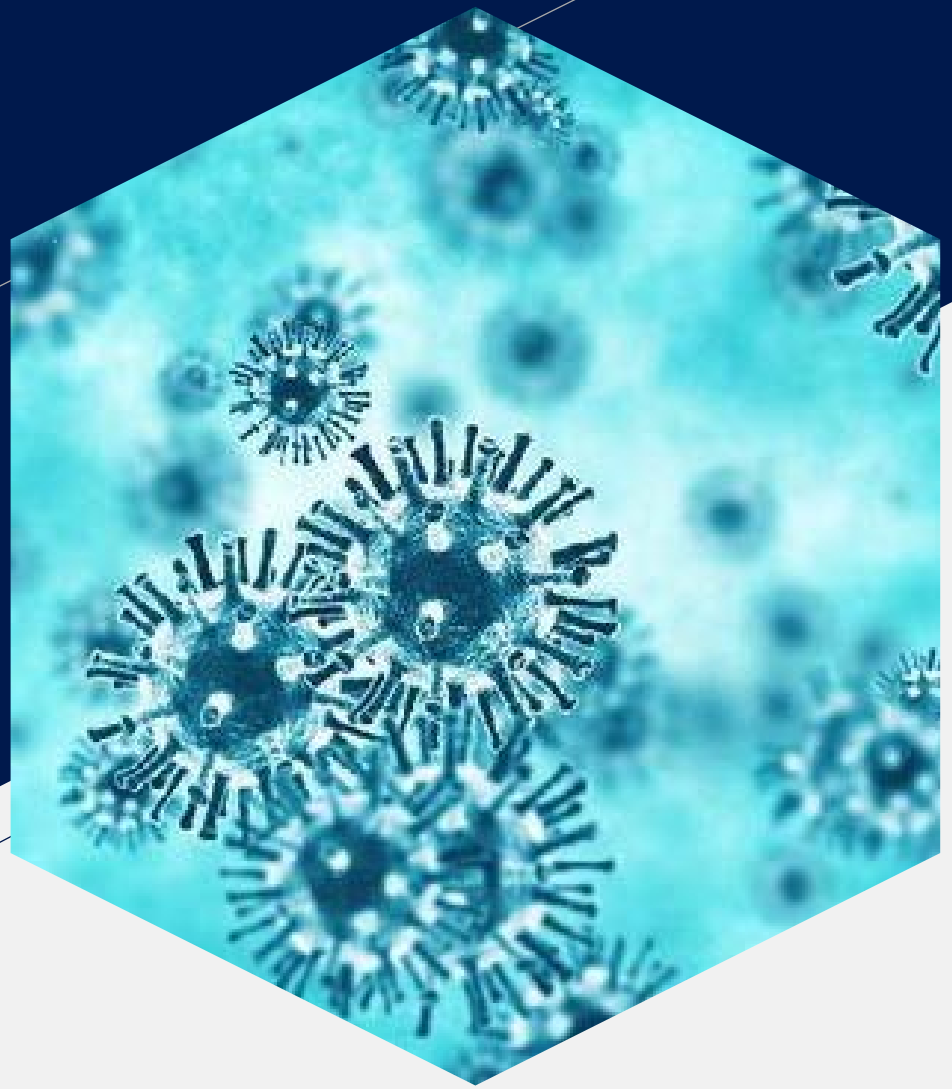

Clinical Management Summary and Guidelines of COVID-19

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1

Clinical Spectrum of SARS-CoV-2 Infection

COVID-19 Disease Severity - Adult

Asymptomatic

Mild

- Symptomatic without evidence of viral pneumonia or hypoxia

Moderate

- Clinical signs of pneumonia (fever, cough, dyspnoea, fast breathing), without signs of severe pneumonia
- SpO2 ≥90% (WHO), ≥94% (NIH), or 93-95% (Indonesia) on room air

Severe

- Clinical signs of pneumonia + either one of respiratory rate >30x/min; severe respiratory distress; or SpO2 <90% (WHO), <94% (NIH), or <93% (Indonesia) on room air

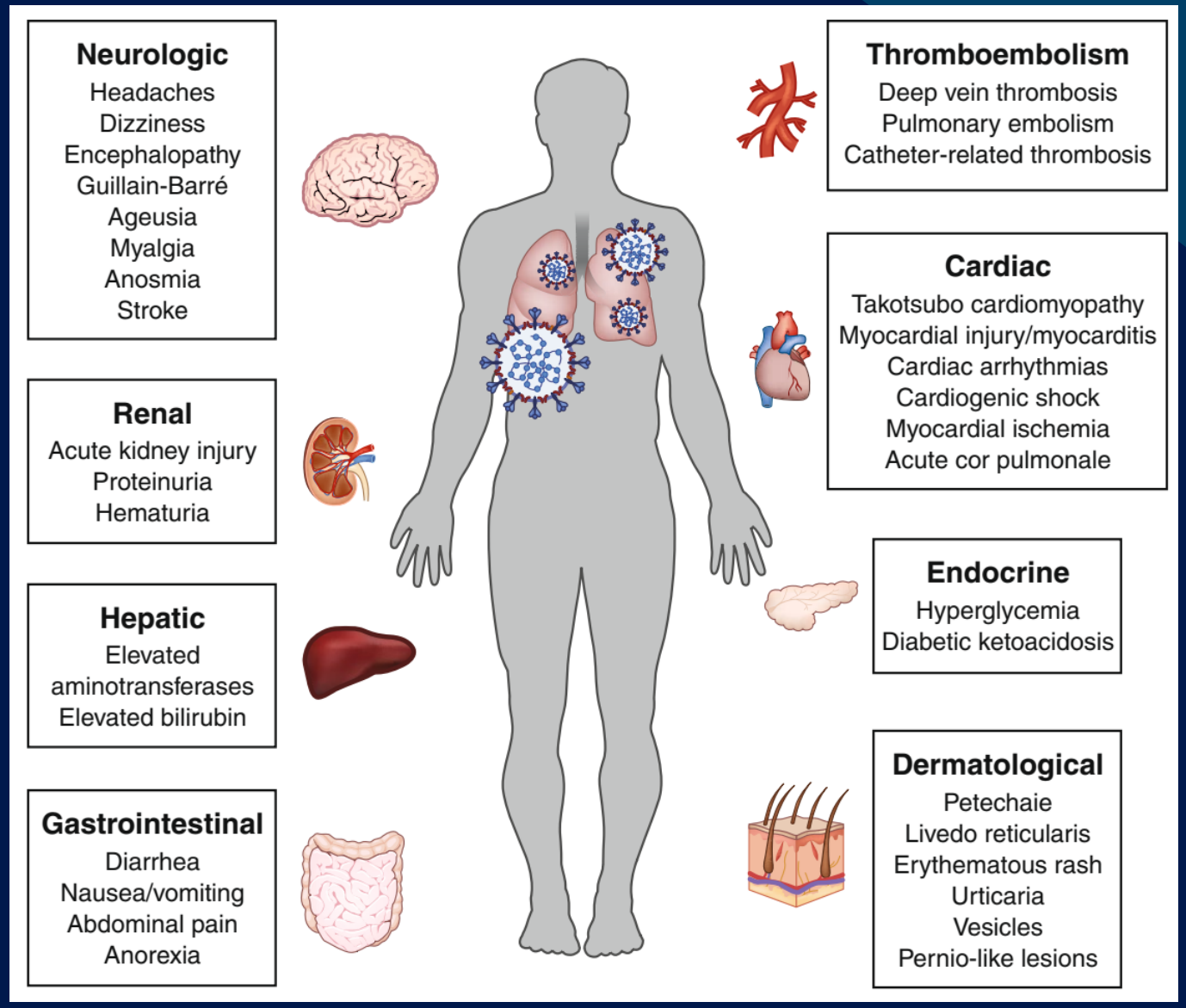
Critical

- ARDS, sepsis, septic shock, or acute thrombosis

WHO. COVID-19 Clinical Management: Living Guidance. Jan 25, 2021
KMK No. HK.01.07/MENKES/5671/2021

Extrapulmonary COVID-19

Clinical Manifestation



Gupta A, Madhavan MV, Sehgal K, Nair N, Mahajan S, Sehrawat TS, et al. Extrapulmonary manifestations of COVID-19. *Nat Med*. 2020 Jul;26(7):1017-32.

Large Clinical Trials to Study Repurposed Drugs

Solidarity Trial

RECOVERY Trial

PRINCIPLE Trial

ACTIV-6 Trial

WHO COVID-19 Solidarity Therapeutics Trial

Large, global randomized controlled trial for hospitalized severe or critical COVID-19

52 Countries

600 Hospitals

2,000 Researchers

14,200 Participants recruited

Repurposed drugs:

- Remdesivir
- Hydroxychloroquine
- Lopinavir
- Interferon
- Preliminary results: **little or no effect**

WHO Solidarity PLUS:

- Artesunate (ongoing)
- Imatinib (ongoing)
- Infliximab (ongoing)

https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov/solidarity-clinical-trial-for-covid-19-treatments

World Health Organization

RECOVERY

Randomised Evaluation of COVID-19 Therapy

International clinical trial
from the **University of Oxford**

44,908
Participants recruited

188
Active sites

For **hospitalized patients** with suspected or confirmed COVID-19

Repurposed drugs:

- **Dexamethasone**
- **Tocilizumab**
- **Casirivimab-Imdevimab**
- Aspirin
- Azithromycin
- Colchicine
- Convalescent plasma
- Hydroxychloroquine
- Lopinavir-Ritonavir
- Baricitinib (ongoing)
- Dimethyl fumarate (ongoing)
- High-dose vs standard corticosteroids (ongoing)
- Empagliflozin (ongoing)

https://www.recoverytrial.net/

RECOVERY: Dexamethasone, Tocilizumab, Casirivimab-Imdevimab

RECOVERY
Randomised Evaluation of COVID-19 Therapy

1. The RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with COVID-19. *N Engl J Med*. 2021;384:693-704.
2. RECOVERY Collaborative Group. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet*. 2021;397:1637-45.
3. RECOVERY Collaborative Group. Casirivimab and imdevimab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. https://doi.org/10.1101/2021.06.15.21258542

Dexamethasone[1]

28-day mortality between treatment and usual care group

- Patients **receiving IMV** at randomization: 29.3% vs 41.4%, ratio 0.64
- Patients **receiving oxygen** without IMV at randomization: 23.3% vs 26.2%, ratio 0.82
- Patients **without respiratory support** at randomization: 17.8% vs 14.0%, ratio 1.19
- **Overall** patients: 22.9% vs 25.7%, ratio 0.83

Useful for patients **receiving respiratory support**, with a dose of **6 mg once daily** for up to 10 d

Tocilizumab[2]

- 28-day mortality between groups: 31% vs 35%, ratio 0.85
- 28-day hospital discharge between groups: 57% vs 50%, ratio 1.22
- IMV needed or death in patients not receiving IMV at baseline, between groups: 35% vs 42%, ratio 0.84

The benefits were additional to the benefits of systemic corticosteroid

Dose: **400-800 mg IV single dose**. A second dose could be given when the patient's condition stays the same after 12-24 h

Casirivimab-Imdevimab[3]

28-day mortality between treatment and usual care group

- **Seronegative** patients: 24% vs 30%, ratio 0.80
- **Overall** patients: 20% vs 21%, ratio 0.94 (0.86-1.03), p=0.17

The benefit is greater on **seronegative patients**

Single dose of casirivimab 4 g + imdevimab 4 g

PRINCIPLE

Platform Randomised Trial of Treatments in the Community for Epidemic and Pandemic Illnesses

UK-wide clinical study from the **University of Oxford**

- For **non-hospitalized patients**, preventing hospital admission

Repurposed drugs:

- **Inhaled budesonide**
- Azithromycin
- Doxycycline
- Colchicine
- Ivermectin (ongoing)
- Favipiravir (ongoing)

7,538

Participants recruited

https://www.principletrial.org/

PRINCIPLE
Platform Randomised Trial of Treatments in the Community for Epidemic and Pandemic Illnesses

PRINCIPLE: Inhaled **Budesonide**

Early treatment with inhaled budesonide **shortens recovery time by 3 days** in ambulatory, high risk COVID-19 patients

Participants: >65 years (or >50 years with comorbidities), self-isolation at home, with symptoms for 14 days

Treatment group: inhaled budesonide 2x800µg for 14 days + usual care

Control group: usual care

Results:

- **Reduction of time to first self-reported recovery by 2.94 days** (11.8 d vs 14.1 d), with high probability of superiority → **significant result**
- Reduction of hospital admission or death outcome rate by 2.0% (6.8% vs 8.8%), with low probability of superiority → nonsignificant result

Yu LM, Bafadhel M, Dorward J, Hayward G, Saville BR, Gbinigie O, et al. Inhaled budesonide for COVID-19 in people at high risk of complications in the community in the UK (PRINCIPLE): a randomised, controlled, open-label, adaptive platform trial. *Lancet*. 2021;398:843-55.

ACTIV-6

Accelerating COVID-19 Therapeutic Interventions and Vaccines

US nationwide double-blind study

- For **non-hospitalized** mild-to-moderate COVID-19, preventing hospital admission

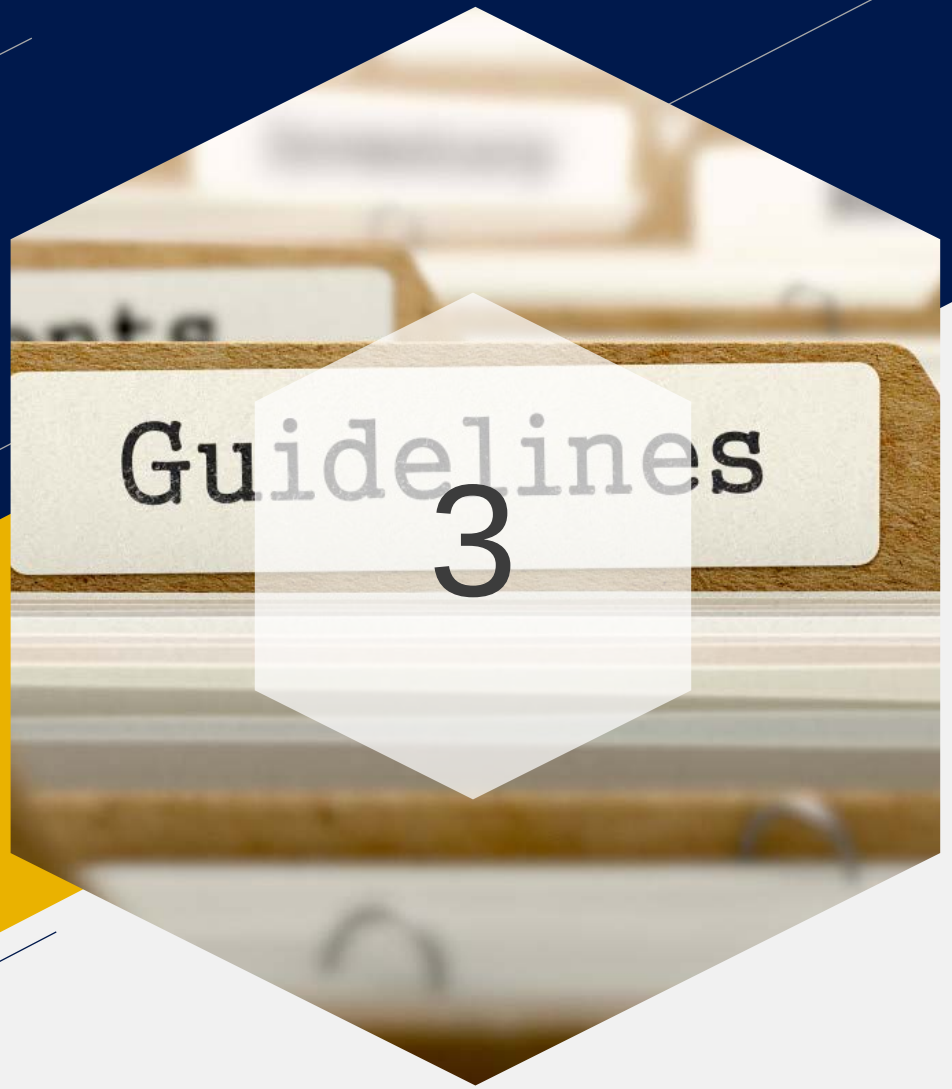
Repurporsed drugs:

- Fluvoxamine (ongoing)
- Fluticasone (ongoing)
- Ivermectin (ongoing)

15,000

Participants needed

https://activ6study.org/



3

Current Management Summary of Available Guidelines

COVID-19 Pharmacological Therapy: Summary

Indonesian MoH (KMK No. HK.01.07/MENKES/5671/2021)

This guideline was made based on the **recommendations from 5 professional organizations**:

- Indonesian Society of Respirology (PDPI)
- Indonesian Society of Internal Medicine (PAPDI)
- Indonesian Heart Association (PERKI)
- Indonesian Society of Anesthesiologists and Intensive Therapy (PERDATIN)
- Indonesian Pediatric Society (IDAI)

Severity	Therapy
Asymptomatic	• Vitamin C, D • Supportive medications • Management of comorbidities and complications
Mild	• Vitamin C, D • Favipiravir • Symptomatic medications • Supportive medications • Management of comorbidities and complications
Moderate	• Vitamin C, D • Favipiravir or Remdesivir • LMWH/UFH anticoagulants based on doctor's evaluation • Symptomatic medications • Management of comorbidities and complications
Severe and Critical	• Vitamin C, B1, D • Favipiravir or Remdesivir • Corticosteroids • Anti IL-6 (Tocilizumab/Sarilumab) • Antibiotics (suspected bacterial co-infection) • LMWH/UFH anticoagulants based on doctor's evaluation • Shock management (if needed) • Management of comorbidities and complications

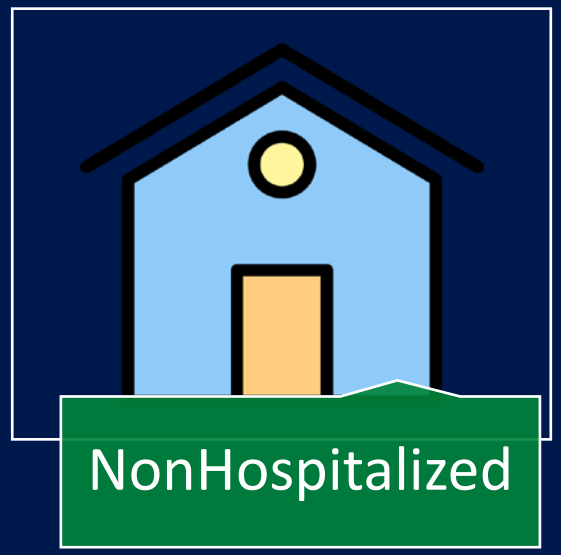
COVID-19 Pharmacological Therapy: Summary

NIH. COVID-19 Treatment Guidelines. October 27, 2021

Severity	Recommendations
Not Requiring Supplemental Oxygen	• Remdesivir can be considered for patients at high risk of disease progression • Prophylactic dose anticoagulant or antiplatelet therapy
Requiring Supplemental Oxygen	• Remdesivir OR Dexamethasone (or equivalent)+Remdesivir OR Dexamethasone* (or equivalent) *Baricitinib or Tocilizumab can be added to Dexamethasone • Prophylactic dose anticoagulant or antiplatelet therapy
Requiring High-Flow Oxygen Device or NIV	• Dexamethasone (or equivalent) OR Dexamethasone (or equivalent)+Remdesivir • Baricitinib/Tofacitinib OR IV Tocilizumab/Sarilumab (for recently hospitalized patients with rapidly increasing oxygen needs and systemic inflammation) • Prophylactic dose anticoagulant or antiplatelet therapy
Requiring IMV or ECMO	• Dexamethasone (or equivalent) OR Dexamethasone (or equivalent)+IV Tocilizumab/Sarilumab • Prophylactic dose anticoagulant or antiplatelet therapy

COVID-19 Pharmacological Therapy: Summary

NIH. COVID-19 Treatment Guidelines. October 27, 2021



Severity	Recommendations
Not Requiring Hospitalization or Supplemental Oxygen	• Bamlanivimab+Etesevimab OR Casirivimab+Imdevimab OR Sotrovimab (for patients at high risk of disease progression) • Symptomatic treatment
Discharged from Hospital, Stable Condition, Not Requiring Supplemental Oxygen	• Symptomatic treatment • Discontinue Remdesivir, Dexamethasone, or Baricitinib after discharge
Discharged from Hospital, Stable Condition, Requiring Supplemental Oxygen	• Oral Dexamethasone for the duration of supplemental oxygen, with careful monitoring, not exceeding 10 days • Symptomatic treatment • Remdesivir and Baricitinib can be continued or discontinued
Discharged from Hospital (ED) Despite New or Increasing Need for Supplemental Oxygen	• Oral Dexamethasone for the duration of supplemental oxygen, with careful monitoring, not exceeding 10 days • Symptomatic treatment • Remdesivir can be continued or discontinued

COVID-19 Pharmacological Therapy: Summary

WHO. Guideline Therapeutics and COVID-19: Living Guideline. Sep 24, 2021

WHO. COVID-19 Clinical Management: Living Guidance. Jan 25, 2021

Severity	Recommendations
Non-severe	• Casirivimab and Imdevimab (conditional to high risk patients) • Symptomatic treatment • Antibiotics only for bacterial co-infection • Thromboprophylaxis dose of anticoagulation (hospitalized patients)
Severe (SatO2 <90%, signs of pneumonia and severe respiratory distress)	• Casirivimab and Imdevimab (seronegative patients) • IL-6 receptor blockers (Tocilizumab or Sarilumab) • Corticosteroids • Antibiotics based on clinical judgment, host factors, and local epidemiology • Thromboprophylaxis dose of anticoagulation • Awake prone positioning
Critical (requires life sustaining treatment, ARDS, sepsis, septic shock)	• Casirivimab and Imdevimab (seronegative patients) • IL-6 receptor blockers (Tocilizumab or Sarilumab) • Corticosteroids • Antibiotics based on clinical judgment, host factors, and local epidemiology • Thromboprophylaxis dose of anticoagulation • Vasopressors (for shock) • Awake prone positioning (12-16 hours daily for severe ARDS)

4

Oxygenation and Ventilation Therapy

Hypoxemia in COVID-19

- COVID-19 disease usually deteriorates approximately after 1 week of the onset of symptoms
- Most common symptom: **dyspnea** and often accompanied by **hypoxemia**
- Severe and critical COVID-19 patients require **supplemental oxygen** and should be monitored

NIH. COVID-19 Treatment Guidelines. October 27, 2021

Goal of Oxygenation

The optimal SpO_2 in adults with COVID-19 with supplemental oxygen therapy is uncertain

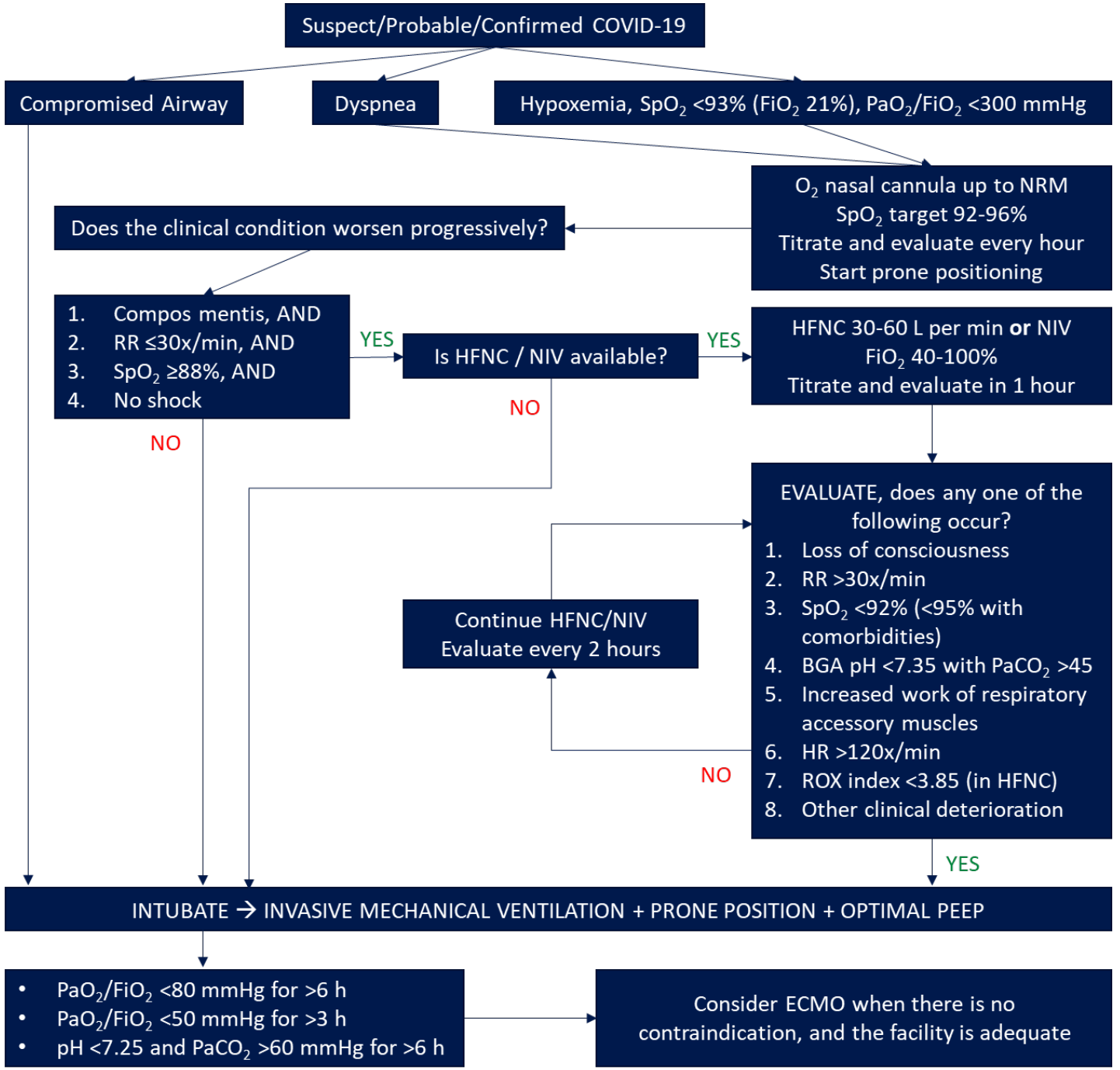
Different goals from various guidelines

Population	WHO	NIH	Indonesian MoH
Patients with emergency signs during resuscitation (unstable)	≥94%	92-96%	92-96%
Patients with emergency signs during resuscitation (unstable, pregnant women)			>94%
Hypoxemic patients without emergency signs (stable)	>90%		92-96%
Hypoxemic patients without emergency signs (stable, pregnant women)	≥92-95%		>94%

1. WHO. COVID-19 Clinical Management: Living Guidance. Jan 25, 2021
2. NIH. COVID-19 Treatment Guidelines. October 27, 2021
3. KMK No. HK.01.07/MENKES/5671/2021

Oxygenation and Ventilation Therapy Algorithm for COVID-19 Patients

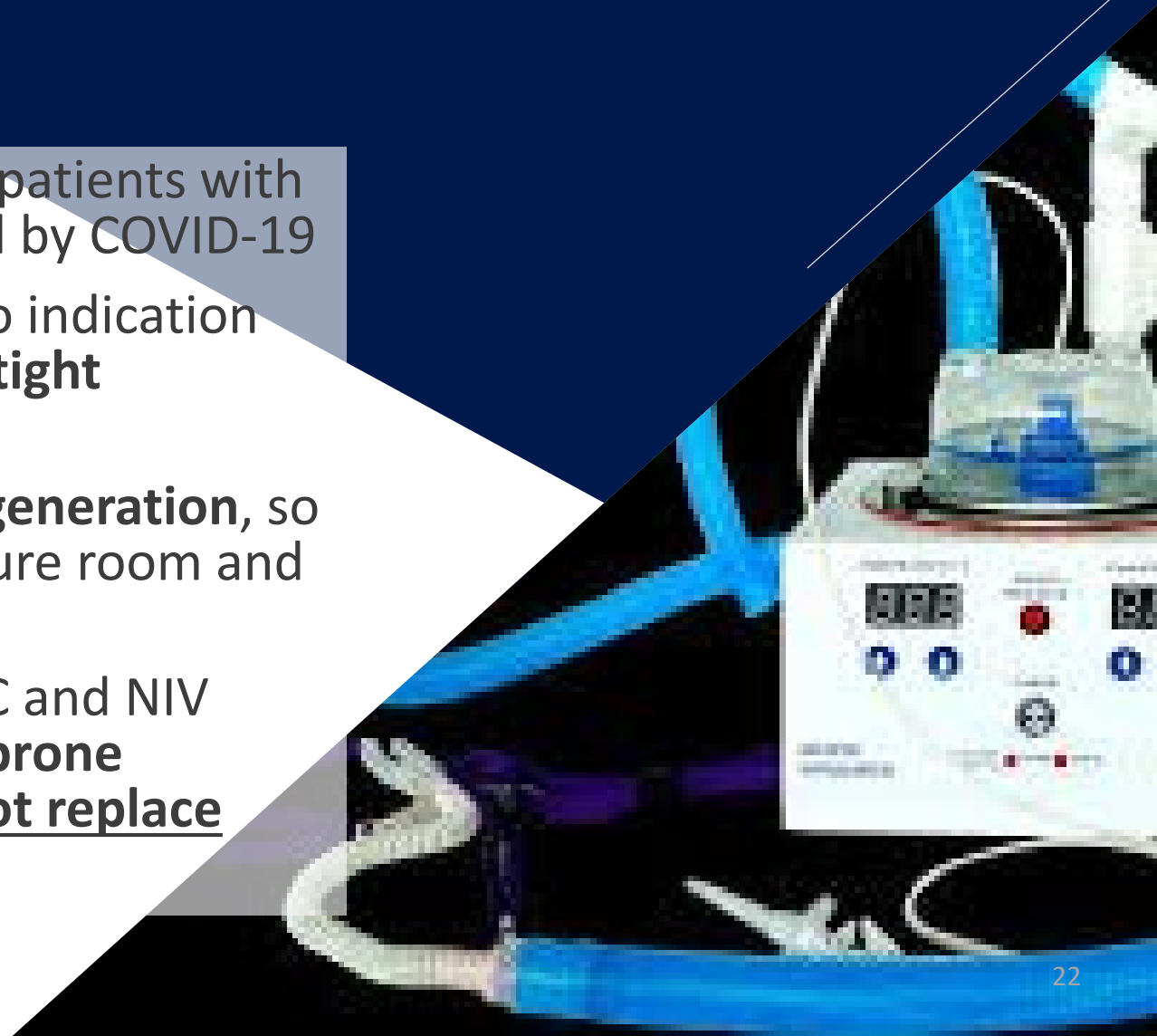
Adapted from Indonesian MoH Guideline



KMK No. HK.01.07/MENKES/5671/2021

HFNC and NIV

- **HFNC is recommended over NIV** for adult patients with acute hypoxemic respiratory failure caused by COVID-19
- When HFNC is not available and there is no indication for intubation, **NIV is recommended with tight monitoring**
- Both **HFNC and NIV are at risk of aerosol generation**, so they should be applied in a negative pressure room and with standard PPE
- For severely and critically ill patients, HFNC and NIV therapy should be **combined with awake prone positioning**. Although this method **does not replace intubation** when the indications are met



1. NIH. COVID-19 Treatment Guidelines. October 27, 2021
2. KMK No. HK.01.07/MENKES/5671/2021
3. WHO. COVID-19 Clinical Management: Living Guidance. Jan 25, 2021

Invasive Mechanical Ventilation

Recommended targets for adults with COVID-19 and ARDS fulfilling indication for intubation:

- **Low tidal volume (VT) ventilation**: 4-8 mL/kgBW
- **Plateau pressures** of <30 cmH_2O
- Target **respiratory rate** of 18-25 x/min
- **Prone ventilation** for 12-16 hours per day for patients with severe ARDS (PaO2/FiO2 < 150) and refractory hypoxemia despite optimized ventilation
- **Higher PEEP strategy** for moderate to severe ARDS, with monitoring
- A **conservative fluid strategy**

1. NIH. COVID-19 Treatment Guidelines. October 27, 2021
2. KMK No. HK.01.07/MENKES/5671/2021
3. WHO. COVID-19 Clinical Management: Living Guidance. Jan 25, 2021

5

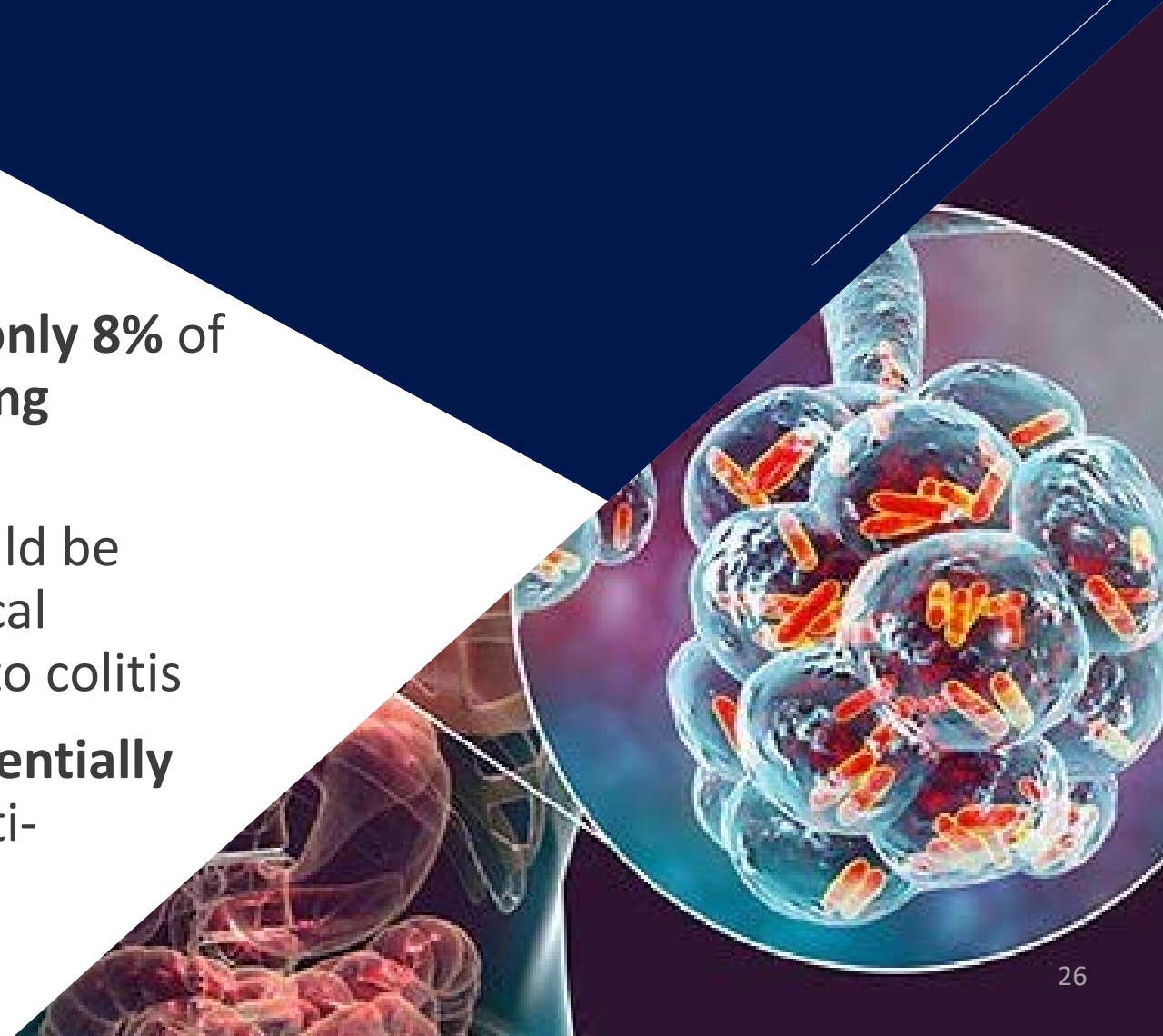
Rational **Antibiotics and Antithrombotic** Therapy

Rational **Antibiotics** and Antithrombotic Therapy

Secondary Bacterial Infections

In hospitalized COVID-19 patients

- A recent systematic review reported that **only 8%** of hospitalized COVID-19 patients **experiencing bacterial/fungal co-infections**
- **One adverse reaction** of antibiotic use could be ***Clostridioides difficile*** **infection,** with clinical disease ranging from diarrhoea and fever to colitis
- **Excessive use of antibiotics** could also **potentially cause global threat** of the increase of multi-resistant pathogens



1. WHO. COVID-19 Clinical Management: Living Guidance. Jan 25, 2021
2. KMK No. HK.01.07/MENKES/5671/2021

The Use of Antimicrobials for Bacterial Co-infections

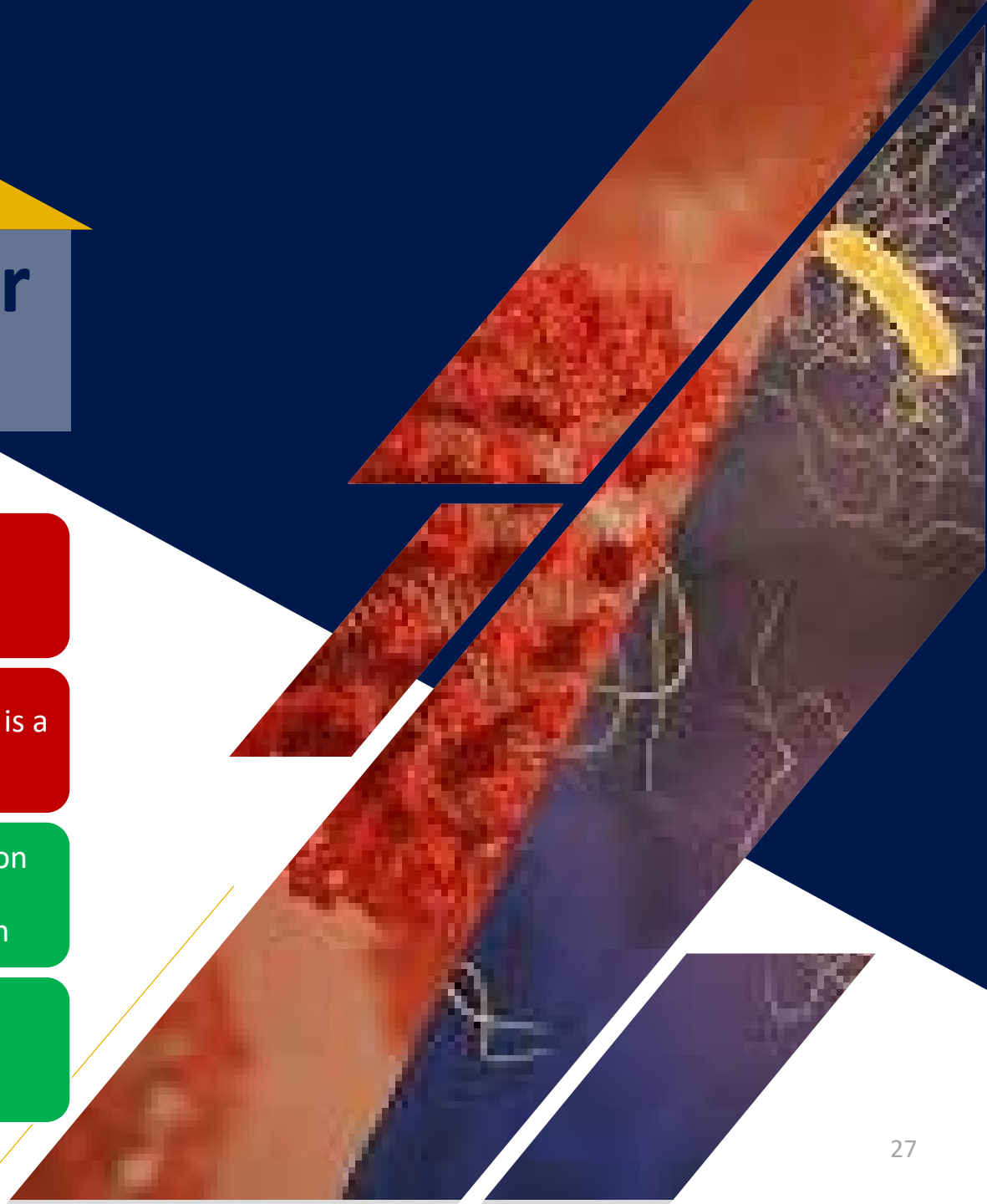
Recommendation from WHO

It is **not recommended** to use antibiotic for mild COVID-19

It is **not recommended** to use antibiotic for moderate COVID-19 unless there is a suspected/confirmed bacterial infection

It is **recommended** to use empiric antimicrobials for severe COVID-19 based on clinical judgement, host factors, and local epidemiology, ideally with blood cultures obtained first. The therapy should be assessed daily for de-escalation

Treatment duration should be as short as possible, generally 5-7 days



WHO. COVID-19 Clinical Management: Living Guidance. Jan 25, 2021

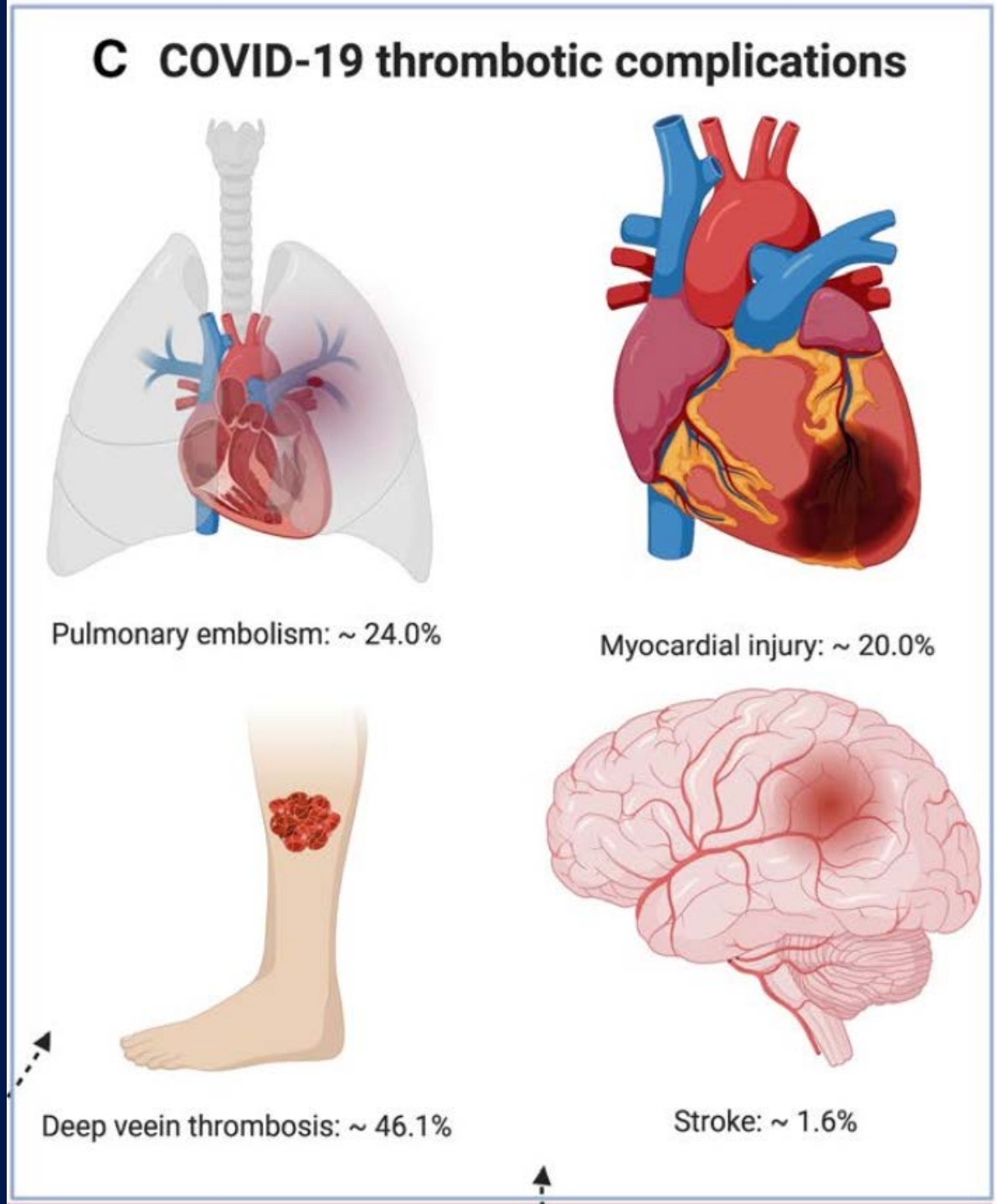
Rational Antibiotics and **Antithrombotic** Therapy

Thrombotic Complications of COVID-19

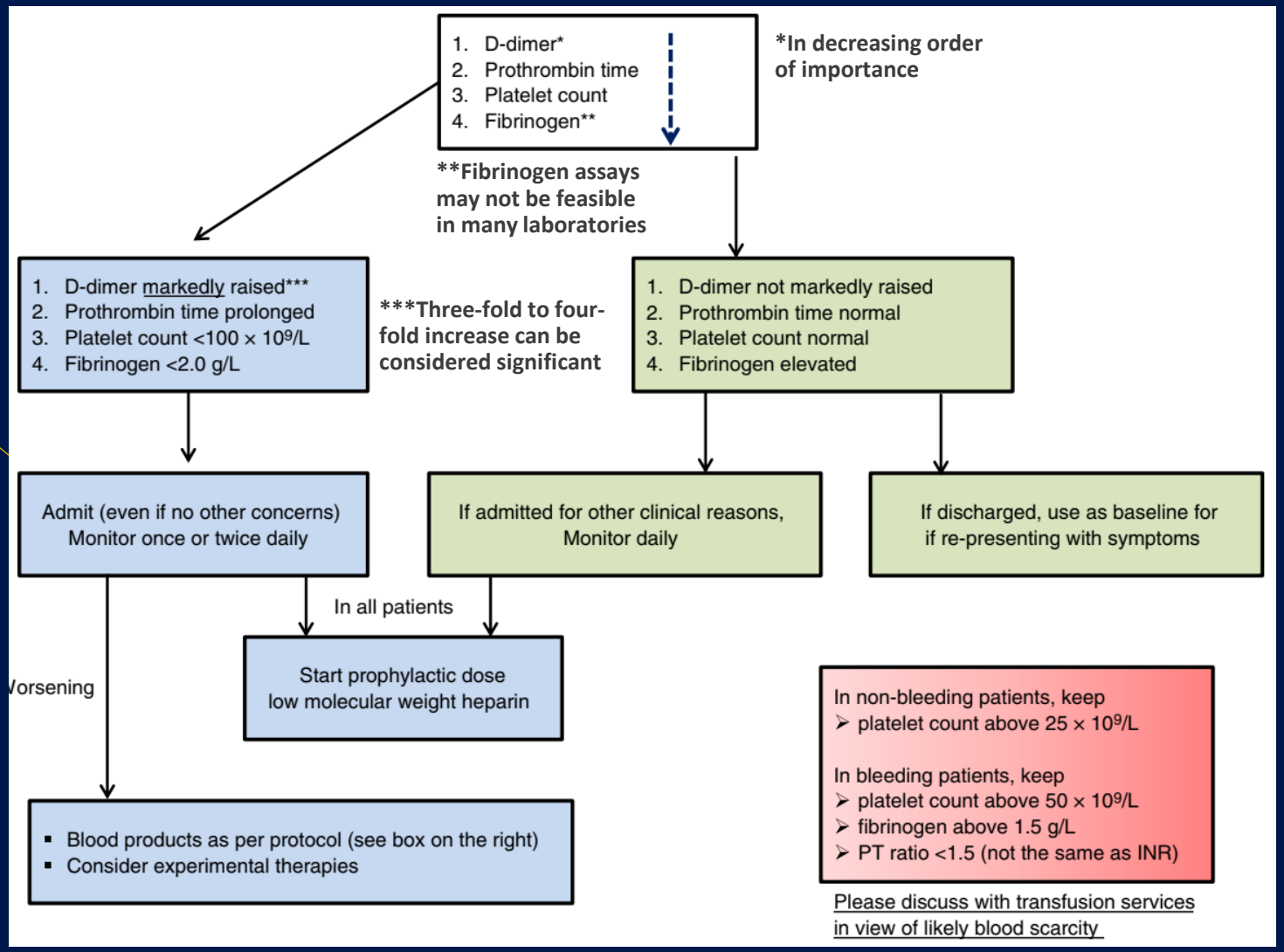
The incidence of venous thromboembolism (VTE) and arterial thromboembolism in hospitalized severe and critical COVID-19 patients is around 25-27% and 3.7% respectively. While the overall VTE prevalence in hospitalized patients is 14.1%

This high risk of VTE is consistent with the increased rates in other severe viral pneumonias, such as H1N1 or MERS-CoV

1. Ortega-Paz L, Capodanno D, Montalescot G, Angiolillo DJ. Coronavirus disease 2019-associated thrombosis and coagulopathy: review of the pathophysiological characteristics and implications for antithrombotic management. *J Am Heart Assoc.* 2021 Feb 2;10(3):e019650.
2. Spyropoulos AC, Levy JH, Ageno W, Connors JM,, Hunt BJ, Iba T, et al. Scientific and standardization committee communication: clinical guidance on the diagnosis, prevention, and treatment of venous thromboembolism in hospitalized patients with COVID-19. J Thromb Haemost. 2020;18:1859-65.
3. https://www.covid19treatmentguidelines.nih.gov/therapies/antithrombotic-therapy/



COVID-19 Coagulopathy Management Algorithm



- **D-dimers, prothrombin time, and platelet count** measurement is recommended for COVID-19 patients at admission and inhospital monitoring
- Antithrombotic **contraindications**: active/history of bleeding, heparin allergy, platelet count <25,000/mm^3, severe liver impairment
- **Standard-of-care objective testing** (ie, computed tomography pulmonary angiogram, ventilation/perfusion scan, MRI venography, Doppler USG) should be done to **patients with clinical suspicion** for the **diagnosis of VTE**
- **Routine VTE screening with bedside Doppler USG of lower extremities** to all hospitalized patients **is not recommended**

1. Thachil J, Tang N, Gando S, Falanga A, Cattaneo M, Levi M, et al. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. *J Thromb Haemost*. 2020;18:1023-6.
2. KMK No. HK.01.07/MENKES/5671/2021
3. Spyropoulos AC, Levy JH, Ageno W, Connors JM,, Hunt BJ, Iba T, et al. Scientific and standardization committee communication: clinical guidance on the diagnosis, prevention, and treatment of venous thromboembolism in hospitalized patients with COVID-19. J Thromb Haemost. 2020;18:1859-65.

Antithrombotic Therapy for Outpatient COVID-19

Based on the ACTIV-4B Trial and NIH Guideline

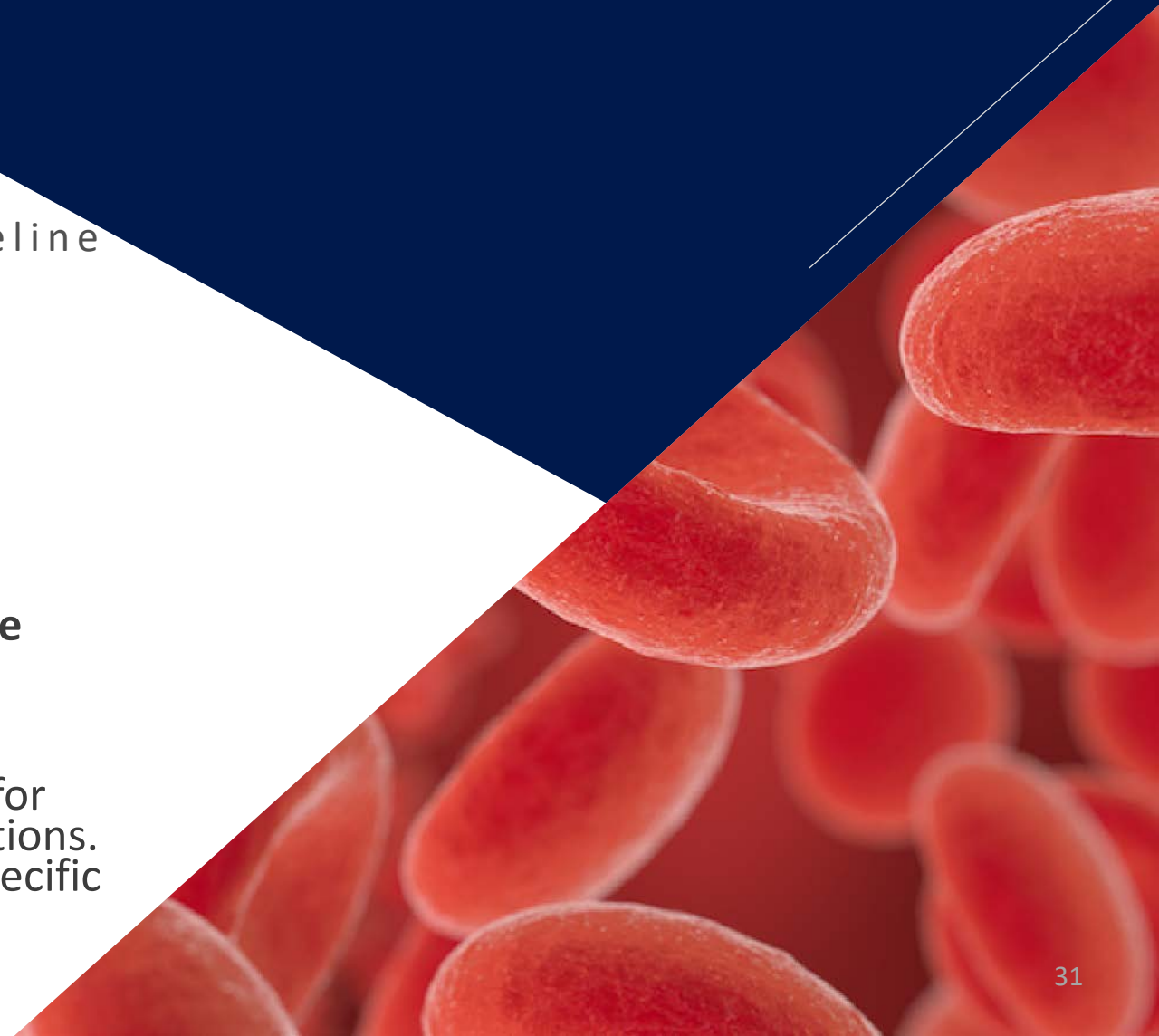
ACTIV-4B Trial: oral doses of:

- Aspirin 1x81 mg
- Apixaban 2x2.5 mg (prophylactic dose)
- Apixaban 2x5 mg (therapeutic dose)

did not reduce the rate of clinical outcomes

Anticoagulants and antiplatelet therapy **should not be initiated** for the prevention of VTE.

Patients who are receiving antithrombotic therapies for underlying conditions **should continue** these medications. The therapy **should not be initiated** without other specific indications

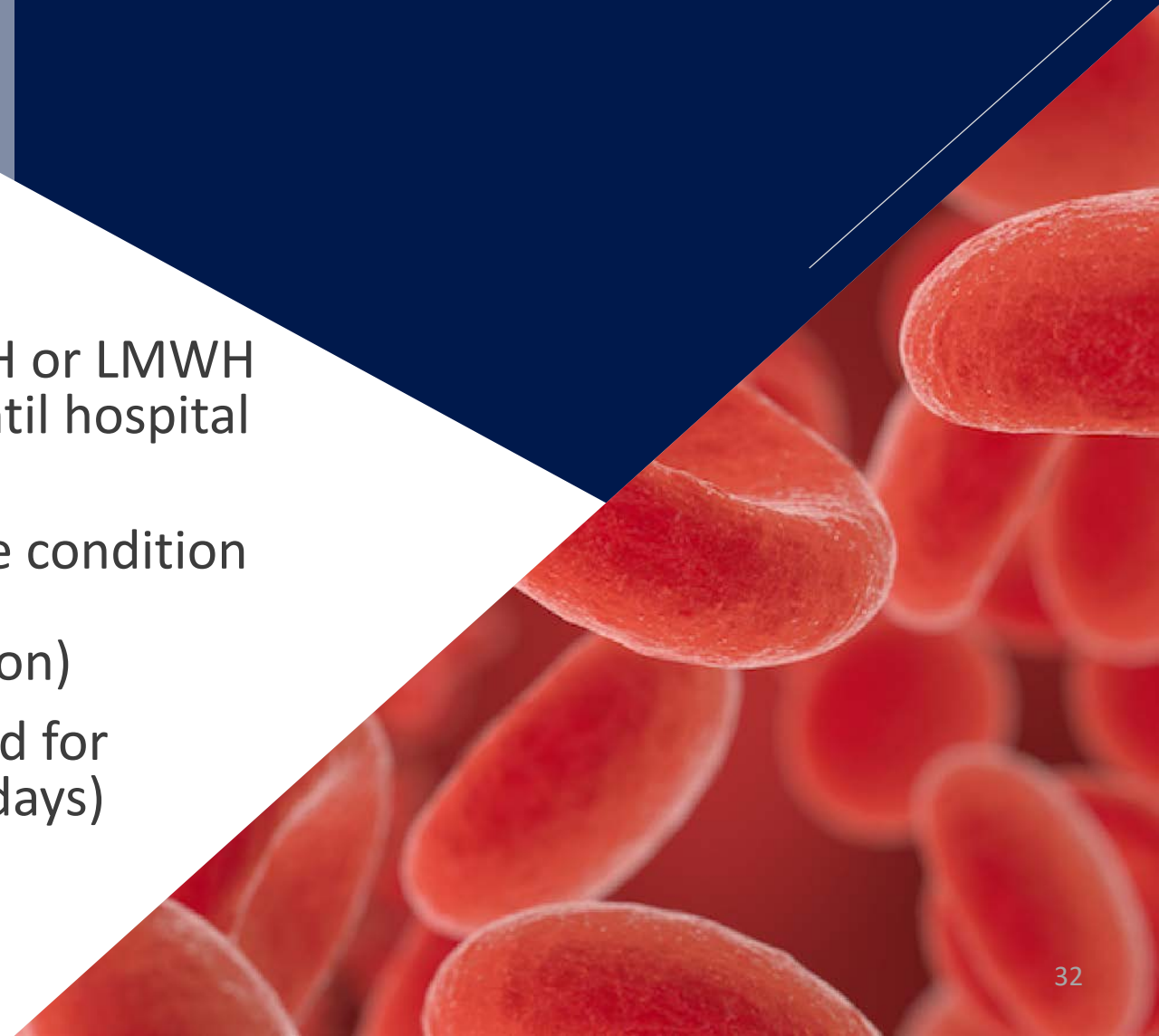


Connors JM, Brooks MM, Sciurba FC, Krishnan JA, Bledsoe JR, Kindzelski A, et al. Effect of antithrombotic therapy on clinical outcomes in outpatients with clinically stable symptomatic COVID-19. *JAMA*. 2021;326(17):1703-12.
https://www.covid19treatmentguidelines.nih.gov/therapies/antithrombotic-therapy/

VTE Prophylaxis for Non-ICU Inpatient COVID-19

Based on ISTH Guideline

- Standard **thromboprophylaxis dose** of UFH or LMWH can be used (LMWH is preferred), given until hospital discharge
- The dose **should be modified** based on the condition of the individual (body weight, severe thrombocytopenia, worsening renal function)
- Post-discharge dosing should be considered for patients with high VTE risk criteria (14-30 days)



Spyropoulos AC, Levy JH, Ageno W, Connors JM,, Hunt BJ, Iba T, et al. Scientific and standardization committee communication: clinical guidance on the diagnosis, prevention, and treatment of venous thromboembolism in hospitalized patients with COVID-19. J Thromb Haemost. 2020;18:1859-65.

UFH or LMWH?

Unfractionated Heparin (UFH)

- Twice or thrice daily
- Rapid reversibility
- Greater risk of heparin-induced thrombocytopenia
- Can be used in renal dysfunction

Low-Molecular-Weight Heparin (LMWH)

- Once daily
- Slower reversibility
- Less risk of heparin-induced thrombocytopenia
- Contraindicated for renal dysfunction

1. Spyropoulos AC, Levy JH, Ageno W, Connors JM,, Hunt BJ, Iba T, et al. Scientific and standardization committee communication: clinical guidance on the diagnosis, prevention, and treatment of venous thromboembolism in hospitalized patients with COVID-19. J Thromb Haemost. 2020;18:1859-65.
2. WHO. COVID-19 Clinical Management: Living Guidance. Jan 25, 2021

VTE Prophylaxis for ICU Inpatient COVID-19

Based on ISTH Guideline

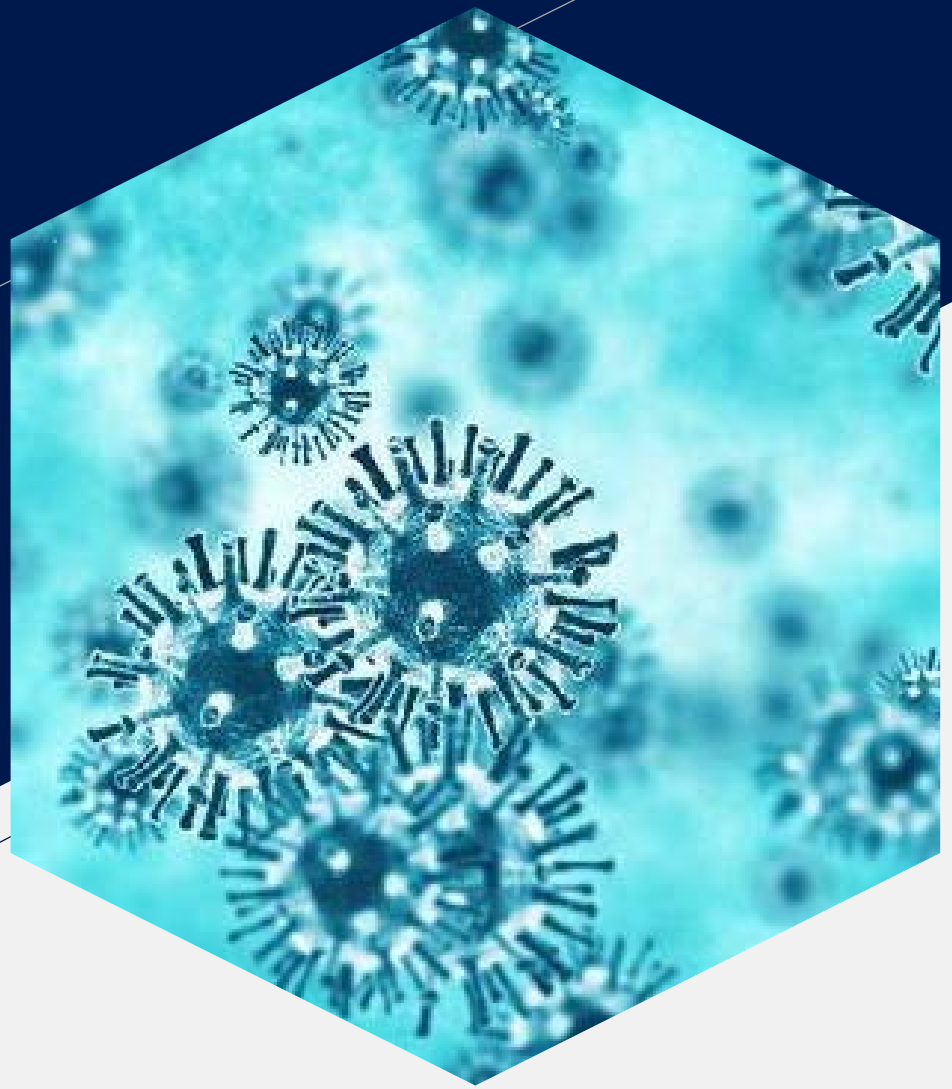
- Standard **thromboprophylaxis dose** of UFH or LMWH can be used, given until hospital discharge
- **Multimodal strategies** (anticoagulant + mechanical prophylaxis such as intermittent pneumonic compression device) should be considered in critically ill or immobile patients
- Mechanical thromboprophylaxis can be considered when **anticoagulants are contraindicated**
- Post-discharge dosing should be considered for patients with low risk of bleeding high risk of VTE (14-30 days)

Spyropoulos AC, Levy JH, Ageno W, Connors JM,, Hunt BJ, Iba T, et al. Scientific and standardization committee communication: clinical guidance on the diagnosis, prevention, and treatment of venous thromboembolism in hospitalized patients with COVID-19. J Thromb Haemost. 2020;18:1859-65.
https://www.covid19treatmentguidelines.nih.gov/therapies/antithrombotic-therapy/

Suggested Thromboprophylaxis Dose of Anticoagulants

Drugs	WHO		Indonesian MoH		
	Dose	Monitoring	Moderate/Severe Dose	Critical Dose	Monitoring
Enoxaparin	• 1x40 mg SC (standard) • 2x40 mg SC (obese)	Not needed	• 1x40 mg SC	• 2x40 mg SC (CrCl ≥ 30 mL/min) • 2x0.5 mg/kgBW SC (obese, CrCl ≥ 30 mL/min); max 2x100 mg • 2x30 mg SC (BW under 60 kg, CrCl ≥ 30 mL/min)	**In line with ISTH recommendation** **Monitor (in decreasing order of importance):** 1. D-dimer 2. PT 3. Platelet count 4. Fibrinogen **In non-bleeding patients:** • Keep platelet count >25x10^9/L or 25,000/mm^3 **In bleeding patients:** • Keep platelet count >50x10^9/L or 50,000/mm^3 • Keep fibrinogen >1.5g/L • Keep PT ratio <1.5 (not the same as INR)
Unfractionated Heparin (UFH)	• 2x5,000 units SC (standard) • 2x7,500 units or 3x5,000 units SC (obese)	Platelet count after 5-7 days	• 2x5,000 units SC	• 3x7,500 units SC (standard) • 3x10,000 units SC (obese)	
Tinzaparin	• 1x4,500 units (standard) • 1x9,000 units (obese)	Not needed	NA	NA	
Dalteparin	• 1x5,000 units (standard) • 2x5,000 units (obese)	Not needed	NA	NA	
Fondaparinux	• 1x2.5 mg SC	Not needed	Prophylaxis dose can be considered	Not recommended, as patients usually have kidney injury	

1. WHO. COVID-19 Clinical Management: Living Guidance. Jan 25, 2021
2. KMK No. HK.01.07/MENKES/5671/2021



Thank You