



***Potential Neurological
Emergencies Related to
COVID-19 Infection***

ARTHUR H.P. MAWUNTU

CURRICULLUM VITAE

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Beranda

Berita

Sebaran

Protokol

Edukasi

Tanya Jawab

Agenda

Info Lain

Hoax Buster

▶ Riwayat Sebaran Covid-19

34

Provinsi

Jumlah Kasus : 76 (0.5%)

📍 **SULAWESI UTARA**

Jumlah Kasus : 74 (0.5%)

📍 **PAPUA BARAT**

Jumlah Kasus : 70 (0.5%)

📍 **SULAWESI BARAT**

Jumlah Kasus : 68 (0.5%)

📍 **LAMPUNG**

Jumlah Kasus : 66 (0.4%)

📍 **JAMBI**

Jumlah Kasus : 65 (0.4%)

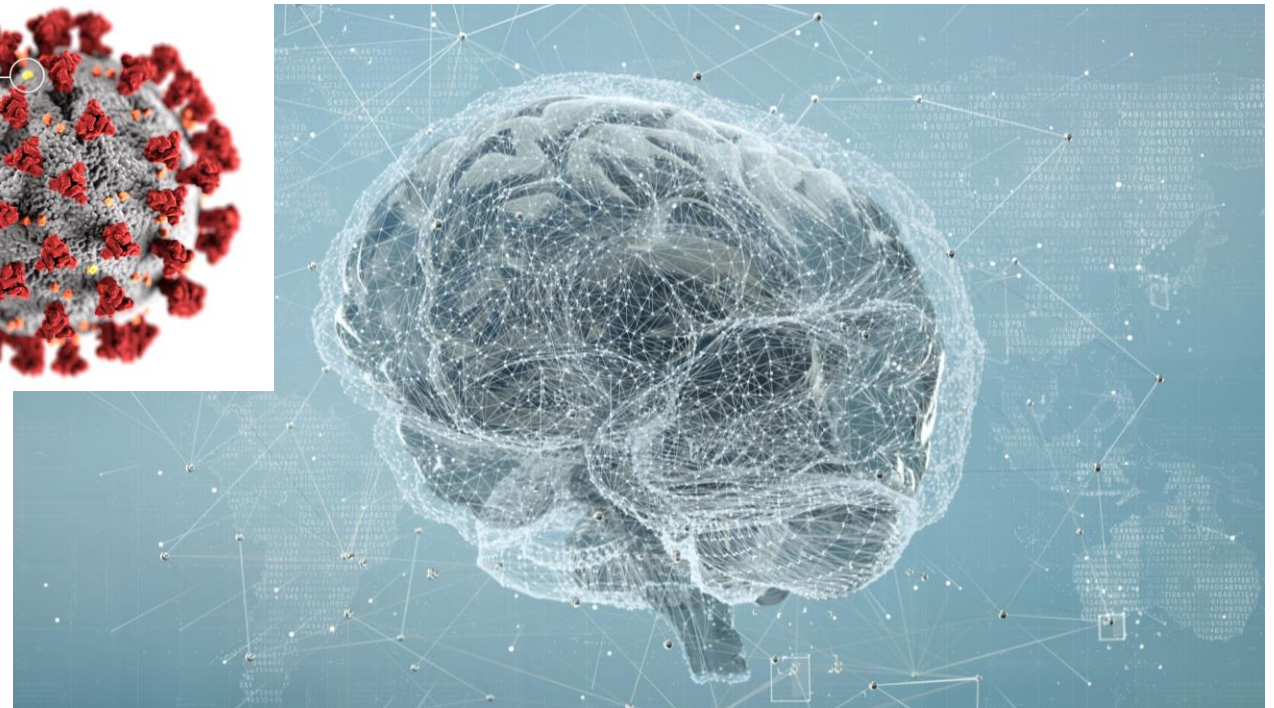
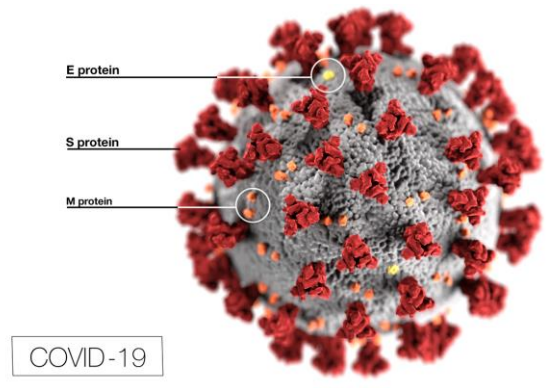


Current situation as access on 13 May 2020, 10.00 pm

Click here for updates: <https://covid19.go.id/peta-sebaran>

Outline

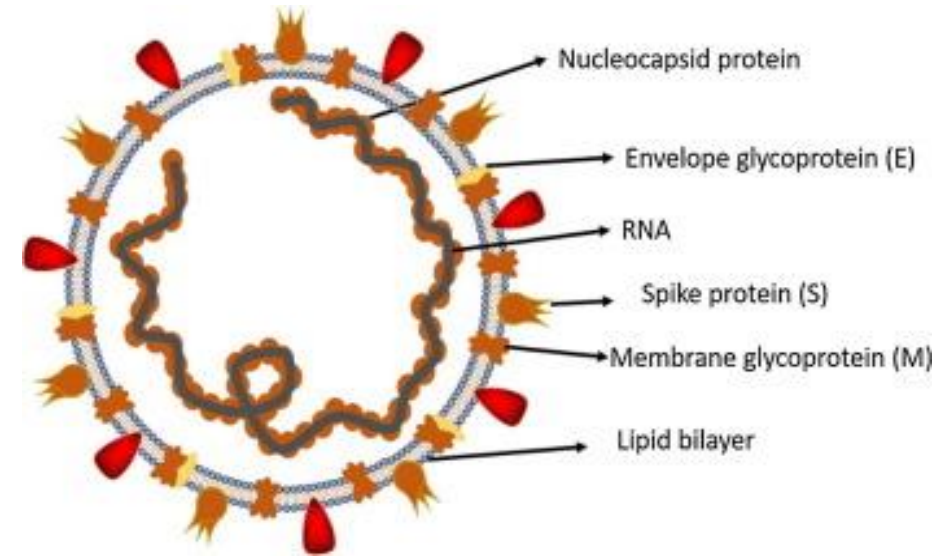
- Introduction
- General Patho-mechanism
- Neurology and COVID-19
 - Neurological Features
 - Serious Neurological Complications:
 - Seizure
 - Stroke
 - Encephalitis
 - GBS
 - Muscle injury
 - LOC



- Guidelines from INA
- Other Challenges
- Case Studies
- Take Home Messages

Introduction

- COVID-19 → a disease caused by a new coronavirus (SARS-COV-2) that mostly affects the lungs & airways
- Currently, nobody was immune
- Mode of transmission → droplet, “aerosol”, etc.
- 80% patients → asymptomatic/mild symptoms → could transmit the virus
- High risk: elderly, some comorbidities, weakened immune system



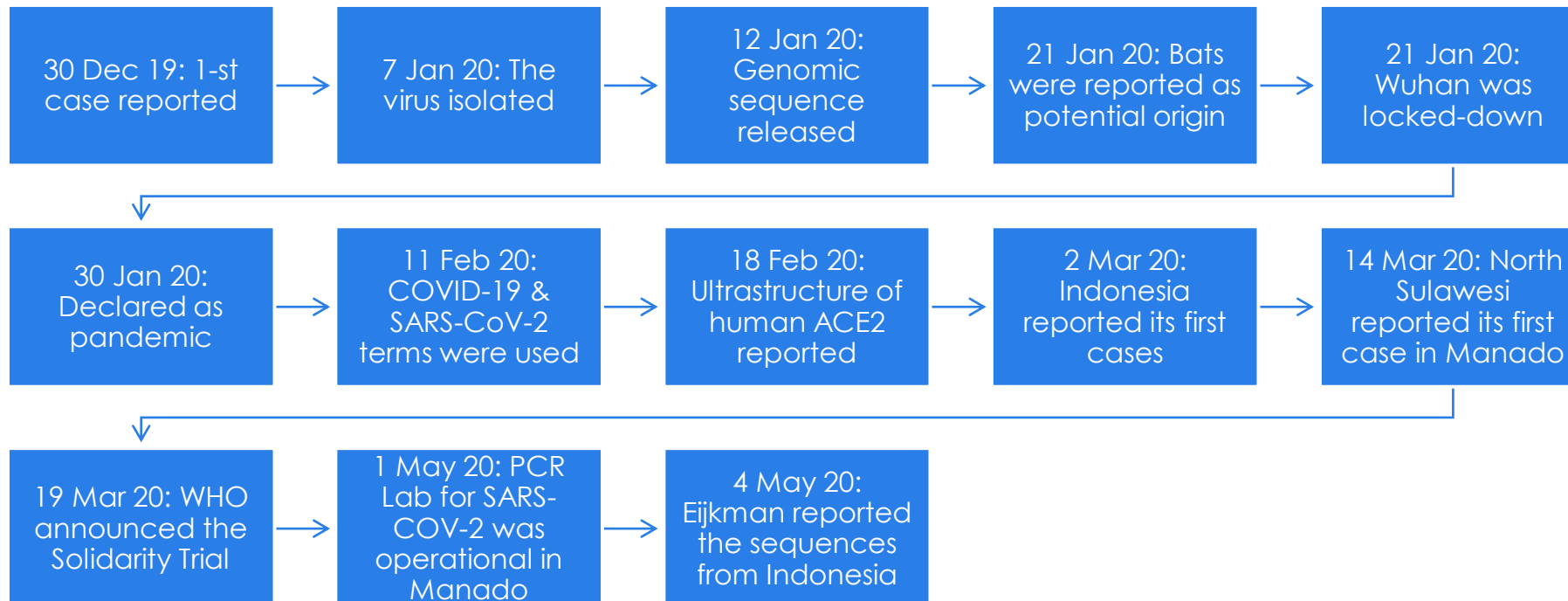
- RNA virus, single-stranded
- The spike proteins :
 - The main viral antigen
 - Important role in virus attachment to the cell membrane and viral entry (viral to viral receptor interaction)
- A metalloproteinase, ACE2, acts as the receptor for viral entry

A Novel Coronavirus from Patients with Pneumonia in China, 2019

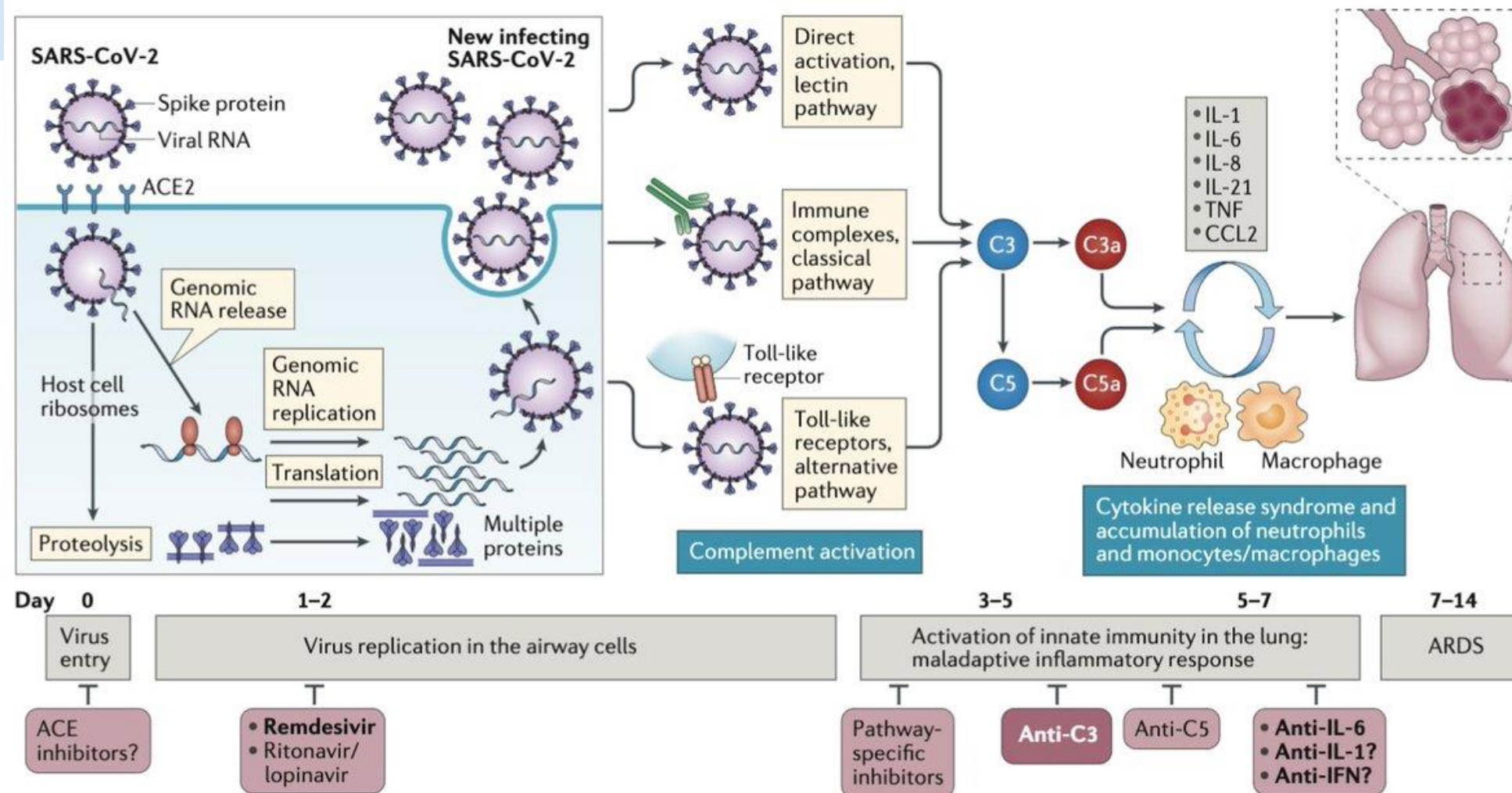
Na Zhu, Ph.D., Dingyu Zhang, M.D., Wenling Wang, Ph.D., Xinwang Li, M.D., Bo Yang, M.S., Jingdong Song, Ph.D., Xiang Zhao, Ph.D., Baoying Huang, Ph.D., Weifeng Shi, Ph.D., Roujian Lu, M.D., Peihua Niu, Ph.D., Faxian Zhan, Ph.D., Xuejun Ma, Ph.D., Dayan Wang, Ph.D., Wenbo Xu, M.D., Guizhen Wu, M.D., George F. Gao, D.Phil., and Wenjie Tan, M.D., Ph.D., for the China Novel Coronavirus Investigating and Research Team

SUMMARY

In December 2019, a cluster of patients with pneumonia of unknown cause was linked to a seafood wholesale market in Wuhan, China. A previously unknown betacoronavirus was discovered through the use of unbiased sequencing in sam-



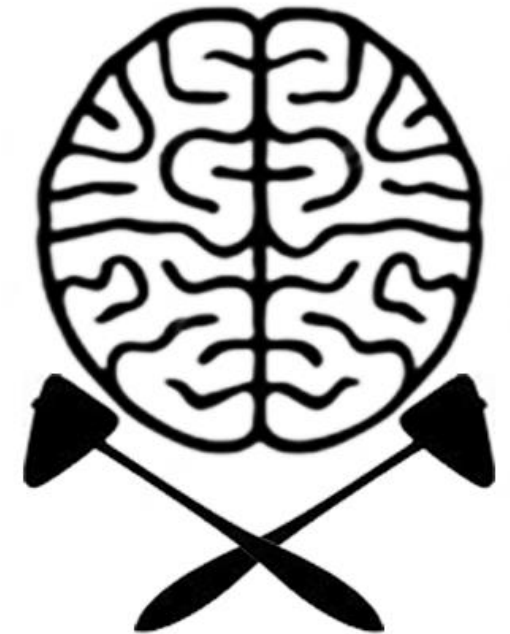
General Patho-mechanism

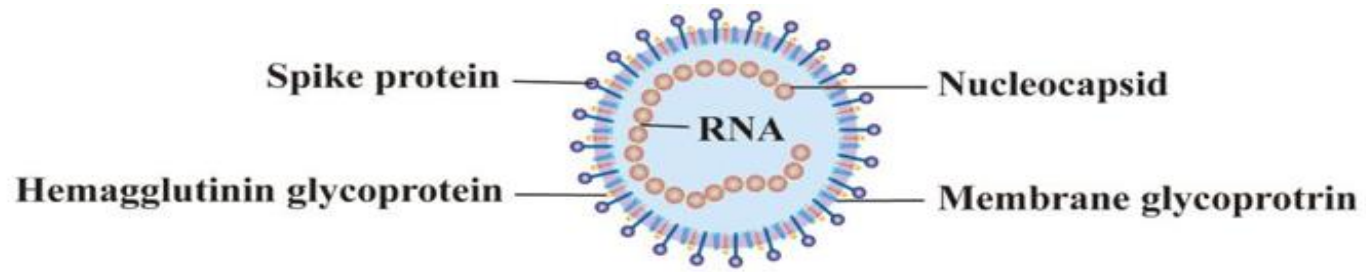


https://pbs.twimg.com/media/EW6_8siWAAAFsmn.jpg

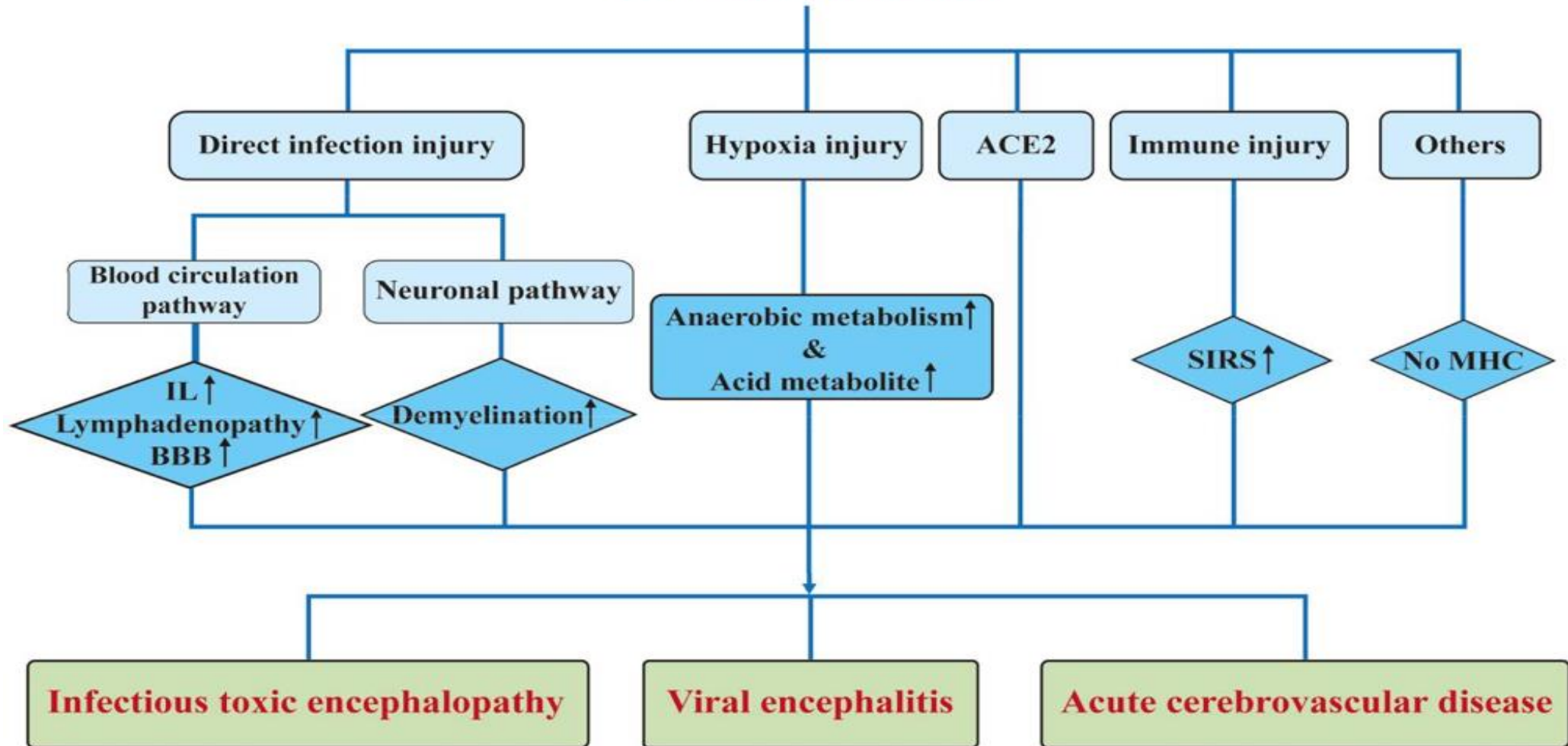
Neurology & COVID-19

- Patients with particular neurological disease and/or receive certain treatments → at risk → MG, NMOSD, MS, Neuro-AIDS, myositis, muscular dystrophies, CNS vasculitis, CIDP, MNDs,
- Neurological features in COVID-19 infection
- Drugs interactions
- Direct infection to CNS or PNS → ??
- **Serious neurological complication:**
 - **Seizures**
 - **Stroke**
 - **Encephalitis**
 - **GBS**
 - **Muscle injury**
 - **LOC**
 - **Etc.**





Coronavirus invasion



Neurological features

Characteristic	No. (%)			P value ^a
	Total (N = 214)	Severe (n = 88)	Nonsevere (n = 126)	
Nervous system symptoms				
Any	78 (36.4)	40 (45.5)	38 (30.2)	.02
CNS	53 (24.8)	27 (30.7)	26 (20.6)	.09
Dizziness	36 (16.8)	17 (19.3)	19 (15.1)	.42
Headache	28 (13.1)	15 (17.0)	13 (10.3)	.15
Impaired consciousness	16 (7.5)	13 (14.8)	3 (2.4)	<.001
Acute cerebrovascular disease	6 (2.8)	5 (5.7)	1 (0.8)	.03
Ataxia	1 (0.5)	1 (1.1)	0	NA
Seizure	1 (0.5)	1 (1.1)	0	NA
PNS	19 (8.9)	7 (8.0)	12 (9.5)	.69
Impairment				
Taste	12 (5.6)	3 (3.4)	9 (7.1)	.24
Smell	11 (5.1)	3 (3.4)	8 (6.3)	.34
Vision	3 (1.4)	2 (2.3)	1 (0.8)	.37
Nerve pain	5 (2.3)	4 (4.5)	1 (0.8)	.07
Skeletal muscle injury	23 (10.7)	17 (19.3)	6 (4.8)	<.001

- Neurological symptoms were seen in 36.4% patients
- More common in patients with severe infection

Mao, et al. JAMA Neurol. April 2020. DOI: 10.1001/jamaneurol.2020.1127



- * **Hyposmia**

- * Hypogeusia
- * Headache
- * Dizziness
- * Ataxia
- * Visual problems
- * Paresthesia-Hypesthesia
- * Weakness
- * Muscle pain



- * Neuronal infiltration
- * Mild-severe inflammation
- * ↑ ICP
- * Hematological complication
- * ↓ brain perfusion
- * Other mechanisms



- * Not specific
- * May present early in the disease course
- * Always look for other manifestations
- * Raise awareness for further COVID-19 work-ups during this pandemic





< cognition??

Drug interactions

	ATV	*DRV/c ¹	*LPV/r	RDV ²	FAVI	CLQ	HCLQ	NITA	RBV	TCZ ³	IFN-β-1a ⁴	OSV
Brivaracetam	↔	↔	↓	↔	↔	↑	↑	↔	↑	↔	↔	↔
Carbamazepine	↓↑	↓↑	↓↑	↓	↔	↓	↓	↔	↔	↓	↔	↔
Cannabidiol	↔	↑	↑	↔	↔	↑	↑	↔	↔	↔	↔	↔
Cenobamate	↓	↓	↑	↔	↔	↓	↓	↔	↔	↔	↔	↔
Clonazepam	↑	↑	↑	↔	↔	↔	↔	↔	↔	↔	↔	↔
Clobazam	↑	↑	↑	↔	↔	↔	↔	↔	↔	↔	↔	↔
Diazepam	↑	↑	↑	↔	↔	↔	↔	↔	↔	↔	↔	↔
Eslicarbazepine	↓♥	↓	↓♥	↓	↔	↓	↓	↔	↔	↔	↔	↔
Ethosuximide	↑	↑	↑	↔	↔	↔	↔	↔	↔	↔	↔	↔
Felbamate	↑	↓	↓	↔	↔	♥↓	♥↓	↔	↔	↔	↔	↔
Gabapentin	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
Lacosamide	♥↔	↑	♥↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
Lamotrigine	↔	↑	↓	↔	↔	↔	↔	↔	↔	↔	↔	↔
Levetiracetam	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
Lorazepam	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
Oxcarbazepine	↓	↓↓	↓	↓	↔	↓	↓	↔	↔	↔	↔	↔
Perampanel	↑	↓	↑	↔	↔	↔	↔	↔	↔	↔	↔	↔
Phenytoin	↓	↓	↓	↓	↔	↓	↓	↑	↔	↓	↔	↔
Phenobarbital	↓	↓↓	↓	↓	↔	↓	↓	↔	↔	↓	↔	↔
Pregabalin	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
Primidone	↓	↓	↓↓	↓	↔	↓	↓	↔	↔	↓	↔	↔
Retigabine	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
Rufinamide	↓	↓	↓	↓	↔	↓	↓	↔	↔	↔	↔	↔
Sulthiame	↑	↑	↑	↔	↔	↔	↔	↔	↔	↔	↔	↔
Tiagabine	↑	↑	↑	↔	↔	↔	↔	↔	↔	↔	↔	↔
Topiramate	↔	↓	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
Valproic acid	↔	↓	↑	↔	↔	↔	↔	↔	↔	↔	↔	↔
Vigabatrin	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
Zonisamide	↔	↑	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔

*Should not be administered without booster drug (ritonavir or cobicistat).

ATV=Atazanavir; DRV/c=Darunavir/cobisistat; LPV/r=Lopinavir/ritonavir; RDV=Remdesivir; FAVI=Favipiravir; CLQ=Cloroquin HCLQ =Hidrocloroquin; NITA=nitazoxamide; RBV=Ribavirin; TCZ=Tocilizumab IFN-B=Interferon B; OSV=oseltamivir

	Should not be co-administered
	Potential interaction with may require a dose adjustment and close monitoring
	Potential interaction likely to be of weak intensity
	No clinically significant interaction expected

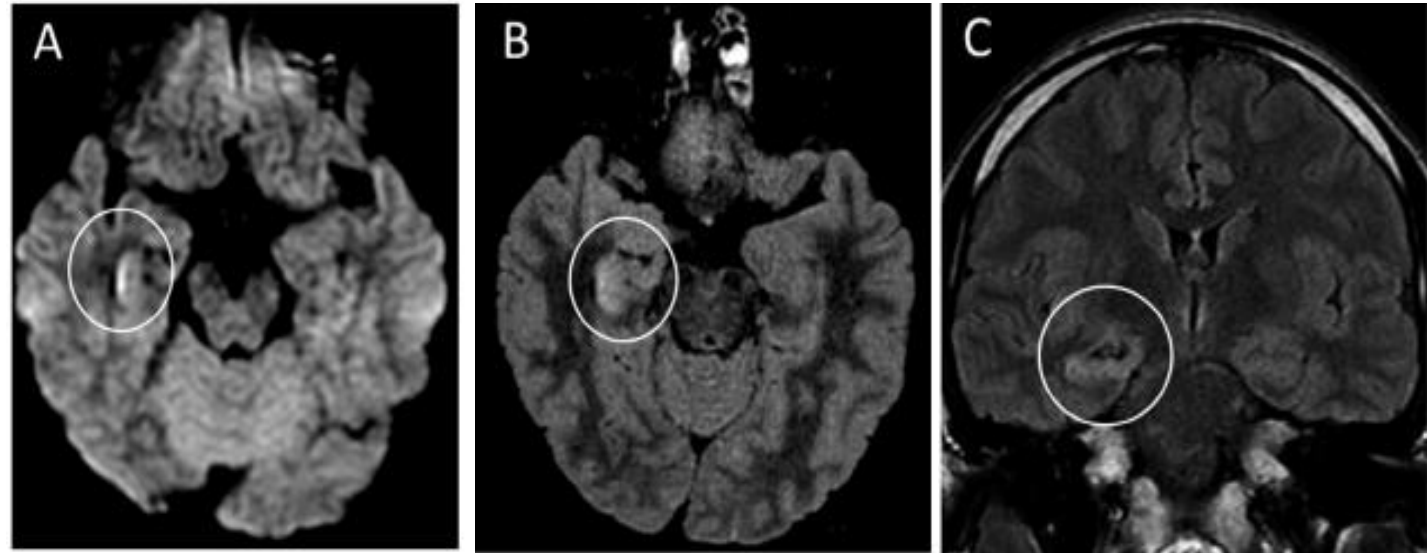
Click here for updates: <https://www.covid19-druginteractions.org/>

Direct infection to CNS or PNS

- CNS direct infection → theoretically plausible:
 - Previous reports in SARS & MERS
 - ACE2 receptors are found in neuron
 - Possible neural transmission from olfactory nerves or hematogenous transmission
 - Autopsy of patients with COVID-19 → hyperemic & edematous brain tissue, degenerated neurons
 - Animal model
- Up until now:
 - Some reports about SARS-CoV-2 associated meningoencephalitis
 - Mostly based on neurological deficits in confirmed COVID-19 cases + abnormal neuroimaging + non-specific abnormality of the CSF + no proof of other direct cause
 - One case report → CSF (+)/NP swab (-)
- PNS direct infection → ??

From Japan

- A 24 y.o. male with headache, generalized fatigue, fever → LOC
- Nuchal rigidity (+)
- Chest CT → GGO
- RT PCR from NP swab for SARS-CoV-2 → (-)
- **RT PCR from CSF for SARS-CoV-2 → (+)**
- ICU
- Levetiracetam
- Steroids
- Antibiotics, acyclovir
- Favipiravir



Brain MRI performed 20 hours after admission.

A: DWI showed hyperintensity along the wall of inferior horn of right lateral ventricle. B,C: FLAIR images showed hyperintense signal changes in the right mesial temporal lobe and hippocampus with slight hippocampal atrophy → right lateral ventriculitis & encephalitis

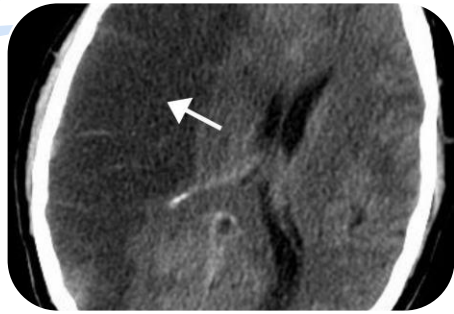
Serious Neurological Complications

Neurological features of COVID-19 patients with ARDS

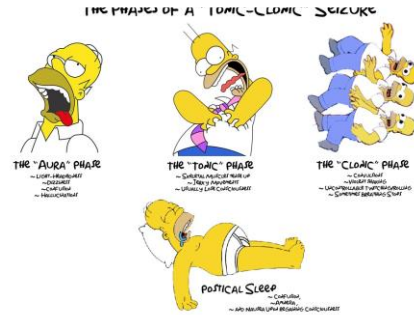
Neurologic signs — no./total no. (%)	49/58 (84)
Temperature >38.5°C at time of clinical examination	8/49 (16)
Positive findings on CAM-ICU‡	26/40 (65)
Agitation	40/58 (69)
Corticospinal tract signs	39/58 (67)
Dysexecutive syndrome	14/39 (36)
Brain MRI — no./total no. (%)	
Leptomeningeal enhancement	8/13 (62)
Perfusion abnormalities	11/11 (100)
Cerebral ischemic stroke	3/13 (23)§
CSF analysis — no./total no. (%)¶	
Oligoclonal bands with the same pattern in serum	2/7 (29)
Elevated CSF IgG and CSF protein levels	1/7 (14)
Low albumin level	4/7 (57)
Negative RT-PCR for SARS-CoV-2 in CSF	7/7 (100)

- Examination are sometimes difficult to perform
- MRI and EEG → no specific findings
- Negative RT-PCR in the CSF

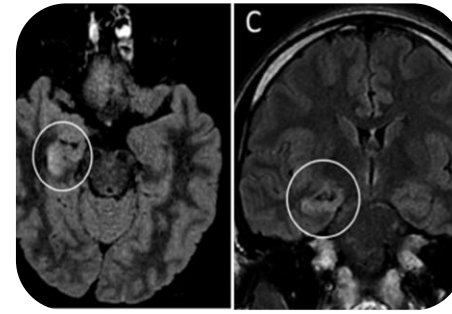
Helms, et al. NEJM. April 2020. DOI: 10.1056/NEJMc2008597



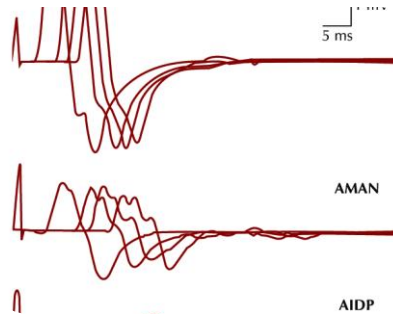
Stroke



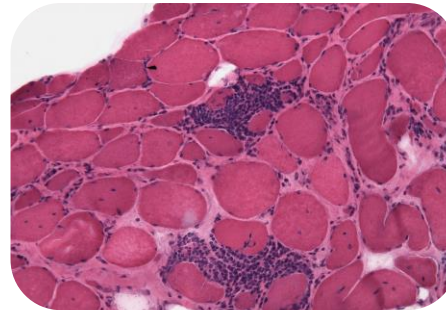
Seizure



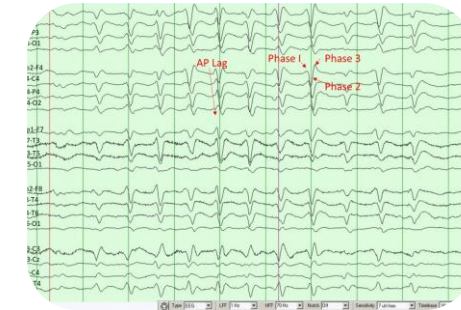
Encephalitis



GBS



Muscle injury



LOC

Stroke

- COVID-19 patients → high risk for developing acute stroke especially if multiple organ dysfunction presents
- A retrospective study from the COVID-19 outbreak in Wuhan → stroke incidence in hospitalized COVID-19 patients ≈ 5%
- Causes: Vasculitis or coagulopathy & vascular endothelial dysfunction
- Treatment approach is similar but with some considerations

- Coagulopathy & vascular endothelial dysfunction
 - Recent case series from New York City reported 5 young patients with COVID-19 & large-vessel stroke
 - Large-vessel stroke was reported in association with the 2004 SARS outbreak in Singapore

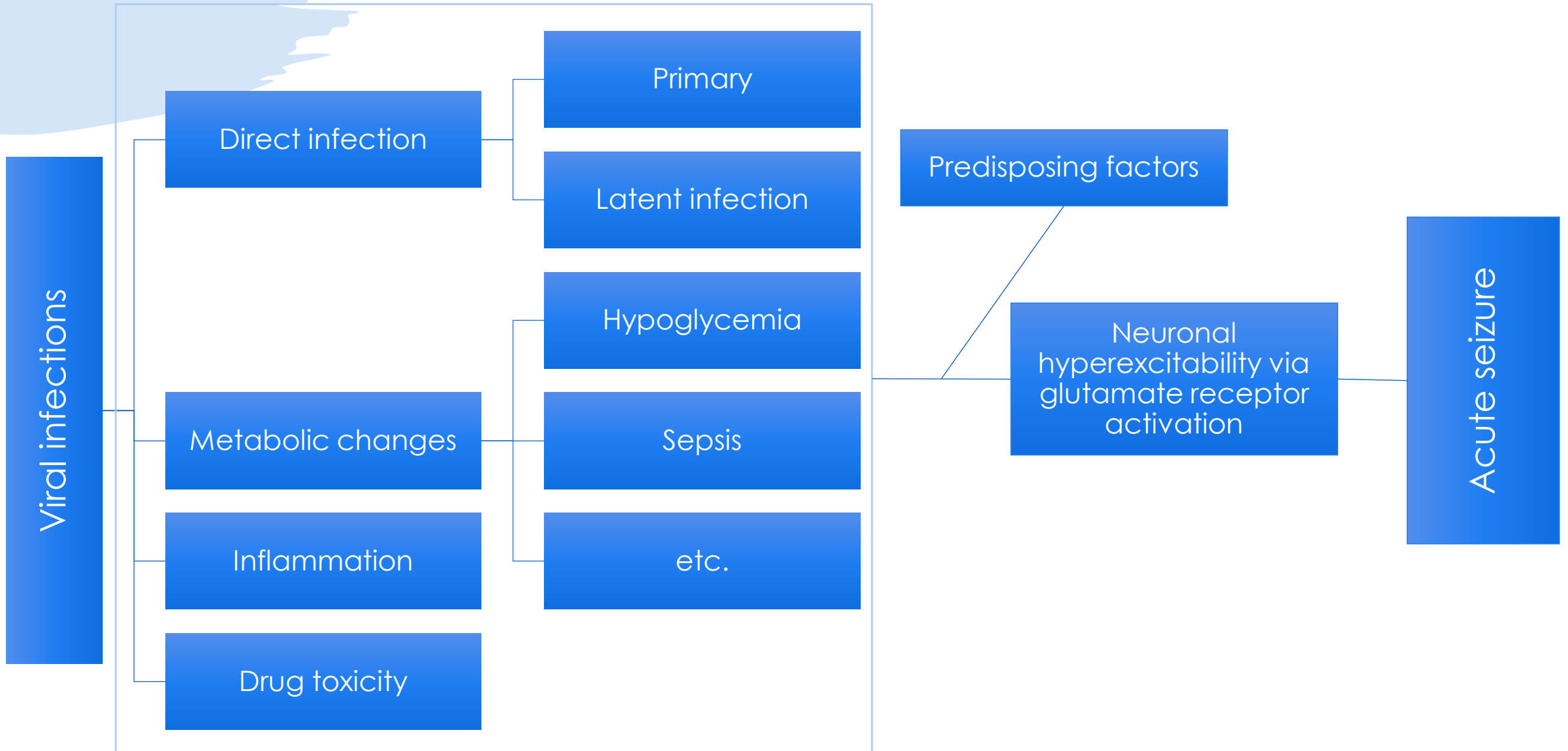
How about stroke in general?

In COVID-19 pandemic:

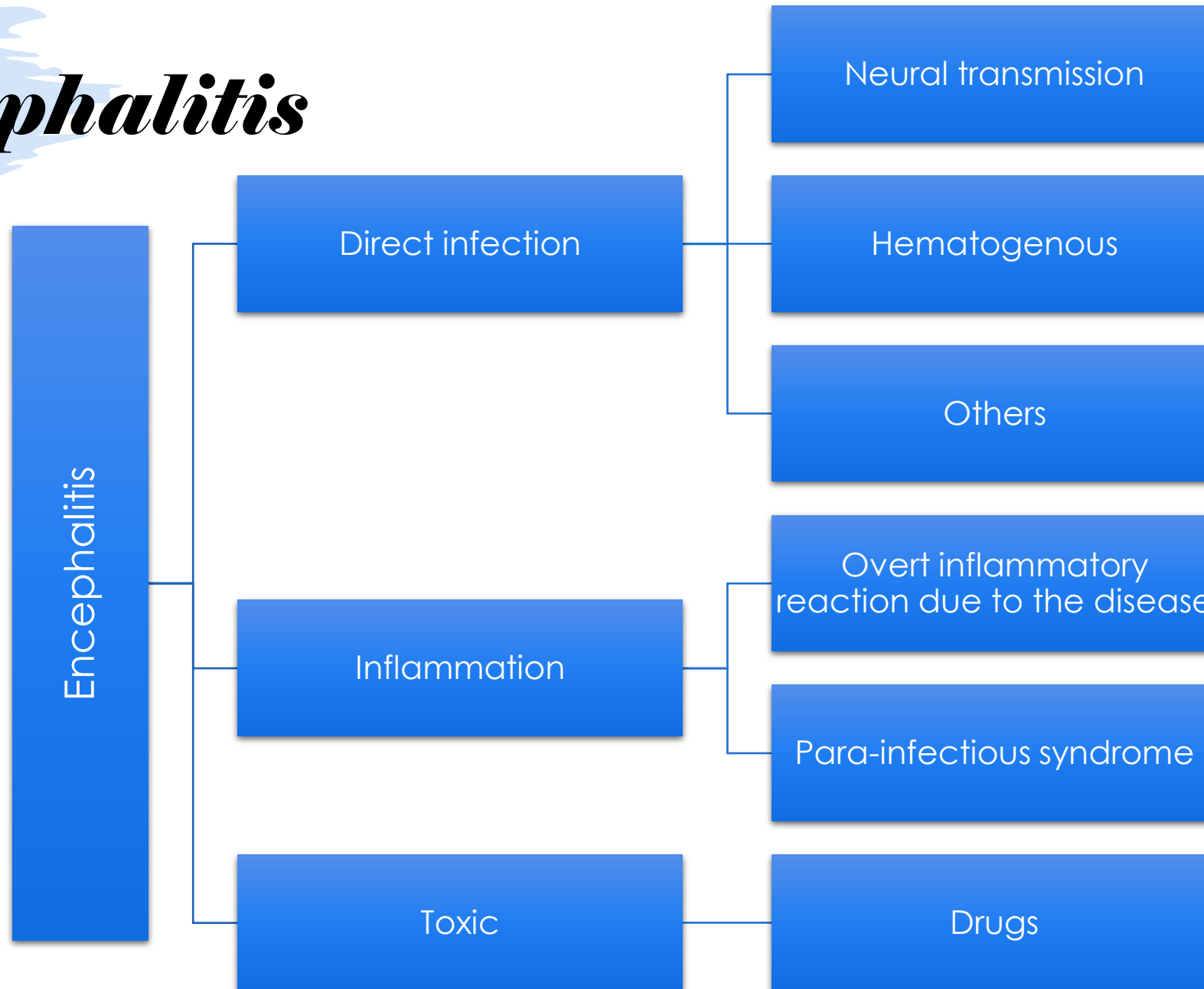
- Social distancing, isolation, and reluctance to present to the hospital may contribute to poor outcomes of stroke patients.
- Propose a protected stroke code

Seizure

- Seizure is not considered a presenting symptom of COVID-19
- During disease progression → release of inflammatory cytokines → brain damage → neuronal hyperexcitability via glutamate receptor activation → seizures
 - Consider also other potential causes (drug toxicity, metabolic changes, direct brain infection, etc.)
- Seizure → poor outcome
- Risk of seizure ↑ in certain conditions → especially a history of previous seizure
- AEDs selection: consider drug-drug interaction, side effects, and disease status
- Recognize subtle seizure or NCSE (exclude with EEG)
- Management:
 - Treat seizure immediately
 - Modification in seizure protocol → preferable to select AED with minimal interaction with other drugs (e.g. Levetiracetam)
 - If unavailable → give classic AED with precaution
 - Causative therapy
 - Supportive therapy

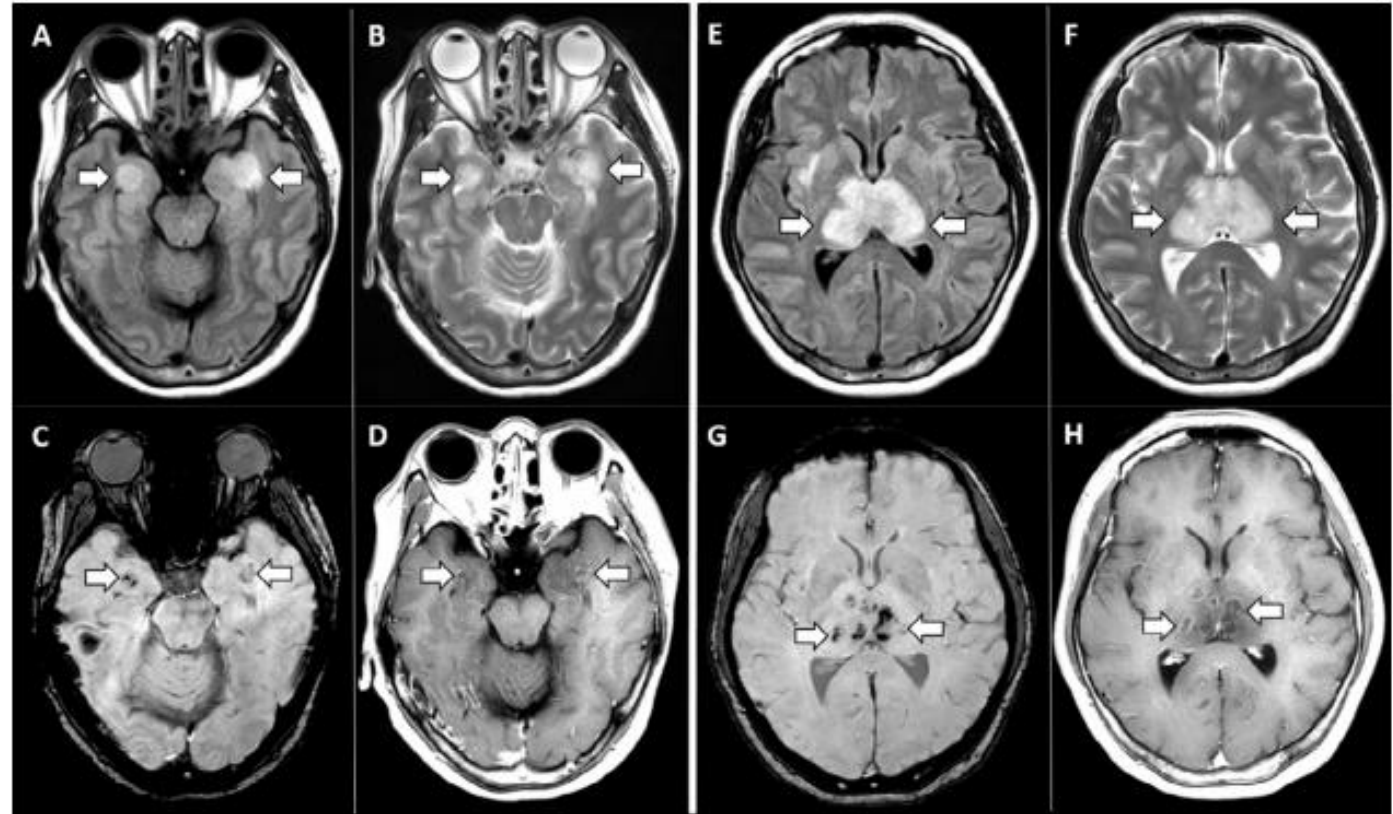


Encephalitis



From USA

- A female airline worker in her late fifties presented with a 3-day history of cough, fever, and **altered mental status**
- RT PCR from NP swab (+) for SARS-CoV-2
- RT PCR from CSF for HSV1, HSV2, VZV, and WNV (-)
- Bacterial culture from CSF (-)
- RT PCR from CSF for SARS-CoV-2 → N/T



T2 FLAIR hyperintensity within the bilateral medial temporal lobes and thalami (A, B, E, F) with evidence of hemorrhage indicated by hypointense signal intensity on susceptibility-weighted images (C, G) and rim enhancement on postcontrast images (D, H)

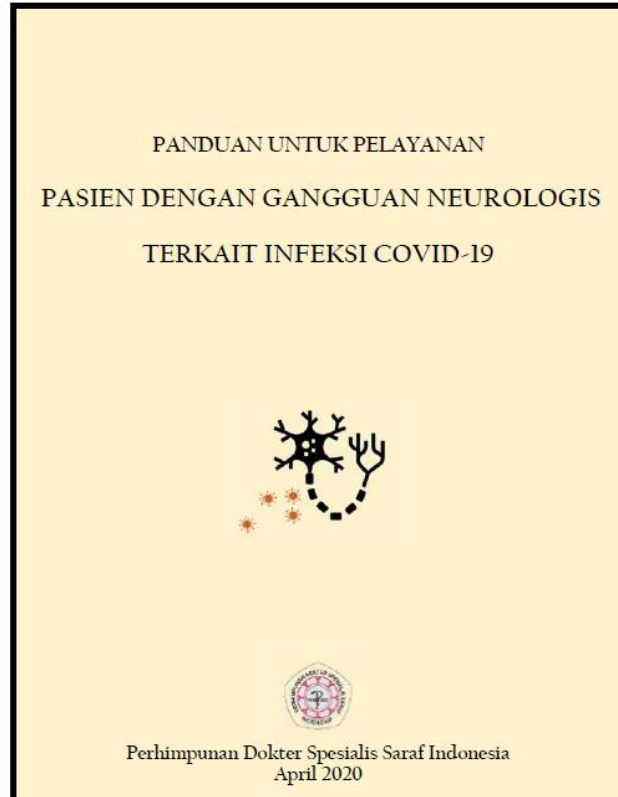
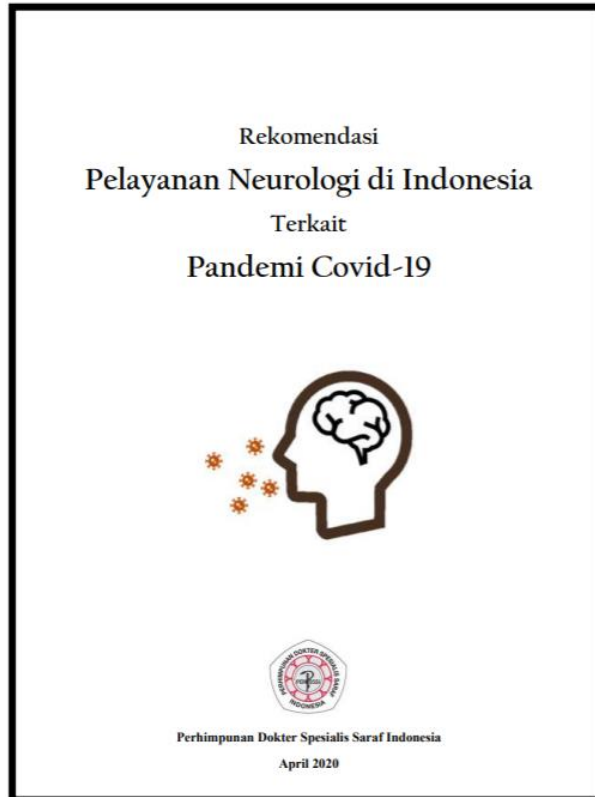
GBS

- Para-infectious/post-infectious syndrome
 - Autoimmune
 - Mostly, targeting myelin and/or axons of the peripheral nerves
 - Classic clinical findings: acute, symmetric, flaccid, ascending paralysis
 - Requires CSF analysis & EMG for diagnosis
 - >> Self-limiting disease; fatal outcomes in some patients
 - Tx: IVIg, PE
- In COVID-19:
 - Already reported in case reports
 - >> follow a para-infectious profile, instead of the classic postinfectious profile
 - Could contribute to the respiratory problem
 - Should be considered in patients with acute general weakness + areflexia, acute cranial nerve palsies
 - Dysautonomia → ↑ mortality

Muscle Injury

- Muscle injury: Skeletal muscle pain + serum CK level >200U/L
- Coronavirus infections may be associated with myopathies
- Myalgia or fatigue → 44%–70% of hospitalized patients and ↑ CK → 33% of admitted patients
- Coronavirus may cause a viral myositis
- Very sick coronavirus patients → critical illness myopathy or polyneuropathy
- Risk from treatment:
 - Hydroxychloroquine and chloroquine → toxic neuropathy and myopathy
 - Antiviral treatments
- Risk from vaccination
 - Possible inflammatory neuropathy

Guidelines From INA



Penasehat

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Dr. dr. Riwanti Estiasari, SpS(K)

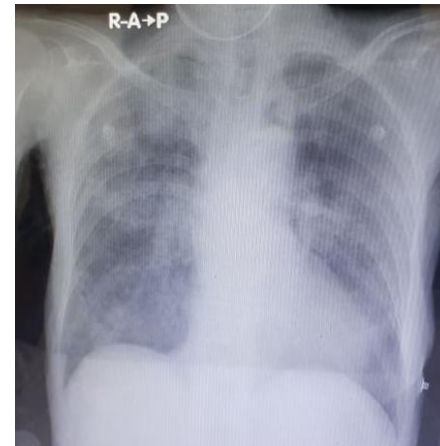
Other Challenges

- The non-COVID-19 patients
 - Triage & screening in patients coming to the hospital
 - Patients w/ chronic treatment
 - Patients receiving immunosuppressive agents
- Telemedicine
 - Feasibility
 - Legal aspect
- CMEs

Case Studies

- A 83 y.o. female
- Found unconscious for 1 hour → **general seizure 7x**
- Screened negative
- GCS on admission: E₃M₅V₁=9
- BP: 190/100, HR: 120 bpm; RR: 30x/min; Temp: 37.5°C; **O₂ sat 80% (↓)**
- Funduscopy → N/T
- No meningeal signs or lateralization
- Hema: Hb 9.8g/dl; Hct 28.9%; WBC 16.000/mm³ (no diff count); Plt 390.000/mm³
- Chem: RBS 155; Ur/Cr 33/0.8; ALT/AST: 30/9; lytes: 133/3.61/91.5
- **ECG: sinus tachycardia 110x/min, complete RBBB, P-pulmonal**

- Oxygen with NRM 10l/min
- **Diazepam 10mg iv → phenytoin 750mg in NS slow IV**
- Nicardipine IV titrating dose
- CXR, ABGA



Viral pneumonia

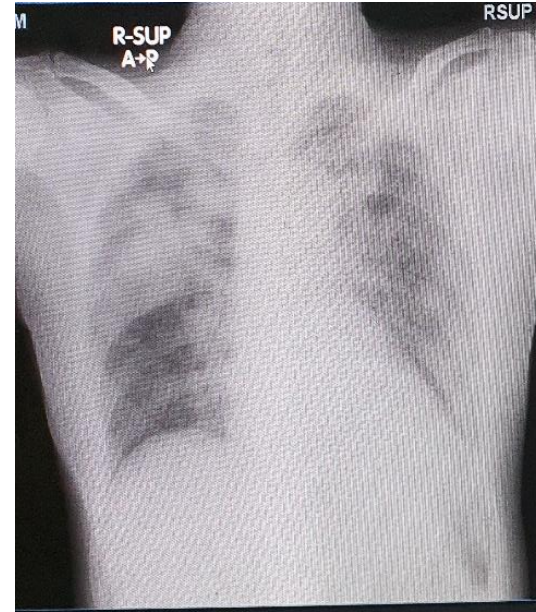


- ABGA: pH: 7.361; pCO₂: 43.5; HCO₃: 24.6; pO₂: 294

- Work-ups for COVID-19 + Brain CT scan
- Sent to Isolation ICU (deceased before transport)

Case Studies

- A 62 y.o. male with hypertension
- Headache + right-sided weakness for 4 days
- **Decreased consciousness** for 1 day → referred
- Screened negative on the first hospital
- GCS on admission: E₂M₄V₁=7
- BP: 190/100, HR: 120 bpm; RR: 30x/min; Temp: 37.5°C; O₂ sat 87% (↓)
- Rales +/- (basal)
- Funduscopy → N/T
- No meningeal signs
- Right hemiparesis
- Hema: Hb 14.9g/dl; Hct 44.5%; WBC 18.000/mm³ (0/0/20/43/34/3); Plt 296.000/mm³
- Chem: RBS 91; Ur/Cr 16/0.5; Iytes: 137/2.76/100.4;



CT scan: not done



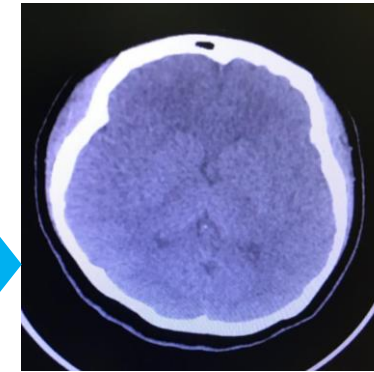
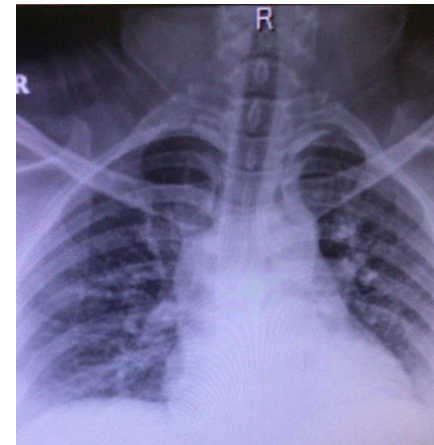
**Hemorrhagic stroke
based on clinical
score**



- Admitted to Isolation Ward
- No anti-thrombotics
- Mannitol
- Antibiotics
- Other treatments

Case Studies

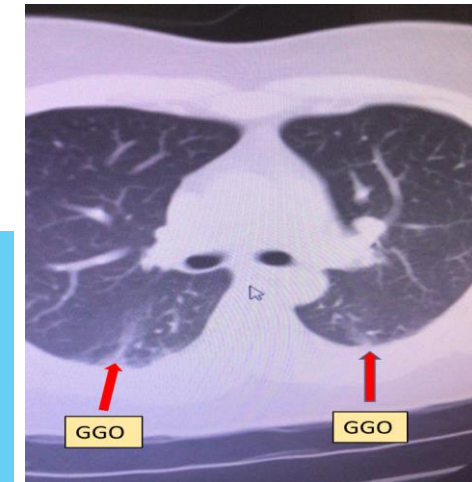
- **A 37 y.o. female, no previously known VD risk factor**
- Sudden left-sided weakness for 18 hours + swallowing difficulty + headache
- **History of fever 1 month ago + cough → now only cough + shortness of breath**
- GCS on admission: 15
- BP: 110/70, HR: 80 bpm; RR: 24x/min; Temp: 36.5°C
- Swallowing test → not done
- Left hemiplegia with decreased tone
- Hema: Hb 13.6; Hct 37%; Plt 400.000 /mm³; WBC 12.000/mm³ (5/1/3/56/28/7)
- Chem: Ur/Cr 16.6/0.72; Iytes: 142/3.2/109



No bleeding

- **Antiplatelets**
- **Statin**
- High resolution Chest CT

Bilateral-posterior, mild subpleural ground glass opacities & parenchymal bands noted; Possible Covid-19, susp. absorption stage, leaving/residual GGO & fibrous – parenchymal bands



- Admitted to Isolation Ward
- Antibiotic
- Pharyngeal swab

Courtesy of Dr. Mohammad Kurniawan, Sp.S(K), M.Sc(stroke med.), Cipto Mangunkusumo Hospital Jakarta

Case Studies

- A 23 y.o. ♂ with upper & lower facial weakness, became bilateral & complete within 2 days, mastoid pain, loss of taste, and lower limb paresthesia.
- **10 days ago** → fever & sore throat for 3 days, treated with AB for 5 days.
- Neuro exam: complete facial palsy, generalized areflexia, sensory ataxia.
- Brain MRI: focal contrast enhancement at the internal acoustic meatus.
- EMG (12th day after admission): axonal sensory-motor damage involving the lower limbs, with sural nerve sparing, + ↓ facial nerve CMAP amplitude.
- **Therapy: IVIg** → mild improvement of the facial weakness + disappearance of limb paresthesia.
- **Normal thorax imaging** → pharyngeal swab (+) for SARS-CoV-2.

Take Home Messages

- COVID-19 → potential serious neurological complications
- COVID-19 patients: **high-risk for stroke** → protected stroke code
- Seizures: poor prognosis → consider **drug-drug interaction** & careful monitoring for treatment
- GBS → anticipate **after the acute phase** but not too long
- CNS infection: needs further research but based on known mechanism & previous CoV outbreaks → **plausible**
- Anticipate other problems like **the non-COVID-19 patients** who are also need our help



LP equipment during COVID-19 pandemic
(consent has been granted from the patient)



thank you!