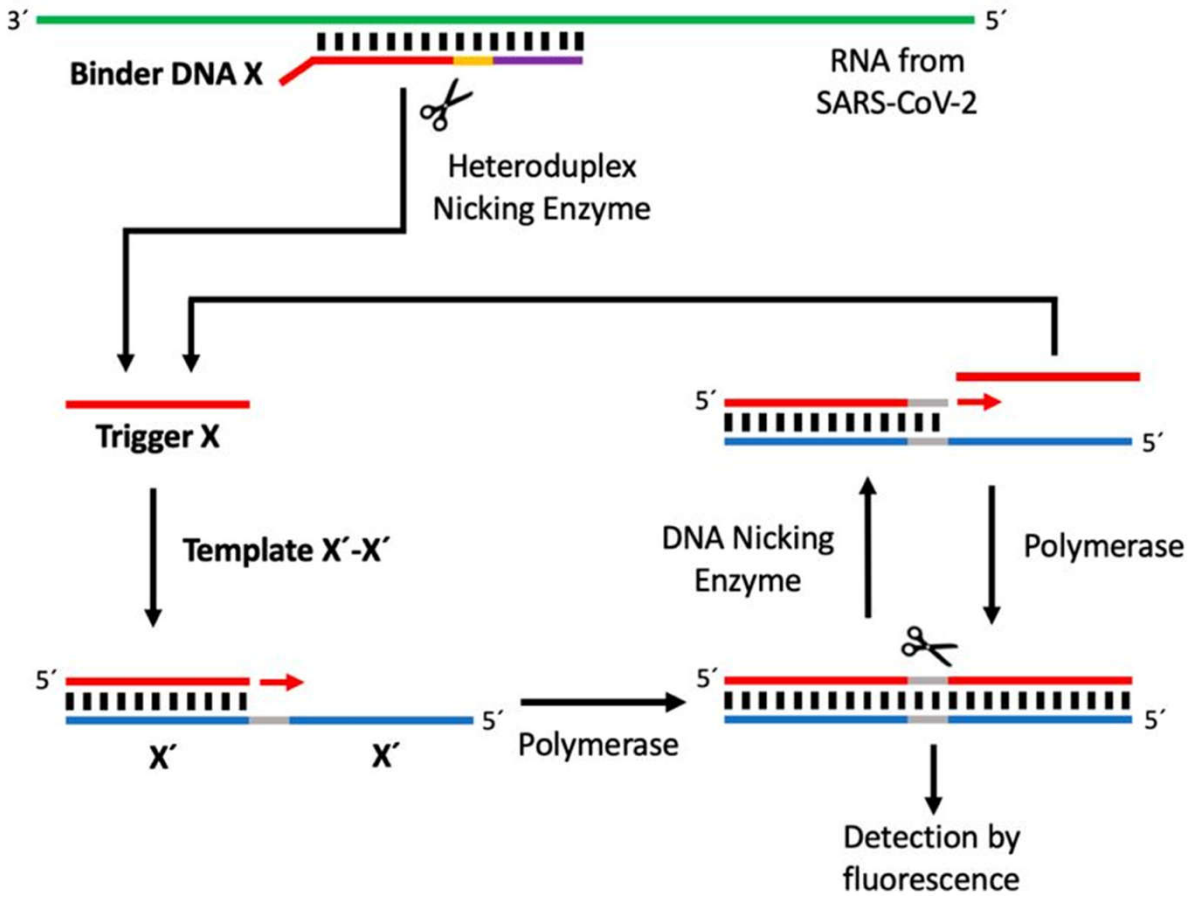
Date: August 17, 2021

Source: University of Birmingham

Summary: Researchers have published a three way comparison study to confirm that the Reverse Transcriptase Free Exponential Amplification Reaction (RTF-EXPAR) method is just as sensitive, but faster, than both PCR and LAMP tests. The study revealed that the RTF-EXPAR method converts under 10 strands of RNA into billions of copies of DNA in under 10 minutes, using a one-pot assay that is compatible with more basic, benchtop equipment than that used with current testing methods.

- RTF-EXPAR achieves it in two ways -- firstly the assay team designed a new RNA-to-DNA conversion step that avoids reverse transcription, making it reverse transcription-free (RTF). Secondly their amplification step to generate the read-out signal uses EXPAR, an alternative DNA amplification process to PCR and LAMP. EXPAR amplifies DNA at a single temperature, thus avoiding lengthy heating and cooling steps found in PCR. However, while LAMP also uses a single temperature for amplification, EXPAR is a simpler and a more direct process, in which much smaller strands are amplified. This makes EXPAR an even faster DNA amplification technique than not only PCR but also LAMP.
- RTF-EXPAR also demonstrated significant improvements over both PCR and LAMP-based assays on time to signal detection. At low concentrations of RNA (7.25 copies/µL), the time to signal detection was 42.67 (± 0.47) minutes for PCR, 11.25 (± 0.20) minutes for LAMP, and 8.75 (± 0.35) minutes for EXPAR. At high (1450 copies/µL) concentrations of viral RNA, the time to signal detection was 34.00 (± 0.00) minutes for PCR, 11.25 (± 0.20) minutes for LAMP, and 3.08 (± 0.42) minutes for EXPAR.
- The analysis showed RTF-EXPAR's sensitivity is equivalent to quantitative PCR testing, with a positive predictive value of 89%, and a negative predictive value of 93%. We expect to publish the full results of this testing in the near future."

B Reverse Transcription-Free EXPAR (RTF-EXPAR)



NEWS RELEASE 13-JUL-2021

"Long COVID": More than a quarter of COVID-19 patients still symptomatic after 6 months

In a new study of adults from the general population who were infected with COVID-19 in 2020, more than a quarter report not having fully recovered after six to eight months. Those findings are described this week in the open-access journal *PLOS ONE* by Milo Puhan and colleagues at the University of Zurich, Switzerland. The most common are persistent fatigue, shortness of breath, cardiac symptoms, neurologic symptoms and psychiatric manifestations. They vary in their presentation and intensity and can also fluctuate over time.

- In the new study, 26% of participants reported that they had not fully recovered at six to eight months after initial COVID-19 diagnosis. 55% reported symptoms of fatigue, 25% had some degree of shortness of breath, and 26% had symptoms of depression.
- The study reveals a trend of long-term symptoms associated with gender. Dr Mayssam Nehme notes that "the incidence seems to be higher in women, especially for fatigue, shortness of breath and headaches. All age groups are affected, including the young and healthy". The prevalence of certain symptoms varies among age groups: for example, 40-60 year olds are more prone to muscle pain.
- People who developed more COVID-19 symptoms in the acute phase of the disease, namely the days following infection, are more likely to develop persistent symptoms. Surprisingly, symptoms fluctuate over time.
- 37% of people with persistent symptoms reported their disappearance after 30 to 45 days and an additional 19% seven to nine months after the infection indicating a remission in 56% of cases.

MHRA approves first monoclonal antibody treatment for COVID-19 in the UK

Reviewed by Emily Henderson, B.Sc. Aug 20 2021

- Following on from a thorough review of the evidence carried out by the MHRA, and recommendation by the Commission on Human Medicines (CHM), the government's independent expert scientific advisory body, the MHRA has approved Ronapreve as the first monoclonal antibody combination product indicated for use in the prevention and treatment of acute COVID-19 infection for the UK.
- Developed by Regeneron/Roche, the drug is administered either by injection or infusion and acts at the lining of the respiratory system where it binds tightly to the coronavirus and prevents it from gaining access to the cells of the respiratory system.
- Clinical trial data assessed by a dedicated team of MHRA scientists and clinicians have shown that Ronapreve may be used to prevent infection, promote resolution of symptoms of acute COVID-19 infection, and can reduce the likelihood of being admitted to hospital due to COVID-19.

Summary Recommendations and Considerations

Recommendation for Individuals With Symptoms That Are Consistent With COVID-19

- The COVID-19 Treatment Guidelines Panel (the Panel) recommends that individuals who have recently been exposed to SARS-CoV-2 and have symptoms that are consistent with COVID-19 be evaluated for SARS-CoV-2 infection by either a nucleic acid amplification test (NAAT) or antigen testing **(AIII)**.
  - Individuals with positive SARS-CoV-2 NAAT or antigen test results who meet the Emergency Use Authorization (EUA) criteria for therapeutic use of anti-SARS-CoV-2 monoclonal antibodies should be referred for treatment (see Anti-SARS-CoV-2 Monoclonal Antibodies).
  - Those with negative test results should be considered for post-exposure prophylaxis (PEP) as discussed below.

Recommendations for Post-Exposure Prophylaxis

- The Panel recommends using **casirivimab 600 mg plus imdevimab 600 mg** administered as subcutaneous (SQ) injections **(AI)** or an intravenous (IV) infusion **(BIII)** as PEP for people who are at high risk for progression to severe COVID-19 if infected with SARS-CoV-2[a] **AND** who have the following vaccination status **AND** exposure history.
  - *Vaccination Status:*
    - Not fully vaccinated (defined as people who were never vaccinated or those who received the second vaccine dose in a two-dose series or a single-dose vaccine <2 weeks ago); *or*
    - Fully vaccinated, but not expected to mount an adequate immune response (e.g., those with immunocompromising conditions, including those who are taking immunosuppressive medications)

AND

  - *Exposure History to SARS-CoV-2:*
    - Had a recent exposure to an individual with SARS-CoV-2 infection that is consistent with the Centers for Disease Control and Prevention (CDC) close contact criteria;[b] *or*
    - At high risk of exposure to an individual with SARS-CoV-2 infection because of recent occurrence of SARS-CoV-2 infection in other individuals in the same institutional setting (e.g., nursing homes, prisons)

Timing and Doses of Casirivimab Plus Imdevimab

- The doses should be administered as soon as possible and preferably within 7 days of high-risk exposure **(AIII)**.

• **Casirivimab 600 mg plus imdevimab 600 mg** should be given as four SQ injections (2.5 mL per injection) at four different sites **(AI)** or as a single IV infusion **(AIII)**. The patient should be observed for at least 1 hour after the injections or infusion. • There is insufficient evidence for the Panel to recommend either for or against repeat dosing every 4 weeks for those who received PEP and who continue to have high-risk exposures.
Rating of Recommendations: A = Strong; B = Moderate; C = Optional **Rating of Evidence:** I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion

[a] For a list of individuals who are considered to be at high risk of progressing to severe COVID-19, see the Food and Drug Administration EUA. It should be noted that the relative risk is not identical for all risk factors listed in the EUA. The presence of multiple risk factors in an individual is associated with a higher risk of progression. Providers should use clinical judgement when determining a patient's risk of progression.

[b] For the CDC definition of close contact, visit the CDC Glossary of Key Terms.

The strength of the COVID-19 Treatment Guidelines Panel's (the Panel) recommendations for using these anti-SARS-CoV-2 monoclonal antibodies for PEP varies based on the available evidence to date:

- **AI** for the population represented in the clinical trial, where the analysis included asymptomatic people with a negative SARS-CoV-2 test result (nucleic acid amplification test [NAAT] or antigen) who were exposed to someone in their household with a positive SARS-CoV-2 test result from a sample that was collected within the previous 96 hours, and who anticipated ongoing exposure over at least the next 28 days.
- **AIII** for individuals who meet the EUA criteria but not the clinical trial criteria.

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PDF

Losartan Inhibits SARS-CoV-2 Replication in Vitro

Losartan promotes cell survival following SARS-CoV-2 infection in vitro

Reza Nejat [1], Ahmad Shahir Sadr [2], Branden Freitas [3], Jackelyn Crabttree [3], Scott D Pegan [3], Ralph A Tripp [3], David Najafi [4]

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- The downregulation of ACE2 has been shown to cause local RAS dysregulation. This can subsequently lead to pro-inflammatory, pro-apoptotic, and pro-thrombotic effects and, ultimately, COVID-19-induced cytokine storm.
- Scientists have hypothesized that selective AT1R antagonism by ARBs can aid in reducing COVID-19-related lung pathology. ARBs achieve this by rebalancing the Ang II/angiotensin (1-7) ratio and by indirectly promoting Ang II-induced activation of AT2R.

Abstract

- **Purpose:** SARS-CoV-2 infection is associated with substantial mortality and high morbidity. This study tested the effect of angiotensin II type I receptor blocker, losartan, on SARS-CoV-2 replication and inhibition of the papain-like protease of the virus.
- **Methods:** The dose-dependent inhibitory effect of losartan, in concentrations from 1µM to 100µM as determined by quantitative cell analysis combining fluorescence microscopy, image processing, and cellular measurements (Cellomics analysis) on SARS-CoV-2 replication was investigated in Vero E6 cells. The impact of losartan on deubiquitination and deISGylation of SARS-CoV-2 papain-like protease (PLpro) were also evaluated.
- **Results:** Losartan reduced PLpro cleavage of tetraUbiquitin to diUbiquitin. It was less effective in inhibiting PLpro's cleavage of ISG15-AMC than Ubiquitin-AMC. To determine if losartan inhibited SARS-CoV-2 replication, losartan treatment of SARS-CoV-2 infected Vero E6 was examined. Losartan treatment one hour prior to SARS-CoV-2 infection reduced levels of SARS-CoV-2 nuclear protein, an indicator of virus replication, by 80% and treatment one-hour post-infection decreased viral replication by 70%.

- **Conclusion:** Losartan was not an effective inhibitor of deubiquitinase or deISGylase activity of the PLpro but affected the SARS-CoV-2 replication of Vero E6 cells in vitro. As losartan has a favorable safety profile and is currently available it has features necessary for efficacious drug repurposing and treatment of COVID-19.

viruses

Open Access Communication

Antiviral Effect of Budesonide against SARS-CoV-2

by Natalie Heinen [1], Toni Luise Meister [1], Mara Klöhn [1], Eike Steinmann [1], Daniel Todt [1,2] and Stephanie Pfaender [1,*]

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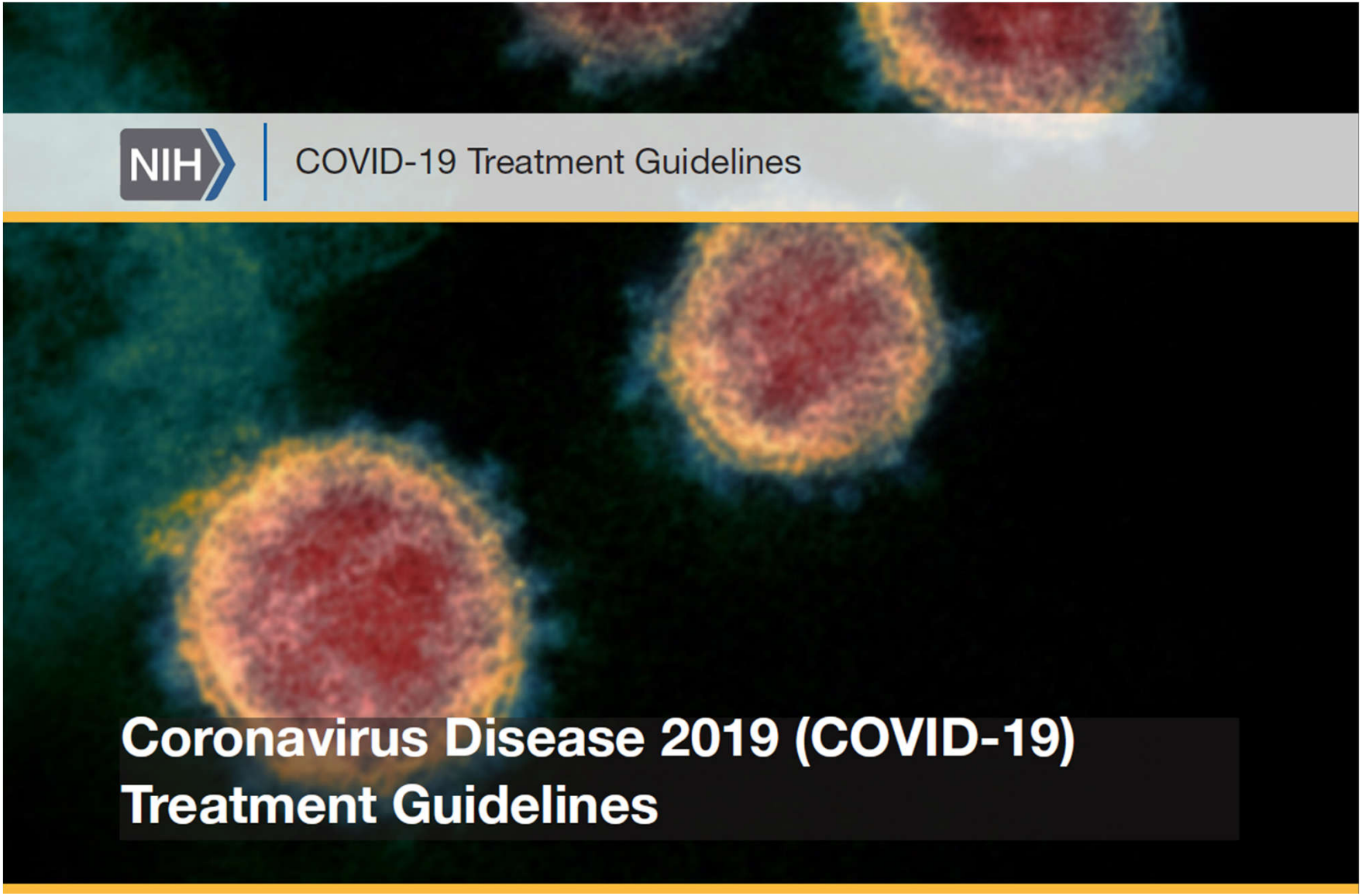
- In the current study, Vero E6 cells were treated with budesonide or Pulmicort® in concentrations of 0.1, 1, 5, and 25 micromolar (µM) or the control vehicle. Following the treatment, cells were infected with either the SARS-CoV-2 WT strain, or one of the VoCs. The scientists observed that treatment with higher concentrations of budesonide, both the pure version as well as Pulmicort®, exhibited antiviral activity and reduced viral titers when compared to the control group.
- Taken together, the scientists concluded that budesonide can significantly reduce SARS-CoV-2 titers *in vitro*. These results are in accordance with previous studies that have shown that the inhalation of corticosteroid ciclesonide suppressed the genetic replication of SARS-CoV-2 and MERS-CoV by targeting the viral replication-transcription complex in human bronchial tracheal epithelial cells.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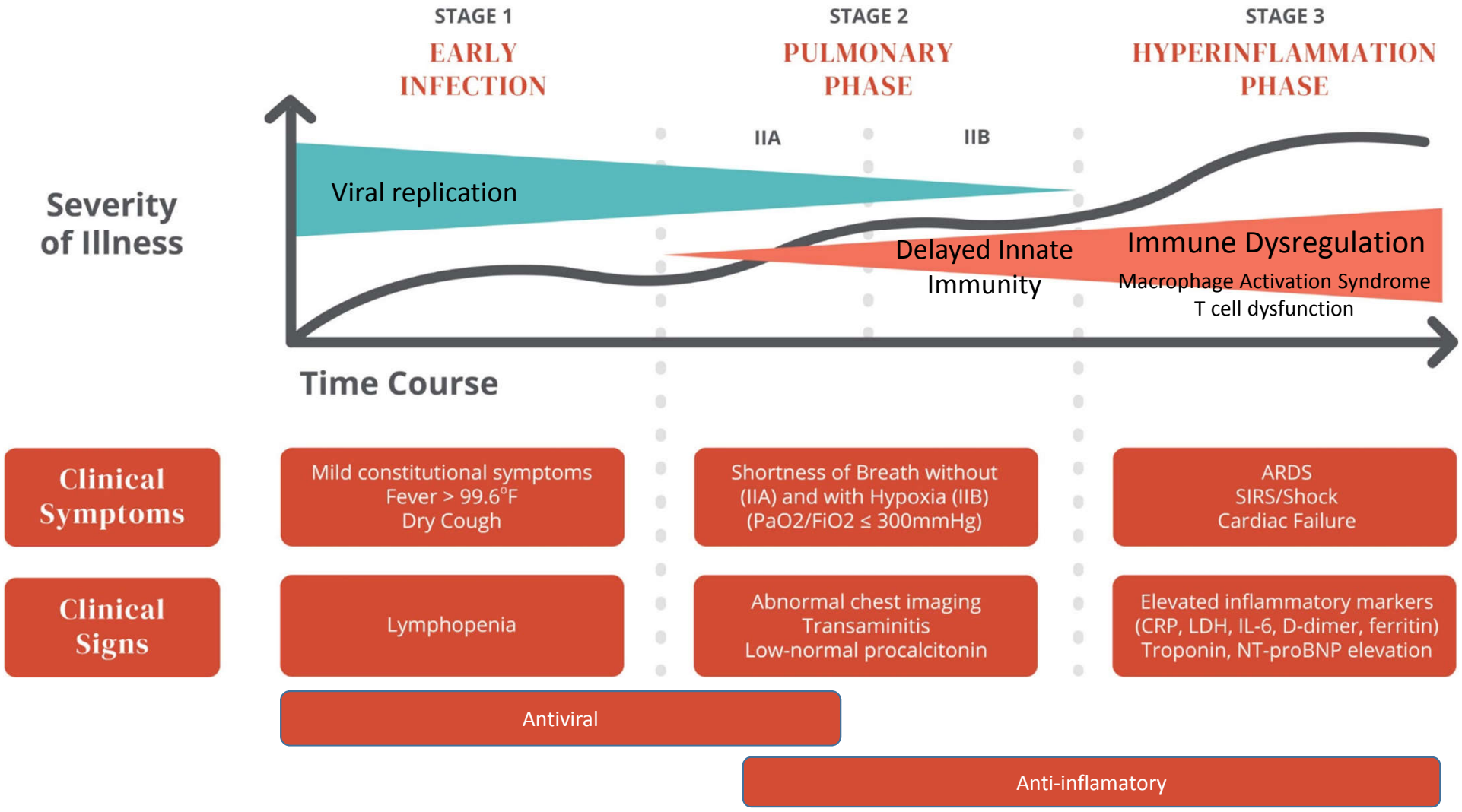
STAGE 1
EARLY INFECTION
STAGE 2
PULMONARY PHASE
IIA
IIB
STAGE 3
HYPERINFLAMMATION PHASE
Severity of Illness
Viral replication
Delayed Innate Immunity
Immune Dysregulation
Macrophage Activation Syndrome
T cell dysfunction
Time Course
Clinical Symptoms
Mild constitutional symptoms
Fever > 99.6°F
Dry Cough
Shortness of Breath without (IIA) and with Hypoxia (IIB) (PaO2/FiO2 ≤ 300mmHg)
ARDS
SIRS/Shock
Cardiac Failure
Clinical Signs
Lymphopenia
Abnormal chest imaging
Transaminitis
Low-normal procalcitonin
Elevated inflammatory markers (CRP, LDH, IL-6, D-dimer, ferritin)
Troponin, NT-proBNP elevation
Antiviral
Anti-inflamatory

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