

Treatment of RR-TB/COVID-19 co-infection

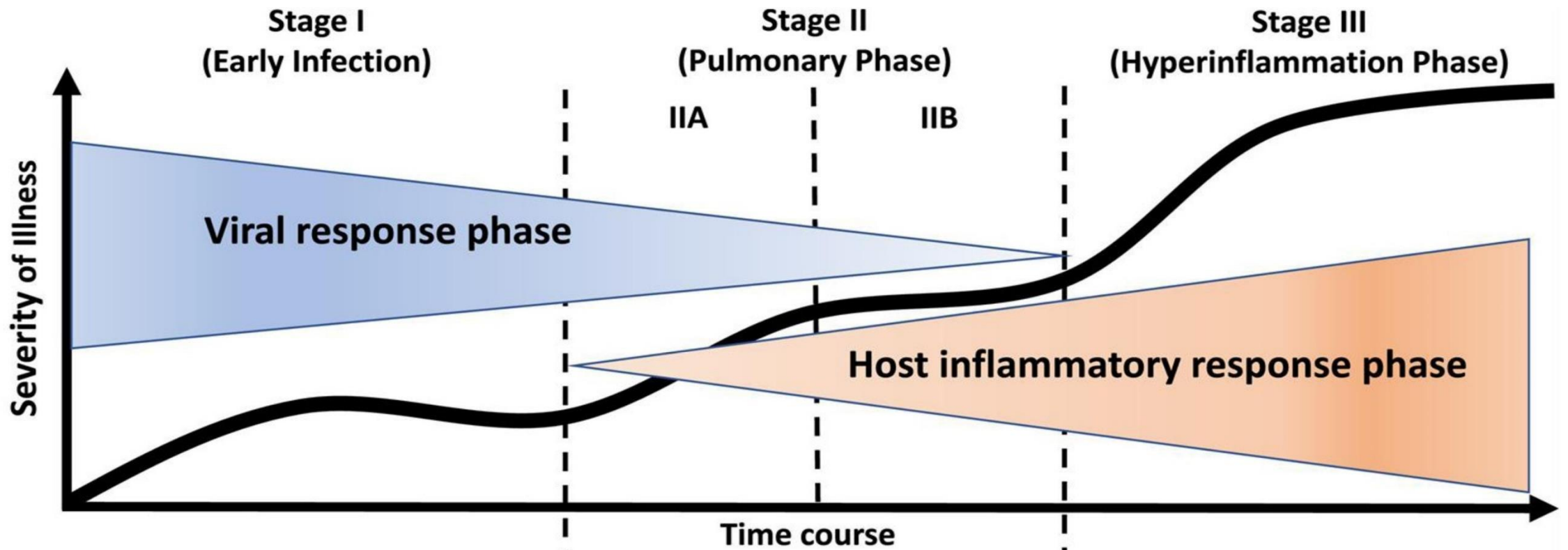
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WHO CC for Research and Training in Management of MDR TB, Riga
VMC expert

15 October 2021

Structure

1. COVID-19 treatment guidelines
2. RR-TB/COVID-19 co-infection



Clinical Symptoms

Mild constitutional symptoms
Fever >99.6°F
Dry Cough, diarrhea, headache

Shortness of Breath
Hypoxia ($PaO_2/FiO_2 \leq 300$ mmHg)

ARDS
SIRS/Shock
Cardiac Failure

Clinical Signs

Lymphopenia, increased prothrombin time, increased D-Dimer and LDH (mild)

Abnormal chest imaging
Transaminitis
Low-normal procalcitonin

Elevated inflammatory markers (CRP, LDH, IL-6, D-dimer, ferritin)
Troponin, NT-proBNP elevation

WHO severity definitions

Non-severe COVID-19 – Defined as absence of any criteria for severe or critical COVID-19.

Severe COVID-19 – Defined by any of:

- **Oxygen saturation < 90%** on room air;
- in adults, signs of severe respiratory distress (accessory muscle use, inability to complete full sentences, respiratory rate > 30 breaths per minute), and, in children, very severe chest wall indrawing, grunting, central cyanosis, or presence of any other general danger signs (inability to breastfeed or drink, lethargy or reduced level of consciousness, convulsions) in addition to the signs of pneumonia.

Critical COVID-19 – Defined by the criteria for acute respiratory distress syndrome (ARDS), sepsis, septic shock, or other conditions that would normally require the provision of life-sustaining therapies such as mechanical ventilation (invasive or non-invasive) or vasopressor therapy.

Therapeutics and COVID-19: living guideline

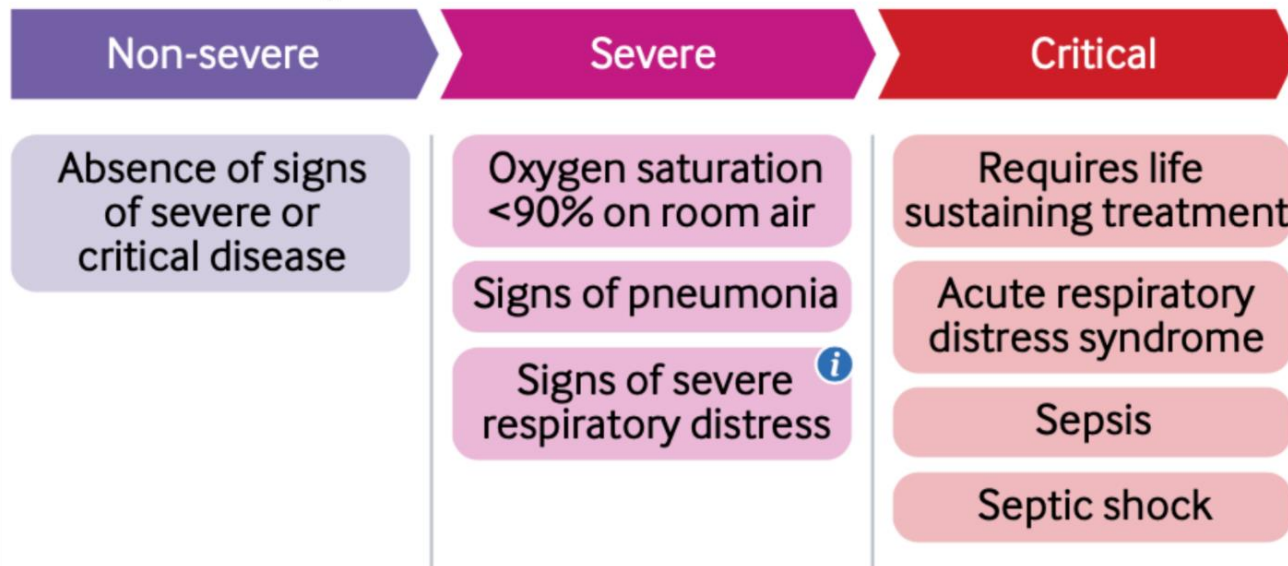
World Health Organization (WHO)

Population

This recommendation applies only to people with these characteristics:



Disease severity



Infographic co-produced by the BMJ and MAGIC; designer Will Stahl-Timmins (see [BMJ Rapid Recommendations](#)).

Mild

Symptomatic treatment such as **antipyretics** for fever and pain, **adequate nutrition** and appropriate **rehydration**.

Counsel patients with mild COVID-19 about signs and symptoms of complications that should prompt urgent care (such as light headedness, difficulty breathing, chest pain, dehydration etc).

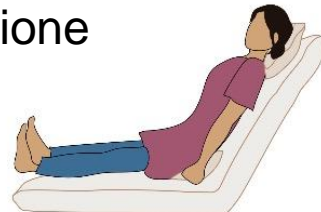
We recommend that **antibiotic** therapy or prophylaxis **should not** be used in patients with mild COVID-19.

Rehabilitation

Prone position



2. Switch to lying on your right side for 30 mins to 2 hours



3. Switch to 30 minutes to 2 hours of sitting up (30-60 degrees)



4. Switch to lying on your left side for 30 minutes to 2 hours



5. Switch to semi-prone position for 30 minutes to 2 hours



6. Return to prone position for 30 minutes to 2 hours. Repeat cycle...

Keep monitoring your oxygen levels after switching between positions. If oxygen levels drop below SpO₂ 92%, consult a doctor and seek hospital care immediately.

Breathing exercises



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Avoid proning in conditions like pregnancy, Deep Vein Thrombosis, cardiac conditions, spinal or fracture issues.

Home care tips for managing COVID-19



Name: _____

Discharge date: _____

Hospital where treated: _____

Healthcare professional providing leaflet: _____

Name and contact of local healthcare professional: _____

<https://openwho.org/courses/clinical-management-COVID-19-rehabilitation?locale=en>

<https://www.who.int/publications/m/item/support-for-rehabilitation-self-management-after-covid-19-related-illness>

Neutralizing monoclonal antibodies

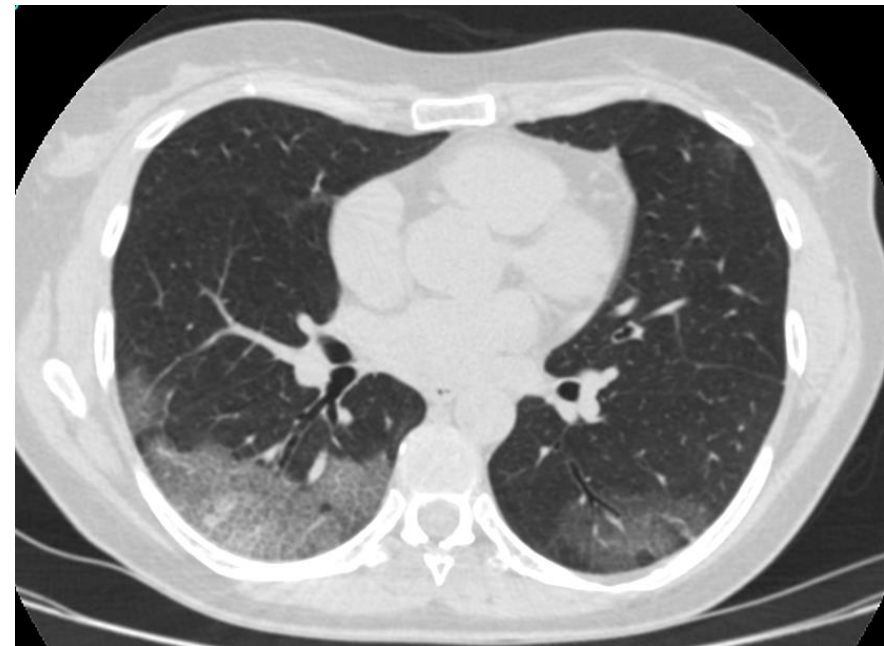
For patients with non-severe COVID-19 (who do not meet criteria for severe or critical infection)

Casirivimab plus imdevimab; *WHO and FDA* (1200 mg–8000 mg (600 mg–4000 mg each antibody), demonstrating efficacy at all doses, including the lowest tested, 1200 mg total dose (600mg of each antibody).

(FDA **Sotrovimab**; **Bamlanivimab plus etesevimab**)

Management of moderate COVID-19: pneumonia treatment

We recommend for patients with suspected or confirmed moderate COVID-19, that **antibiotics should not be** prescribed unless there is clinical suspicion of a bacterial infection.



Management of severe COVID-19: severe pneumonia treatment

All areas where severe patients may be cared for should be equipped with **pulse oximeters**, functioning **oxygen systems** and disposable, single-use, oxygen-delivering interfaces.

We recommend immediate administration of supplemental **oxygen therapy** to any patient with emergency signs during resuscitation to target **SpO₂ ≥ 94%** and to any patient without emergency signs and hypoxaemia (i.e. stable hypoxaemic patient) to target SpO₂ > 90% or ≥ 92–95% in pregnant women.

Deliver oxygen flow rates using appropriate delivery devices



Nasal cannula for rates up to 5 L/min



Simple face mask for flow rates 6–10 L/min



Face mask with reservoir bag for flow rates 10–15 L/min)



High flow nasal cannula 60 L/min

NIV



Systemic corticosteroids - for patients with severe and critical COVID-19

We recommend systemic corticosteroids rather than no corticosteroids.

- **6 mg of dexamethasone** (half-life 36 to 72 hours, administer once daily).

Equivalent in terms of glucocorticoid effect:

- 150 mg of hydrocortisone (half-life 8 to 12 hours, administer in two to four divided doses daily) or
- 40 mg of prednisone or
- 32 mg of methylprednisolone (administer once daily or in two divided doses daily).

Therapy 7 days or more **after symptom onset**

Treatment duration: 7–10 days

IL-6 receptor antagonist monoclonal antibody

We recommend treatment with IL-6 receptor blockers (tocilizumab or sarilumab) for patients with severe or critical COVID-19 infection.

- IL-6 receptor blocker therapy should be administered in **combination with systemic corticosteroids**
- Tocilizumab and sarilumab are administered as single intravenous doses, typically over 1 hour.
- Tocilizumab dosed 8 mg per kilogram of actual body weight (maximum of 800 mg).
- Sarilumab dosed at 400 mg.

Ivermectin - we recommend **not to use** ivermectin in patients with COVID-19 except in the context of a clinical trial. Conditional recommendation against. (Only in research settings)

Hydroxychloroquine - We recommend **against** administering hydroxychloroquine or chloroquine for treatment of COVID-19. (Recommendation against)

Lopinavir/ritonavir - We recommend **against** administering lopinavir/ritonavir for treatment of COVID-19. (Recommendation against)

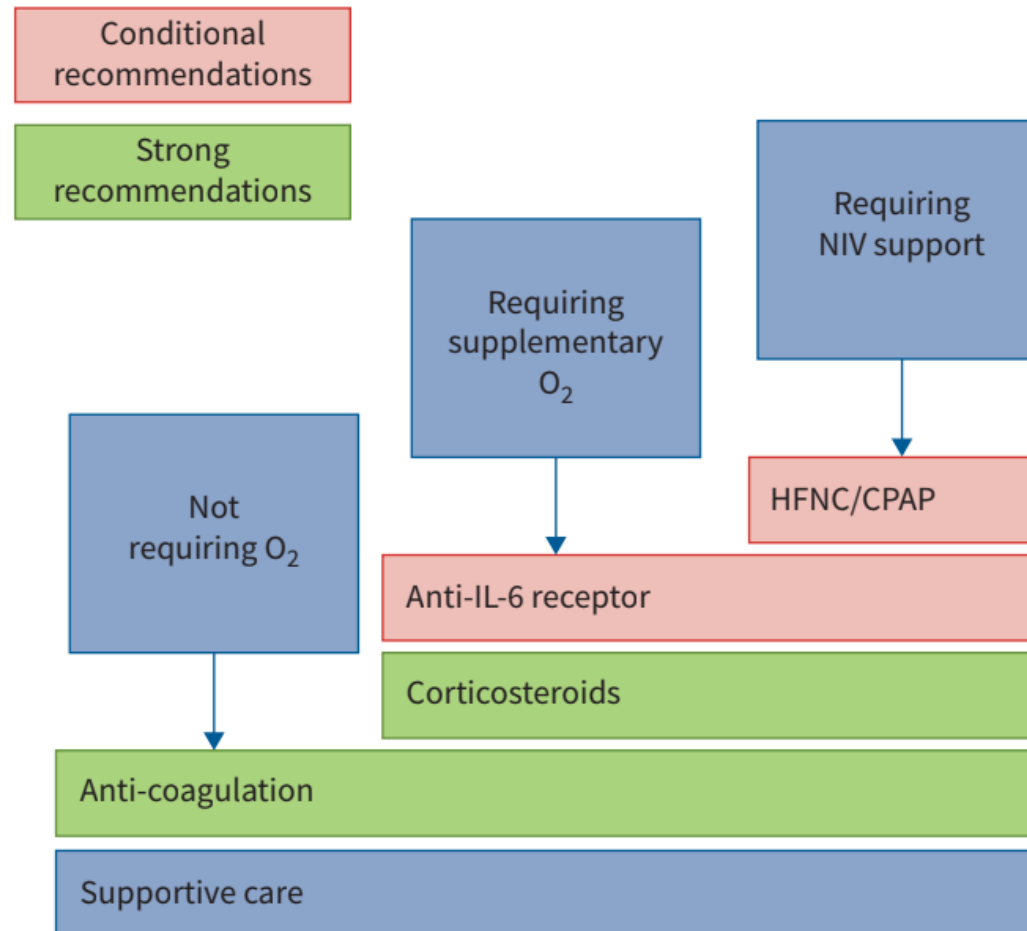
Remdesivir - We suggest **against** administering remdesivir in addition to usual care. (Conditional recommendation against)



Management of hospitalised adults with coronavirus disease-19 (COVID-19): A European Respiratory Society living guideline

James D. Chalmers, Megan L. Crichton, Pieter C. Goeminne, Bin Cao, Marc Humbert, Michal Shteinberg, Katerina M. Antoniou, Charlotte Suppli Ulrik, Helen Parks, Chen Wang, Thomas Vandendriessche, Jieming Qu, Daiana Stolz, Christopher Brightling, Tobias Welte, Stefano Aliberti, Anita K. Simonds, Thomy Tonia, Nicolas Roche

European Respiratory Journal 2021; DOI: 10.1183/13993003.00048-2021



Anti-coagulation

PICO 10: In hospitalised patients with COVID-19 should anticoagulants be used versus no anticoagulant?

Recommendation: The panel **recommends** offering a form of **anticoagulation for hospitalised patients** with COVID-19 (strong recommendation, very low quality of evidence).

Notes accompanying this recommendation: the panel are unable to make a recommendation regarding the dose of anticoagulation (prophylactic, high-dose prophylactic or therapeutic) or the preferred type of anticoagulant medication.

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	<p>The Panel recommends against the use of dexamethasone (AIIa) or other corticosteroids (AIII).^a</p> <p>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.</p>
Hospitalized and Requires Supplemental Oxygen	<p>Use one of the following options:</p> <ul style="list-style-type: none"> • Remdesivir^b (e.g., for patients who require minimal supplemental oxygen) (BIIa) • Dexamethasone plus remdesivir^b (e.g., for patients who require increasing amounts of supplemental oxygen) (BIII) • Dexamethasone (when combination with remdesivir cannot be used or is not available) (BI)
Hospitalized and Requires Oxygen Delivery Through a High-Flow Device or Noninvasive Ventilation	<p>Use one of the following options:</p> <ul style="list-style-type: none"> • Dexamethasone (AI) • Dexamethasone plus remdesivir^b (BIII) <p>For recently hospitalized^c patients with rapidly increasing oxygen needs and systemic inflammation:</p> <ul style="list-style-type: none"> • Add either baricitinib (BIIa) or IV tocilizumab (BIIa) to one of the two options above^d <ul style="list-style-type: none"> • If neither baricitinib nor IV tocilizumab is available or feasible to use, tofacitinib can be used instead of baricitinib (BIIa) or IV sarilumab can be used instead of IV tocilizumab (BIIa).
Hospitalized and Requires IMV or ECMO	<ul style="list-style-type: none"> • Dexamethasone (AI) <p>For patients who are within 24 hours of admission to the ICU:</p> <ul style="list-style-type: none"> • Dexamethasone plus IV tocilizumab (BIIa) <ul style="list-style-type: none"> • If IV tocilizumab is not available or not feasible to use, IV sarilumab can be used (BIIa).



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

Remdesivir

Remdesivir is an intravenous nucleotide prodrug of an adenosine analog. Remdesivir binds to the viral RNA-dependent RNA polymerase and inhibits viral replication through premature termination of RNA transcription.

Remdesivir is approved by FDA for the treatment of COVID-19 in **hospitalized** adult and pediatric patients (aged ≥ 12 years and weighing ≥ 40 kg).

Remdesivir is not recommended for patients with an eGFR < 30 mL/min due to lack of data.

Dosage: in the first day 200mg, then 100mg (5-10 days).

Therapeutics and COVID-19

LIVING GUIDELINE
24 SEPTEMBER 2021



Conditional recommendation against

We suggest **against** administering remdesivir in addition to usual care.



Original Investigation | Infectious Diseases

Comparison of Time to Clinical Improvement With vs Without Remdesivir Treatment in Hospitalized Patients With COVID-19

Brian T. Garibaldi, MD, MEHP; Kunbo Wang, MS; Matthew L. Robinson, MD; Scott L. Zeger, PhD; Karen Bandeen-Roche, PhD; Mei-Cheng Wang, PhD; G. Caleb Alexander, MD; Amita Gupta, MD; Robert Bollinger, MD, MPH; Yanxun Xu, PhD

Conclusions

This study suggests that remdesivir was associated with a **significant decrease in the time to clinical recovery among patients admitted to the hospital** for treatment of COVID-19. These results provide further evidence that remdesivir **may be effective in reducing the duration of COVID-19 illness**, that a 5-day treatment course may be sufficient, and that patients with **milder disease** likely benefit most. The combination of remdesivir and corticosteroids was not associated with reduced mortality, suggesting that additional studies assessing patients with COVID-19 are warranted.

RR-TB/COVID-19 co-infection

TB and COVID19

In most cases TB treatment is **not different** in people with or without COVID-19 infection.

TB preventive treatment, treatment for drug-susceptible or drug-resistant TB disease **should continue uninterrupted** as it is important to safeguard the patient's health. Suspension of TB treatment in COVID-19 patients should be exceptional.

If COVID-19 patients being considered for treatment with interleukin-6 inhibitors, testing and treatment of TB infection may be considered.

Immunosuppressants:

- Risk for reactivation of LTB
- Worsening of TB

Continuation of Treatment at home under lock-down conditions

TB and MDR-TB patients to stay home

- Shift to virtual care

Multiple months of medicines given to patients at home

- Early procurement, careful planning of local drug distribution

Shift to injection-free all-oral MDR-TB regimen

Family member as treatment supporter

Virtual treatment support and digital adherence tools

Telemedicine for managing adverse events

- Avoid hospital visit unless there are medical complications because of TB treatment, co-morbidity, including Covid-19

Manage contacts

Follow country guidelines

National Governments Actions /
Recommendations on TB and
COVID-19

INDIA

INDONESIA

MOLDOVA

PHILLIPINES

Vaccinate TB patients against Covid19!!!!



New COVID therapy - interactions with molnupiravir now available

Drugs	Co-medications	Drug Interactions
<input type="text" value="toc"/>	<input type="text" value="Search co-medications..."/>	<input checked="" type="checkbox"/> Check COVID/COVID drug interactions Reset Checker
<input checked="" type="radio"/> A-Z <input type="radio"/> Class	<input checked="" type="radio"/> A-Z <input type="radio"/> Class	Switch to table view Results Key
<input checked="" type="checkbox"/> Remdesivir	<input checked="" type="checkbox"/> Bedaquiline	<div style="background-color: #4CAF50; color: white; padding: 5px; text-align: center;"> No Interaction Expected </div>
<input checked="" type="checkbox"/> Enoxaparin (Covid-19 Adjunct Therapy)	<input checked="" type="checkbox"/> Levofloxacin	<div style="background-color: #f5f5f5; padding: 5px;"> Dexamethasone (low dose) </div>
<input checked="" type="checkbox"/> Dexamethasone (low dose)	<input checked="" type="checkbox"/> Clofazimine	<div style="background-color: #f5f5f5; padding: 5px;"> Bedaquiline </div>
<input type="checkbox"/> Tocilizumab	<input checked="" type="checkbox"/> Linezolid	<div style="background-color: #f5f5f5; padding: 5px;"> More Info </div>
	<input checked="" type="checkbox"/> Cycloserine	<div style="background-color: #4CAF50; color: white; padding: 5px; text-align: center;"> No Interaction Expected </div>



When expect problems with COVID19 + RR-TB?

COVID19 gastrointestinal symptoms

- Loss of appetite, diarrhea, anorexia, nausea, vomiting, abdominal discomfort, and gastrointestinal bleeding (risk for hypokalaemia, malnutrition, hypoalbuminemia)
- Liver function damage with elevated aspartate amino transaminase (AST), glutamate moderately amino transaminase (ALT), and total bilirubin

Cardiovascular complications associated with COVID-19 infection

- Acute myocarditis, acute myocardial infarction, acute heart failure and cardiomyopathy (23% and 33%), dysrhythmias (7%), venous thromboembolic event

Acute kidney injury and Covid19

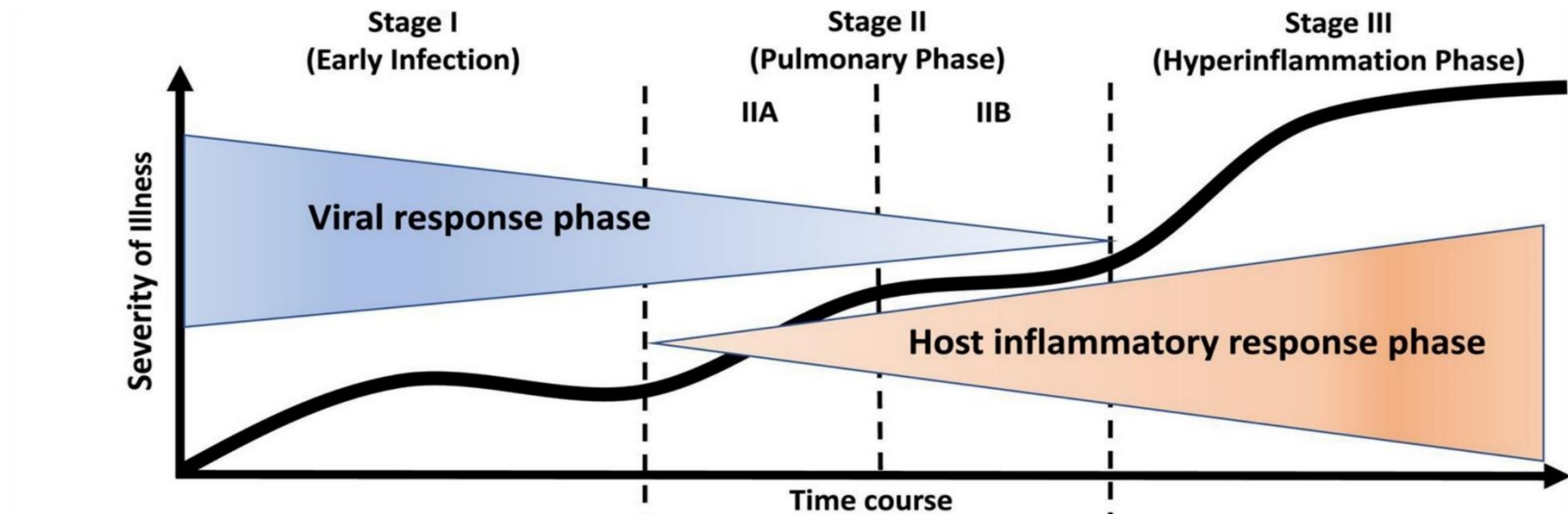
- AKI frequently occurs among patients suffering from COVID-19 and is most common among severely ill patients and among those that ultimately succumb to this disease. Incidence was lower in Asia (6.9%) compared to Europe (22.9%) and North America (34.6%).

Acute kidney injury and renal replacement therapy in COVID-19 patients: A systematic review and meta-analysis. Yang X et al. Int Immunopharmacol.2021 Jan; 90: 107159

COVID-19 and its effects on the digestive system. Ting-Ting Cao et al. World J Gastroenterol 2021 June 28; 27(24): 3502-3515 DOI: 10.3748/wjg.v27.i24.3502

Cardiovascular complications in COVID-19. Long B et al. J Emerg Med. 2020 Jul; 38(7): 1504–1507

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2): a Systemic Infection. Aleksandra Synowiec A et al. Clin Microbiol Rev.2021 Apr; 34(2): e00133-20



	Stage I (Early Infection)	Stage II (Pulmonary Phase)	Stage III (Hyperinflammation Phase)
Clinical Symptoms	Mild constitutional symptoms Fever >99.6°F Dry Cough, diarrhea, headache	Shortness of Breath Hypoxia (PaO ₂ /FiO ₂ ≤ 300mmHg)	ARDS SIRS/Shock Cardiac Failure
Clinical Signs	Lymphopenia, increased prothrombin time, increased D-Dimer and LDH (mild)	Abnormal chest imaging Transaminitis Low-normal procalcitonin	Elevated inflammatory markers (CRP, LDH, IL-6, D-dimer, ferritin) Troponin, NT-proBNP elevation

Antipyretics
Adequate nutrition
Rehydration
Rehabilitation

Neutralizing monoclonal antibodies

Remdesivir?

Oxygen therapy
Systemic corticosteroids
IL-6 receptor antagonist monoclonal antibody
Anti-coagulation



Thank you!