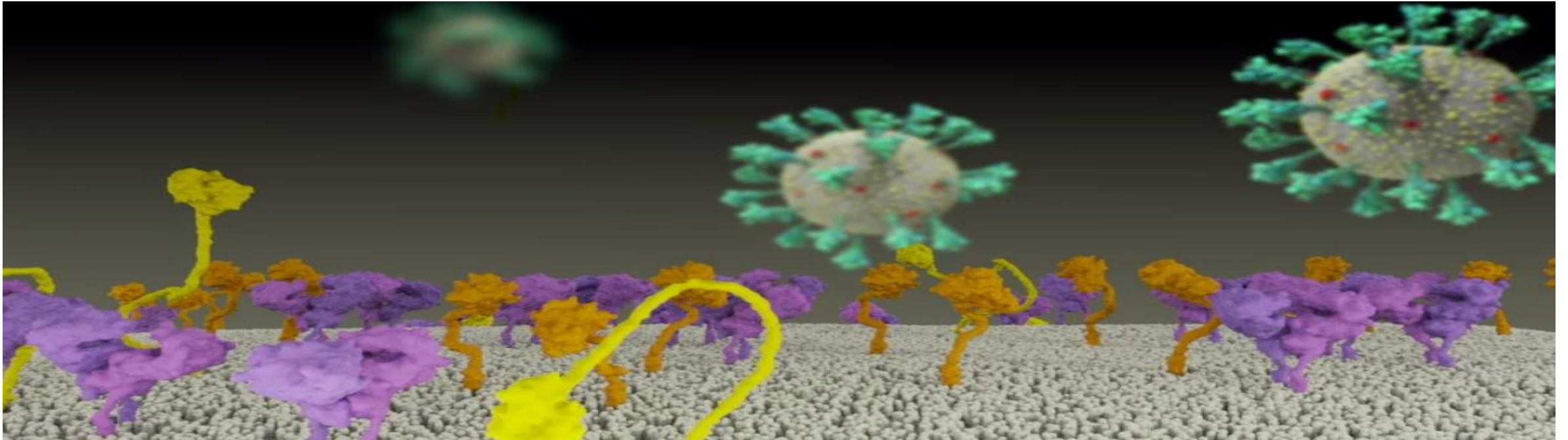




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CANBERRA HOSPITAL
AND HEALTH SERVICES



EXTRA-PULMONARY MANIFESTATIONS OF COVID-19

MARK POLIZZOTTO

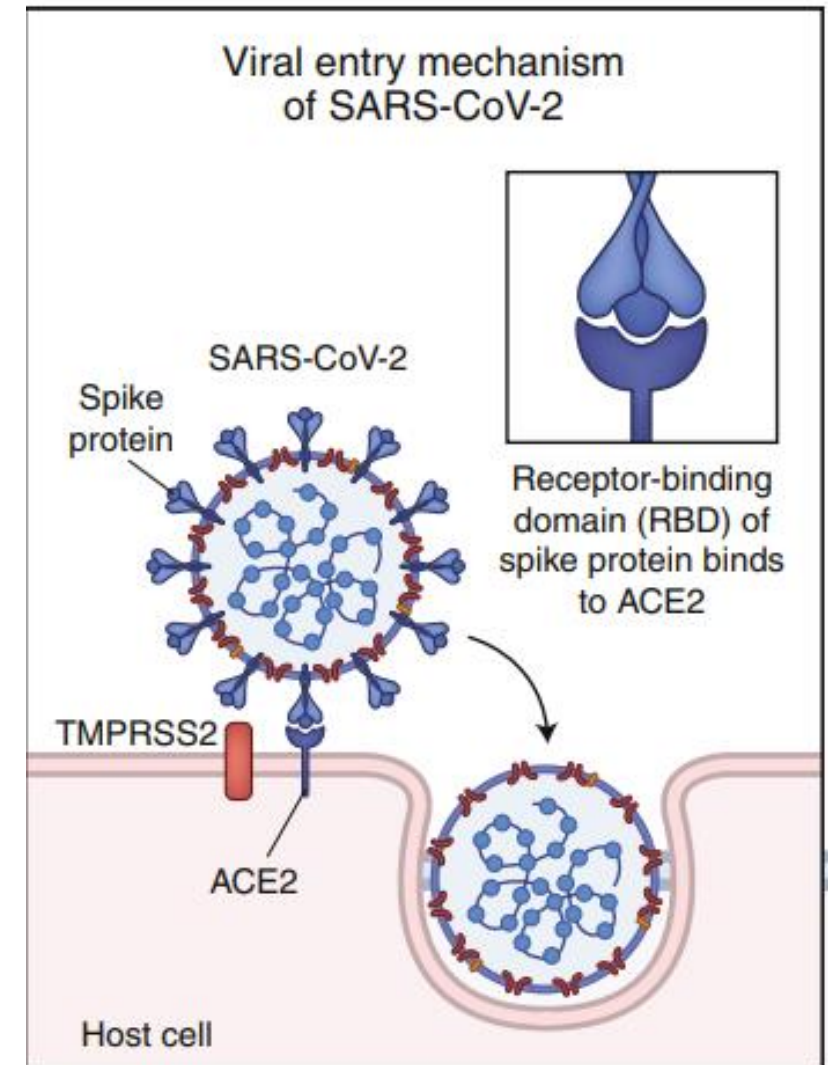
ANU CHOIR CLINICAL HUB FOR INTERVENTIONAL RESEARCH, JOHN CURTIN SCHOOL OF MEDICAL RESEARCH, THE AUSTRALIAN NATIONAL UNIVERSITY
CANBERRA REGIONAL CANCER CENTRE, THE CANBERRA HOSPITAL

OUTLINE

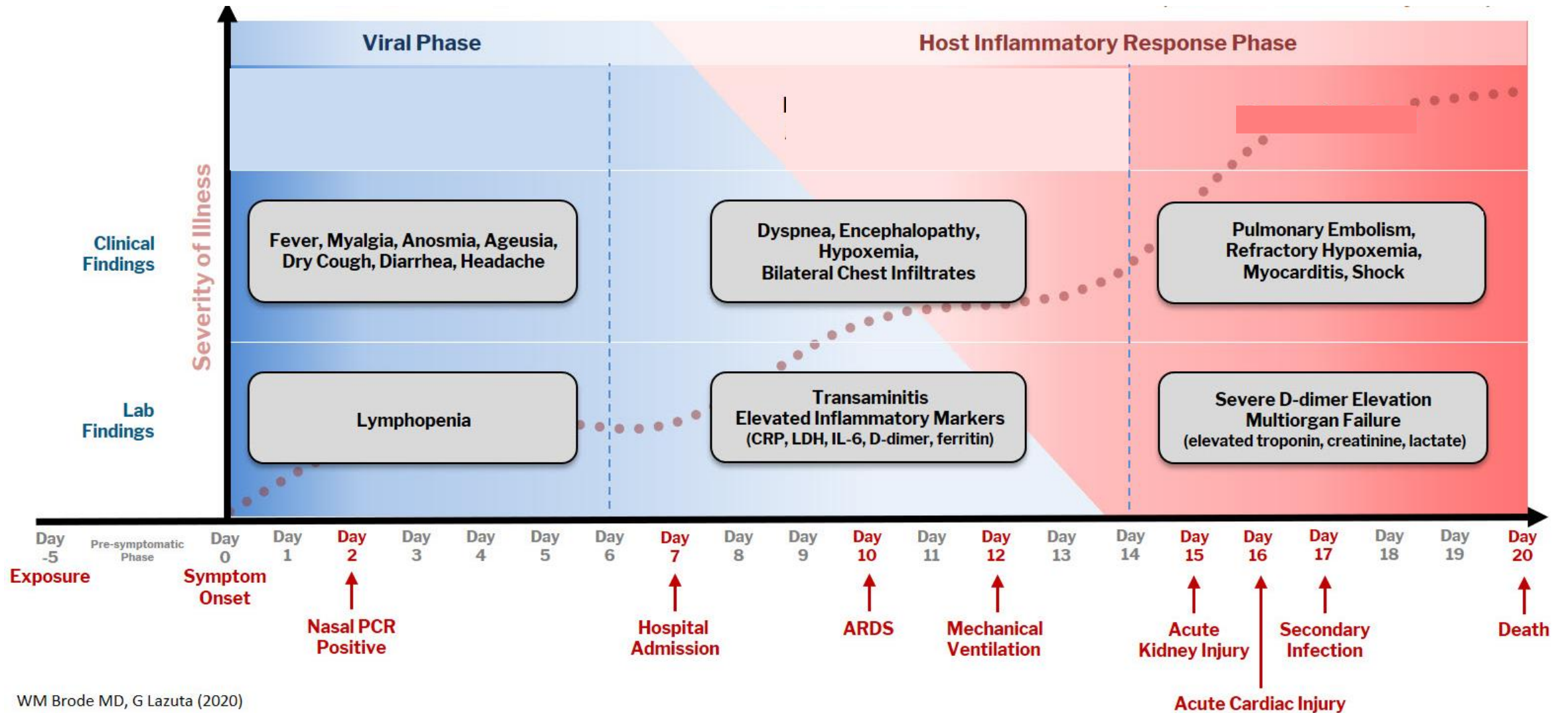
- Overview of extra-pulmonary manifestations of COVID-19
- Review of possible mechanisms of extra-pulmonary injury
- Focus on key manifestations with current clinical recommendations for monitoring and prevention
 - Thrombosis and other haematological events
 - Cardiovascular events
 - Other organ systems

SARS-COV-2 LIFE CYCLE

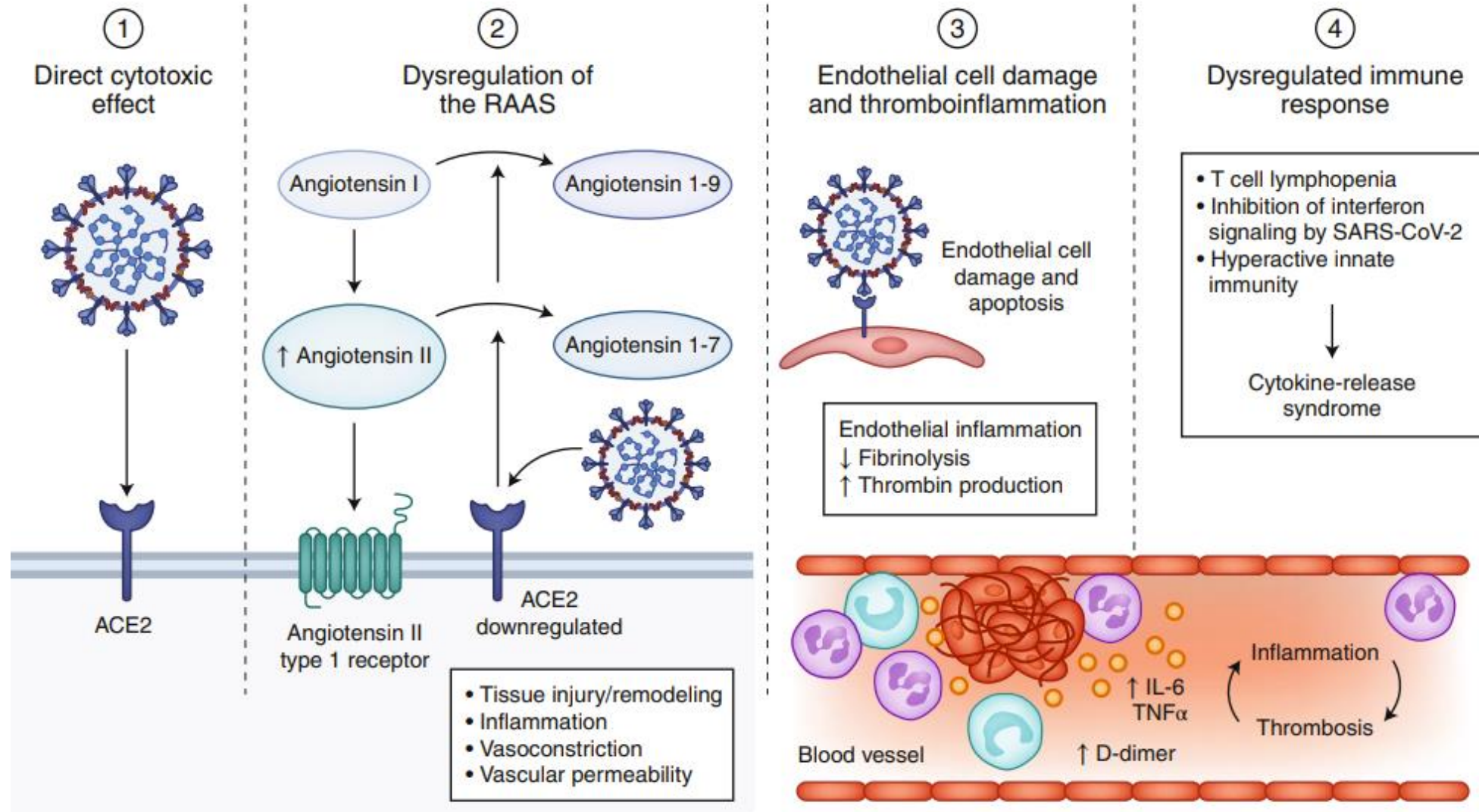
- Spike protein facilitates entry of the virus into cells
- Engages ACE2 (angiotensin-converting enzyme 2) as entry receptor (highly expressed in airways)
- Cell entry also requires priming of spike by the cellular serine protease TMPRSS2 or other proteases.
- Co-expression on the cell surface of ACE2 and TMPRSS2 is required



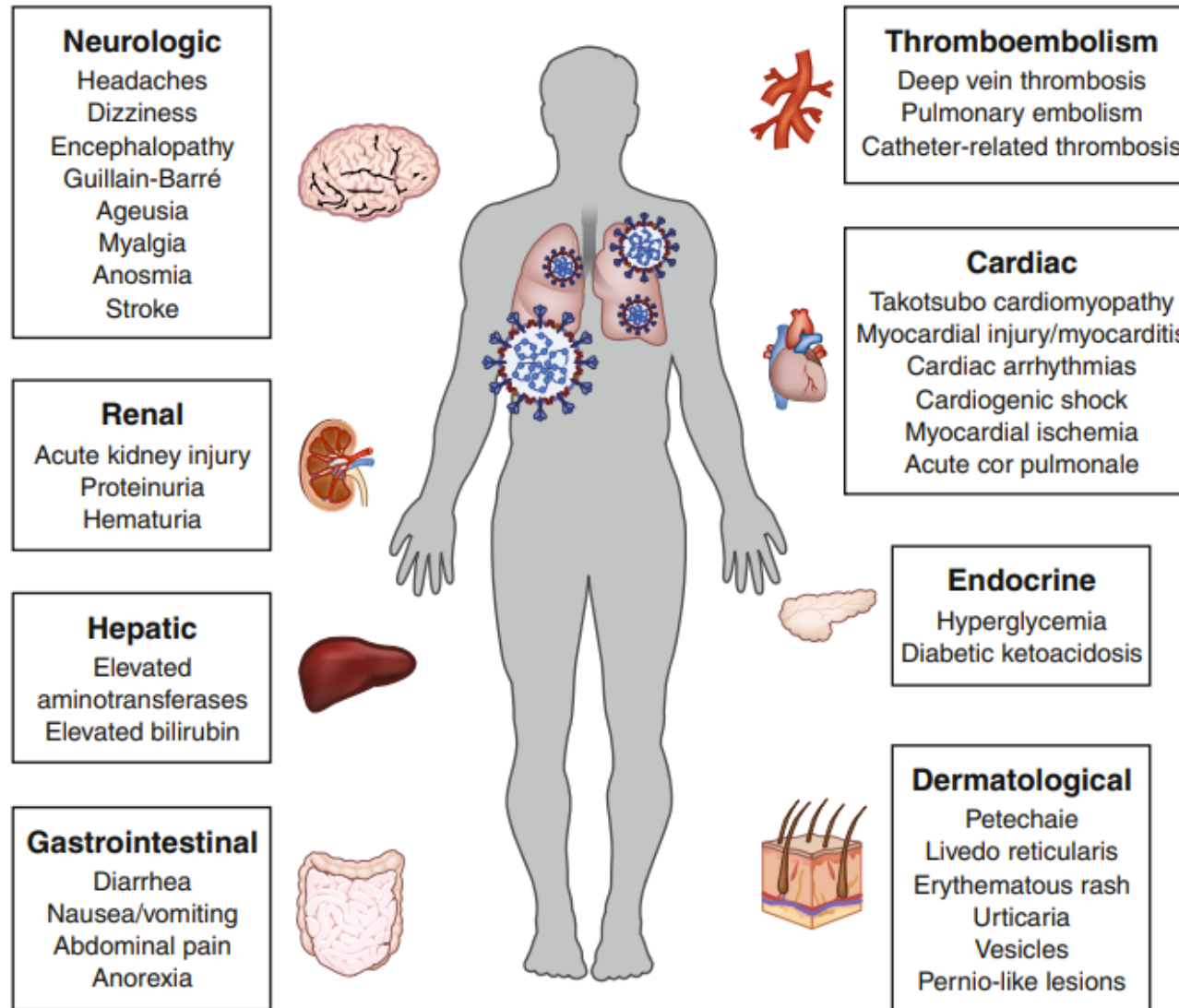
CLINICAL COURSE OF COVID-19



MECHANISMS OF EXTRA-PULMONARY EFFECTS OF SARS-COV-2



KEY EXTRA-PULMONARY MANIFESTATIONS



ITAC PRIMARY ORDINAL ENDPOINT

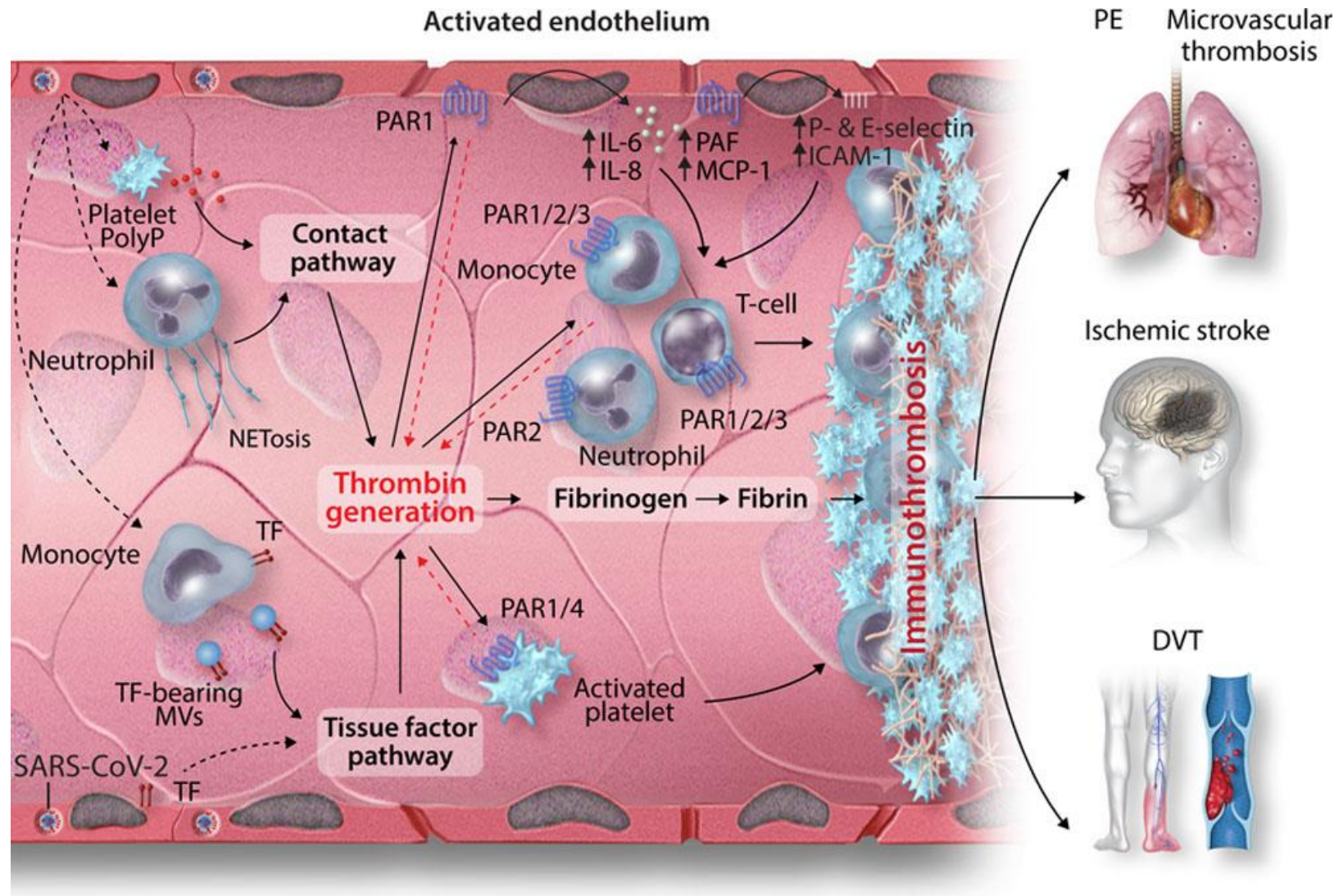
Category	Definition
1. No limiting symptoms due to COVID-19	Can independently undertake usual activities with minimal or no symptoms
2. Limiting symptoms due to COVID-19	Symptomatic and currently unable to independently undertake usual activities
3. Moderate end-organ dysfunction	Requiring supplemental oxygen < 4 liters/min, or < 4 liters/min above premorbid requirements
4. Serious end-organ dysfunction	<p>Currently requiring supplemental oxygen (≥ 4 liters/min, or ≥ 4 liters/min above premorbid requirements) but not high-flow oxygen</p> <p>Extra-pulmonary: Stroke (NIH Stroke Scale/Score [NIHSS] ≤ 14), meningitis, encephalitis, or myelitis, myocardial ischemia, myocarditis, pericarditis, or New York Heart Association Class 3 or 4 congestive heart failure, arterial or deep venous thrombosis.</p>
5. Life-threatening end-organ dysfunction	<p>Currently requiring non-invasive assisted ventilation or high-flow oxygen</p> <p>Extra-pulmonary: Symptoms and signs of an acute stroke (NIHSS > 14)</p>
6. End-organ failure	Currently requiring invasive assisted ventilation, extracorporeal membrane oxygenation, mechanical circulatory support, vasopressor therapy or renal replacement therapy
7. Death	Death



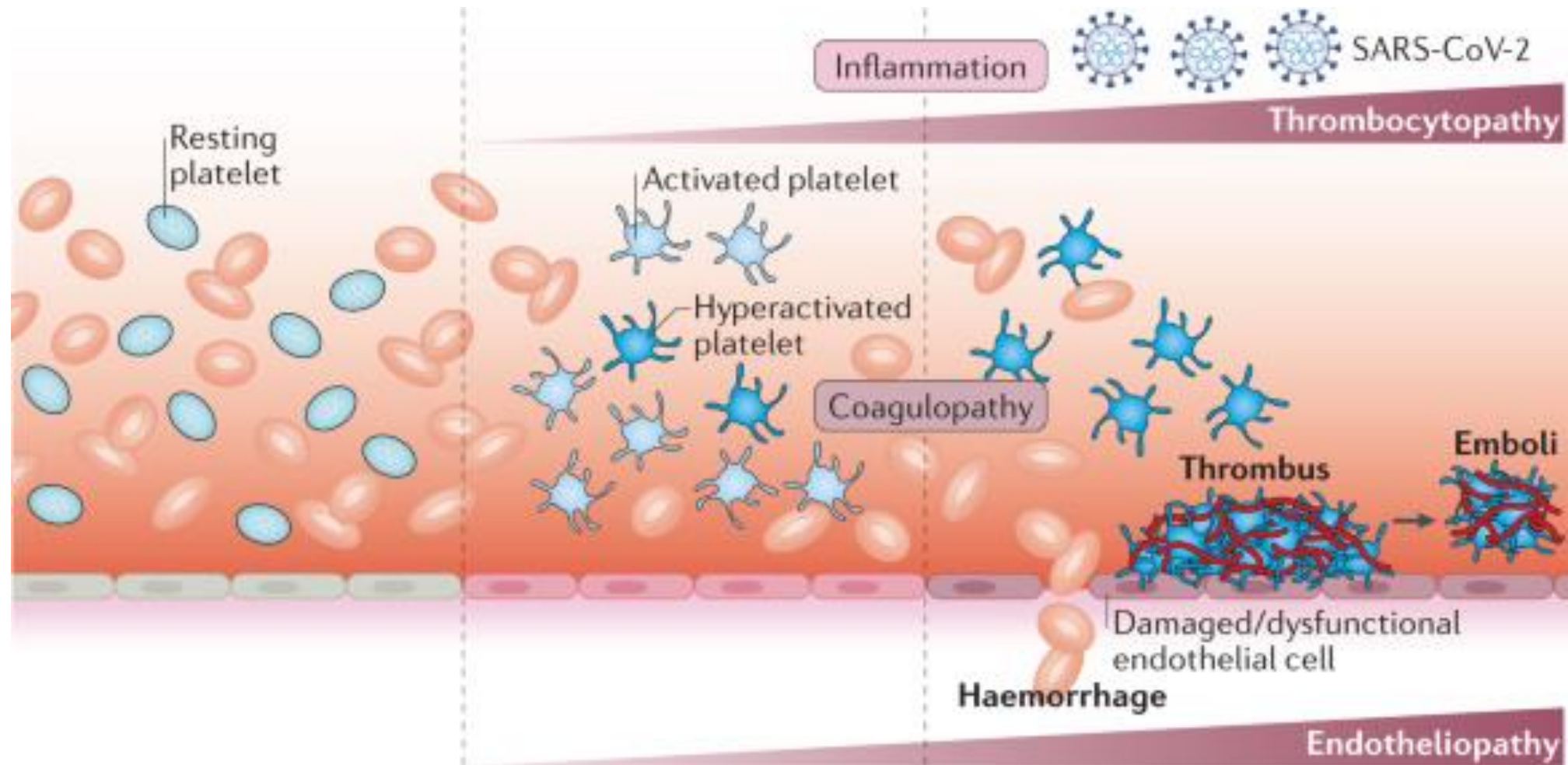
HAEMATOLOGIC COMPLICATIONS: OVERVIEW

- **Changes in Laboratory Indices**
 - Cell counts: lymphopenia, leukocytosis, neutrophilia, thrombocytopenia
 - Inflammatory markers: elevations in erythrocyte sedimentation rate, C-reactive protein, ferritin, lactate dehydrogenase
 - Coagulation indices: elevated D-dimer and fibrinogen; prolonged prothrombin time and partial thromboplastin time
- **Clinical Complications**
 - *Arterial thrombotic complications:* MI, ischemic stroke, acute limb, and mesenteric ischemia
 - *Venous thrombotic complications:* deep vein thrombosis and pulmonary embolism, cerebral sinus and mesenteric thrombosis
 - *Catheter-related thrombosis:* thrombosis in arterial and venous catheters and extracorporeal circuits

HAEMATOLOGIC COMPLICATIONS: POSSIBLE MECHANISMS



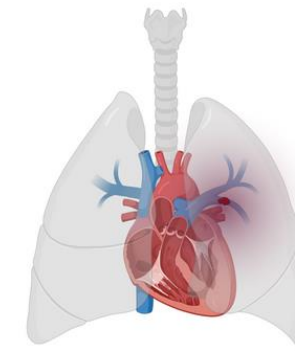
HAEMATOLOGIC COMPLICATIONS: POSSIBLE MECHANISMS



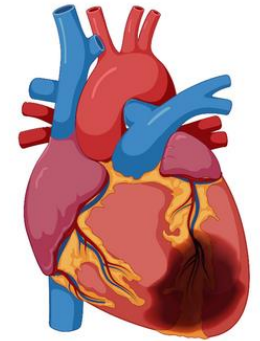
HAEMATOLOGIC COMPLICATIONS: THROMBOSIS

- Significantly elevated risk of arterial and venous thrombosis
 - Compared with other viral infections, and other critical illnesses
- May include thrombosis at unusual sites, but most commonly deep venous thrombosis and pulmonary embolus
- Rates:
 - Higher in hospitalized, highest in ICU
 - Associated with underlying thrombotic risk factors
- Role of anticoagulation
 - Multiple ongoing studies
 - No clear role established in outpatients, but under evaluation
 - In inpatients, comparisons of dosing strategies (prophylactic versus intermediate or full dose) have not shown convincing benefit for 'pre-emptive' or prophylactic full dose anticoagulation

Approximate Thrombotic Complication Rates in Hospitalized Patients



Pulmonary embolism: ~ 24.0%



Myocardial injury: ~ 20.0%



Deep vein thrombosis: ~ 46.1%



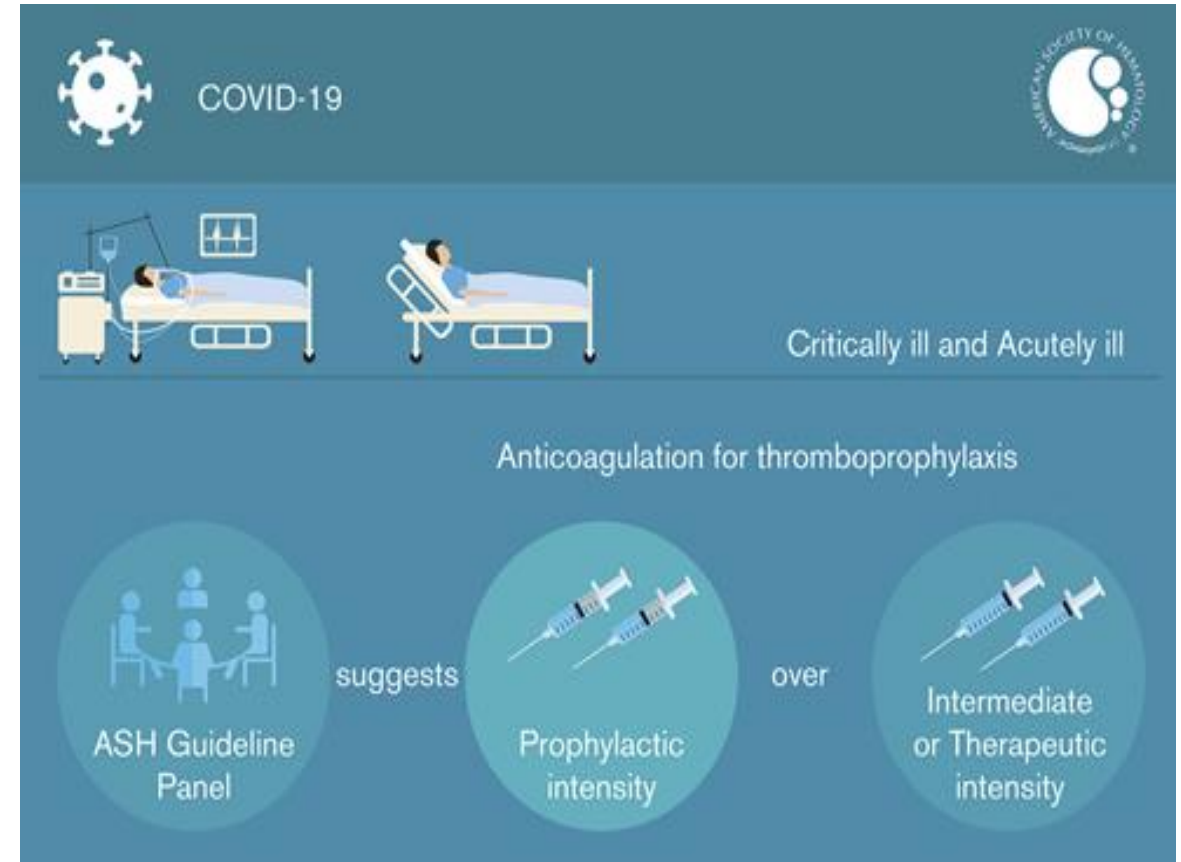
Stroke: ~ 1.6%

HAEMATOLOGIC COMPLICATIONS: THROMBOSIS

Coagulation parameter	Survivors n=162	Non-survivors n=21	Percentage difference
PT	13.6 s	15.5 s	13.97
aPTT	41.2 s	44.8 s	8.74
Fibrinogen	4.51 g/L	5.16 g/L	14.41
d-dimer	0.61 mcg/mL	2.12 mcg/mL	247.54
FDP	4 mcg/mL	7.6 mcg/mL	90.00
AT	91%	84%	-7.69

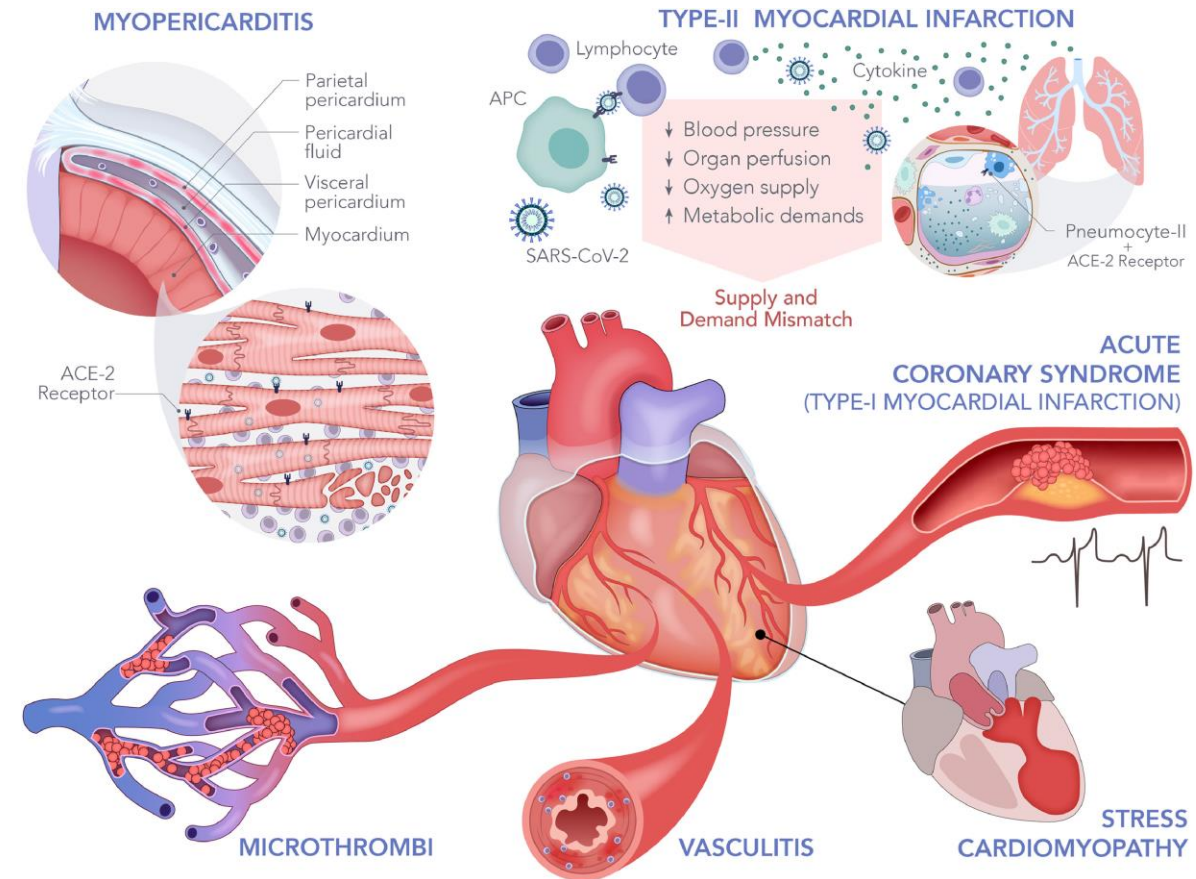
HAEMATOLOGIC COMPLICATIONS: CLINICAL APPROACH

- Recommend pharmacological prophylaxis for venous thromboembolism in the absence of absolute contraindications (active bleeding or severe thrombocytopenia). No consensus for intermediate or full dose anticoagulation outside of usual guidelines.
- Prefer heparins over oral anticoagulants in most patients
- Evaluate hepatic and renal function when determining appropriate dose and type of antithrombotic drugs
- Routine monitoring of D-Dimer and blood counts is common but does not dictate clinical management
- May consider post-hospitalization extended thromboprophylaxis on an individual patient basis

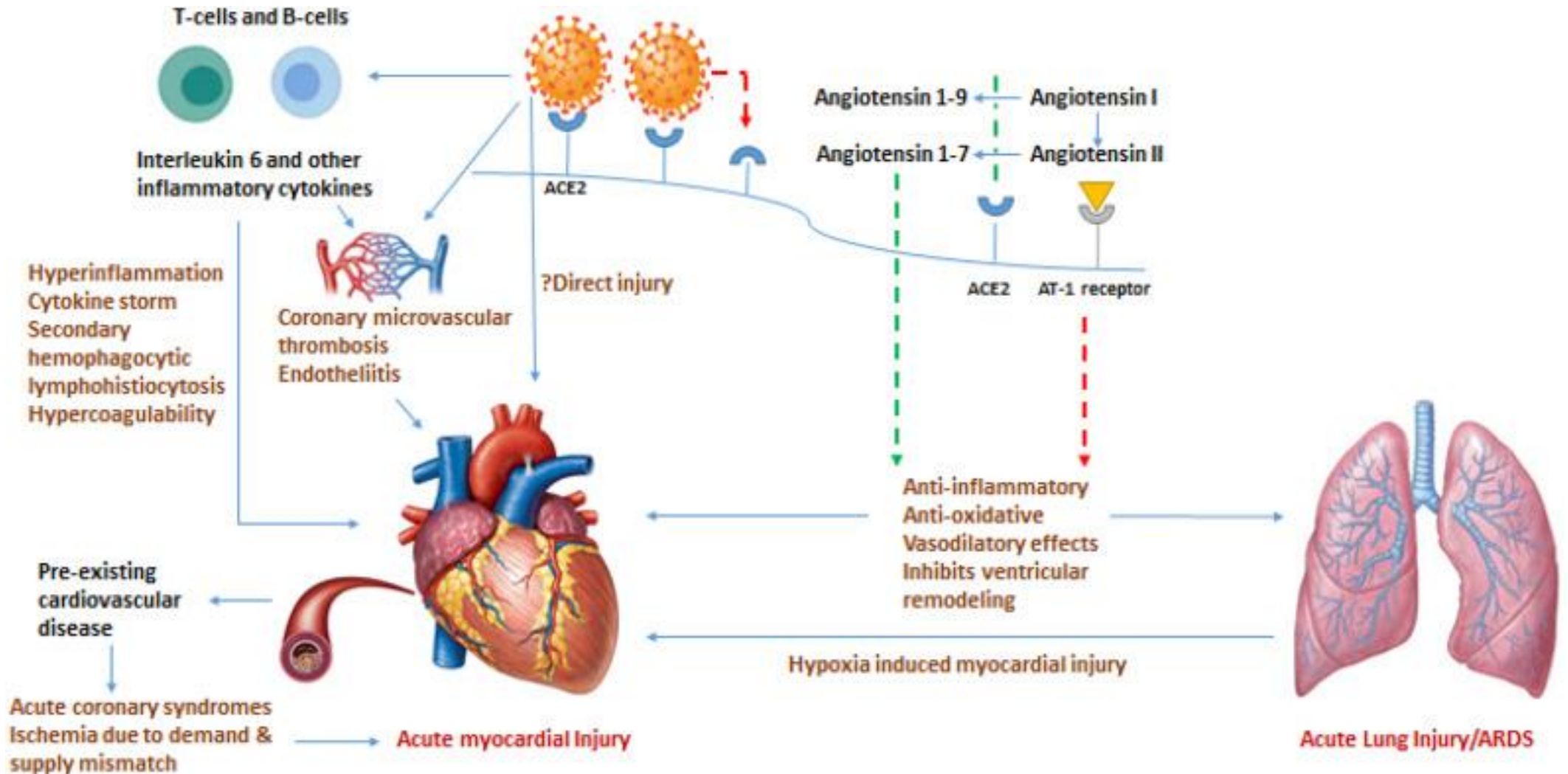


CARDIAC MANIFESTATIONS: OVERVIEW

- **Clinical presentations**
- Myocardial ischemia and MI (type 1 and 2)
- Myocarditis
- Arrhythmia: new-onset atrial fibrillation and flutter, sinus tachycardia, sinus bradycardia, QTc prolongation (often drug induced), torsades de pointes, sudden cardiac death, pulseless electrical activity
- Cardiomyopathy: biventricular, isolated right or left ventricular dysfunction
- Cardiogenic shock



CARDIAC MANIFESTATIONS: POSSIBLE MECHANISMS OF CARDIAC INJURY



CARDIOVASCULAR COMPLICATIONS: CLINICAL APPROACH

- **COVID-19-specific considerations**
- Do not routinely discontinue ACE inhibitors or ARBs in patients already on them at home; assess on a case-by-case basis
- Perform an electrocardiogram or telemetry monitoring for patients at medium to high risk for torsades de pointes who are being treated with QTc-prolonging drugs
- Carefully consider the utility of diagnostic modalities, including cardiac imaging, invasive hemodynamic assessments, and endomyocardial biopsies, to minimize the risk of viral transmission
- Primary percutaneous coronary intervention remains preferred approach for most patients with STEMI; consider fibrinolytic therapy in select patients, especially if personal protective equipment is not available

CARDIOVASCULAR COMPLICATIONS: CLINICAL APPROACH

- **General considerations**
- Monitor and correct electrolyte abnormalities to mitigate arrhythmia risk
- Utilize non-invasive hemodynamic assessments, and measurement of lactate, troponin, and beta-natriuretic peptide concentrations for guidance about fluid resuscitation, vasoactive agents, and mechanical circulatory support
- Minimize invasive hemodynamic monitoring and use routine echocardiography selectively, but consider in select patients
- Consider point-of-care echocardiography to assess regional wall-motion abnormalities to help distinguish type 1 MI from myocarditis

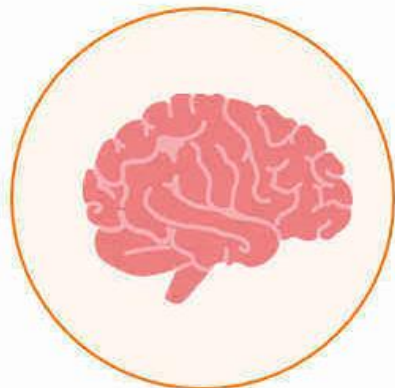
NEUROLOGICAL AND OPHTHALMIC MANIFESTATIONS

■ Clinical presentations

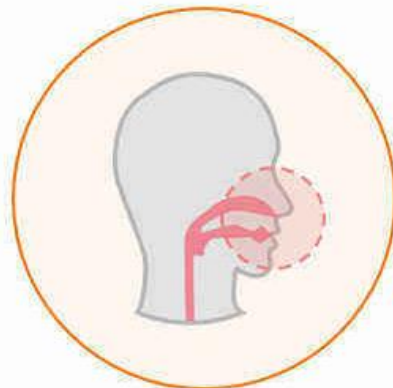
- Anosmia, ageusia
- Ischaemic stroke
- Encephalopathy, encephalitis, Guillain-Barré syndrome,
- Conjunctivitis

■ Clinical considerations

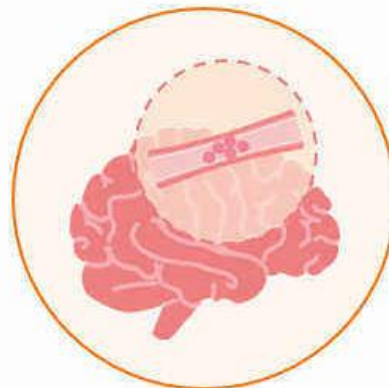
- Anticoagulation guidelines as previously outlined
- Continue established guidelines for ischemic stroke, including thrombolysis and thrombectomy



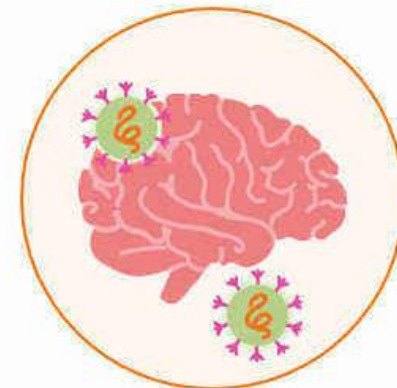
Encephalopathies
Meningoencephalitis
Neuromuscular disorders



Anosmia
and Ageusia



Acute Cerebrovascular
Disease



Infectious Toxic
Encephalopathies (Hypoxia,
metabolic disturbance and

RENAL AND HEPATIC MANIFESTATIONS

- **Renal clinical presentations**

- Acute kidney injury
- Electrolyte abnormalities (hyperkalemia, hyponatremia, and hypernatremia, among others)

- Proteinuria and haematuria

- Metabolic acidosis

- **General considerations**

- Individualize fluid-balance strategies guided by markers of volume status (serum lactate, urinary electrolytes, and hemodynamic measures), and of pulmonary, myocardial, and renal function
- Consider continuous RRT in critically ill patients with severe AKI and/or serious or life-threatening metabolic complications that do not respond to medical therapy

- **Hepatic Clinical Manifestations**

- Laboratory markers: elevated hepatic transaminases, elevated bilirubin, low serum albumin

- **General Considerations**

- Consider additional diagnostic tests where clinical features raise the pre-test probability of actionable findings (hyperbilirubinemia, right upper quadrant pain, hepatomegaly)
- Evaluate other aetiologies of abnormal liver biochemistries, including infection with other viruses (such as hepatitis A, B, or C viruses), myositis, cardiac injury and ischemia

ENDOCRINE MANIFESTATIONS

- Key illustration of importance of host factors in COVID-19 outcomes: the metabolic syndrome
- Patients with diabetes mellitus and/or obesity are at elevated risk of developing more-severe COVID-19 illness including hospitalization, critical illness and death
- Contributory factors:
 - Inflammatory milieu alterations
 - Underlying risk factors, especially cardiac and thrombotic
 - Direct effects of obesity (predominantly severe obesity) on pulmonary function
- Endocrine clinical presentations
 - Hyperglycemia
 - Ketoacidosis, including that in patients with previously undiagnosed diabetes or no diabetes
 - Euglycemic ketosis

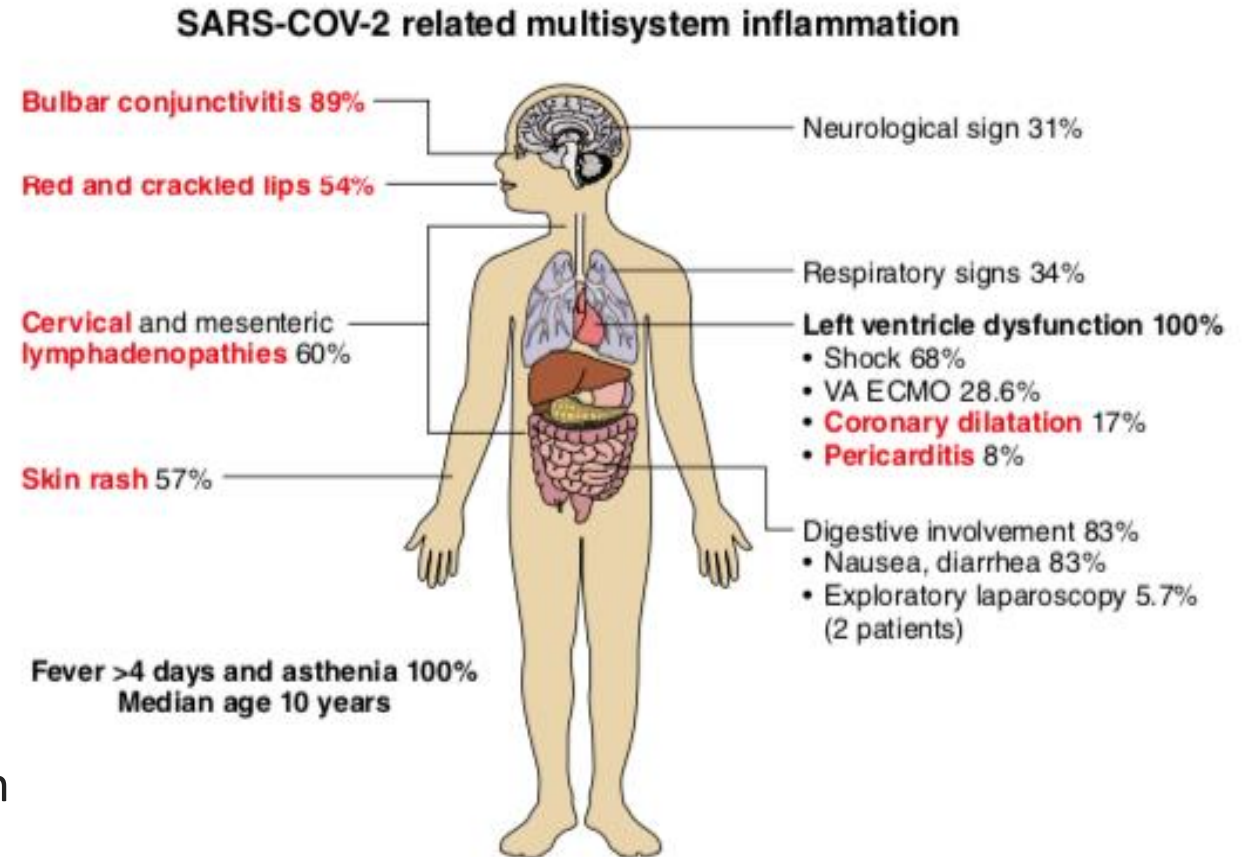
SPECIAL CONSIDERATIONS IN CHILDREN

- Disease course generally milder in children
 - May reflect differences in ACE2 expression and the immune system at younger ages
- However, a rare multisystem inflammation has been described in some children with COVID-19: MIS-A
- Adult from (MIS-A) also described, case definition requires age ≥ 21 years



SPECIAL CONSIDERATIONS IN CHILDREN: MIS-C

- **Case Definition:**
- Person <21 years of age P
- Presenting with
 - Fever
 - Laboratory evidence of inflammation
 - Clinically severe illness requiring hospitalization,
 - Multisystem (two or more) organ involvement
- In the setting of current or recent infection with SARS-CoV-2.

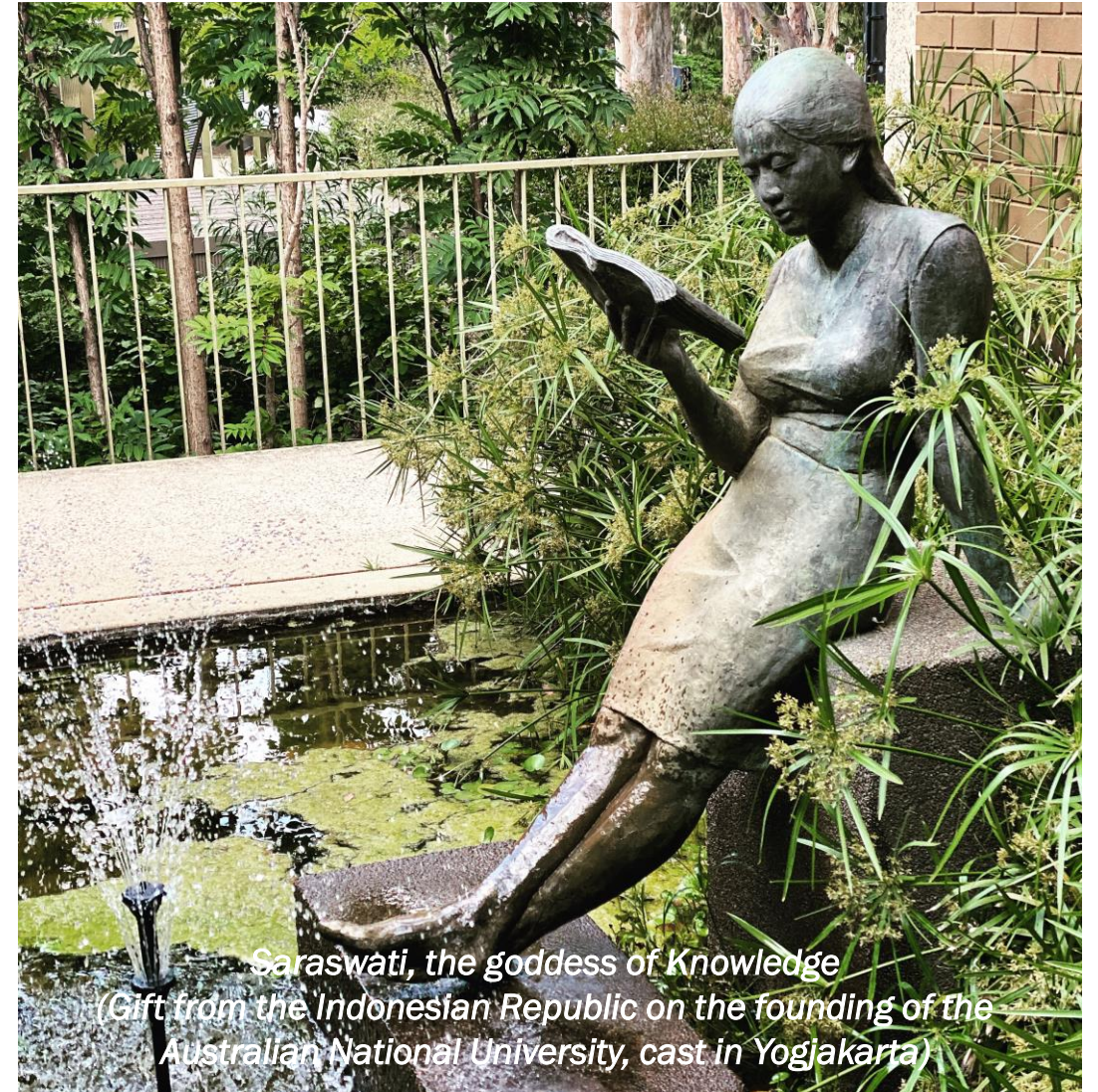


SUMMARY

- COVID-19 is best thought of as a multisystem illness
- While pulmonary manifestations are most prominent, other organ systems are involved and contribute significantly to morbidity and mortality
- Extra-pulmonary manifestations are multifactorial in origin,
 - Mechanisms include direct cellular and endothelial injury and indirect inflammatory mechanisms
- Extra-pulmonary manifestations are most prominent in sicker patients
 - Including those hospitalized and those with critical illness (in ICU)
- Key issues include venous and arterial thrombosis (cardiac) and myocarditis, and in children MIS-C
- Specific interventions to prevent extra-pulmonary manifestations are under evaluation

ACKNOWLEDGMENTS

- **INSIGHT Leadership and Team**
 - Jim Neaton, Cliff Lane, Jens Lundgren, Ginny Kan, Ab Babiker, Sarah Pett, Daniel Murray
 - Cate Carey, Sally Hough, Christina Chang and others at Sydney ICC
- **INA-Respond Team**
 - Muhammad Karyana, Herman Kosasih, Dona Arlinda and many others
- **NIAID Division of Clinical Research Team**
- **Indonesia Organizing Committee**



*Saraswati, the goddess of Knowledge
(Gift from the Indonesian Republic on the founding of the
Australian National University, cast in Yogyakarta)*

A photograph of a modern architectural structure featuring a series of cantilevered balconies or terraces that create a rhythmic, stepped profile. The balconies are illuminated from within, casting a warm, golden glow. In the foreground, a wide, multi-level outdoor staircase with metal railings leads up towards the building. The sky is clear and blue, suggesting a bright day.

QUESTIONS?