兒童重症新冠病毒感染之臨床表現、支持性療法與葉克膜使用時機

台大兒童醫院 兒童加護病房
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- **COVID -19 is an emerging, rapid evolving situation**
- **Much of the information you will hear will be out of date within hours to days**
- **Best websites for up-to-date information: CDC, WHO, local media??**
- **https://www.sccm.org/SurvivingSepsisCampaign/Guidelines/COVID-19**
- **https://services.aap.org/en/search/?context=all&k=covid%2019**

We want to know…..

- How many percentages of COVID-19 (+) children need PICU care
  - Symptoms? PICU indications?
  - Outcome?
- PICU guidelines in COVID-19 pandemic?
- ECMO indication and outcome?
- Impact on PICU epidemiology?
  - Source allocation
- Pivot into adult care?
  - Space management
  - Staff training
  - Equipment

Data on pediatric COVID-19

Area	All COVID-19	<18-20 y/o	PICU admission	pediatric mortality	Reference
China	N=72314	1.3 %	NA	0	JAMA 2020 Feb 24
Italy	N=22512	1.2%	NA	0	JAMA 2020 Mar 17
Korean	N=4212	4.8%	NA	0	J Korean Med Sci 2020; 35:e12
China	(Wuhan Children's Hospital)		3/171	1/171	N Engl J Med 2020; 382:1663-1665
Spain		41	4/41	1	JAMA pediatrics 2020
Spain			7	0	PCCM 2020
USA		67	13/46 admitted (28%)	1/13	J Pediatrics 2020
USA	N=150000	2572 (1.7%)	15	3 ??	2020 MMWR
USA, Canada			48	2	JAMA Pediatr. 2020;174(9):868-873.
USA		24	7 (36.8%)	1	PCCM 2020;21

Clinical Characteristics and Outcomes of Hospitalized and Critically Ill Children and Adolescents with Coronavirus Disease 2019 at a Tertiary Care Medical Center in New York City

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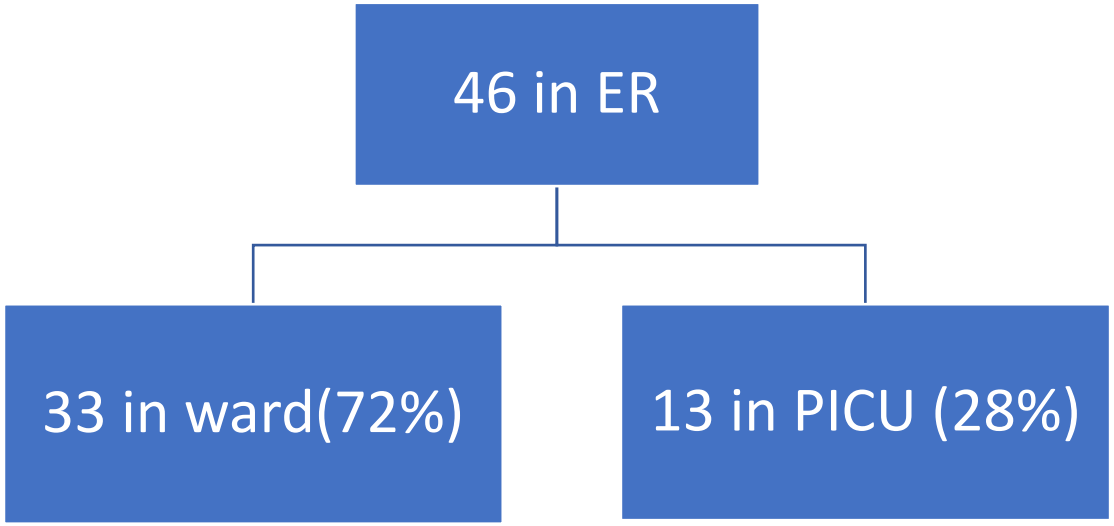
- 

Obesity and asthma were highly prevalent but not significantly associated with PICU admission (P = .99).
PICU risk factors: higher CRP , procalcitonin, and pro-BNP levels and platelet counts.
Patients in the PICU were more likely to require high-flow nasal cannula (P = .0001) and were more likely to have received Remdesivir through compassionate release (P < .05).
Severe sepsis and septic shock syndromes were observed in 7 (53.8%) patients in the PICU. ARDS was observed in 10 (77%) PICU patients, 6 of whom (46.2%) required invasive mechanical ventilation for a median of 9 days.

J Pediatr 2020;223:14-9

Of the 13 patients in the PICU, 8 (61.5%) were discharged home, and 4 (30.7%) patients remain hospitalized on ventilatory support at day 14. One patient died after withdrawal of life-sustaining therapy because of metastatic cancer.

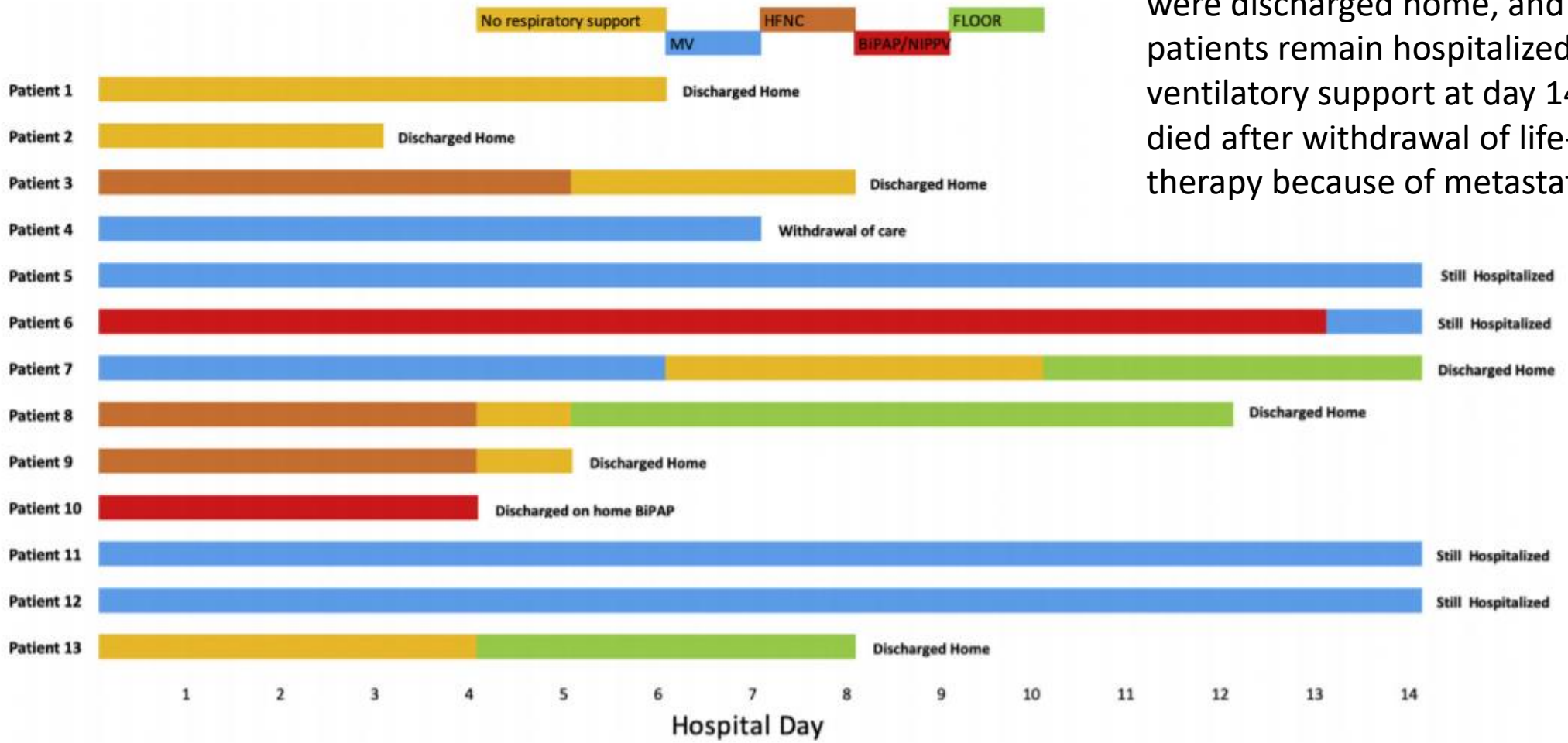


Figure. Outcomes for individual patients in the PICU. Respiratory support modalities as a function of time (in hospitalization days) presented by patient. *Light orange color* denotes no respiratory support. *Blue color* denotes mechanical ventilation (MV). *Dark orange color* denotes high flow nasal cannula (HFNC). *Red color* denotes bilevel positive airway pressure/non-invasive positive pressure ventilation (BiPAP/NIPPV). *Green color* denotes transfer to the pediatric floor.

Characteristics and Outcomes of Children With Coronavirus Disease 2019 (COVID-19) Infection Admitted to US and Canadian Pediatric Intensive Care Units

Table 1. Presentation and Demographic Characteristics of 48 Children Treated in Pediatric Intensive Care Units for Coronavirus Disease 2019 (COVID-19)

Characteristic	No. (%)
Age, median (IQR), y	13 (4.2-16.6)
Age group, y	
<1	8 (17)
1-5	6 (13)
6-10	7 (15)
11-21	27 (56)
Male	25 (52)
Presentation	
Asymptomatic	1 (2)
Respiratory	35 (73)
Gastrointestinal	1 (2)
Neurological	2 (4)
Circulatory	2 (4)
Other	7 (15)
Comorbidities	
None	8 (17)
Medically complex[a]	19 (40)
Immune suppression/malignancy	11 (23)
Obesity	7 (15)
Diabetes	4 (8)
Seizures	3 (6)
Congenital heart disease	3 (6)
Sickle cell disease	2 (4)
Chronic lung disease	2 (4)
Other congenital malformations	2 (4)

Abbreviation: IQR, interquartile range.

[a] Defined as children who had a long-term dependence on technological support (including tracheostomy) associated with developmental delay and/or genetic anomalies.

Table 2. Clinical Course and Outcomes of 48 Children With Coronavirus Disease 2019 (COVID-19) Treated in Pediatric Intensive Care Units (PICUs)

Characteristic	No. (%)
Severity of illness	
Asymptomatic/mild	14 (29)
Moderate	1 (2)
Severe	16 (33)
Critical	17 (35)
Vasoactive support	12 (25)
Organ system failure	
0	6 (13)
1	30 (63)
2	7 (15)
≥3	4 (8)
Maximum respiratory support	
None	9 (19)
Oxygen only	6 (13)
HFNC	11 (23)
CPAP or BiPAP	4 (8)
Intubation/tracheostomy ventilation	18 (38)
Advanced therapies	
None	41 (85)
iNO	3 (6)
ECMO	1 (2)
Plasma exchange	1 (2)
Prone ventilation	2 (4)
Pharmacotherapy	
None	20 (42)
Hydroxychloroquine	21 (44)
Azithromycin	8 (17)
Remdisivir or other antiviral therapy	8 (17)
Tocilizumab	5 (10)
2 agents	10 (21)
3 or more agents	3 (7)
Length of stay, median (IQR), d[b]	
PICU	5 (3-9)
Hospital	7 (4-13)
Outcome at follow-up[c]	
Discharged	31 (65)
Died	2 (4)
Still hospitalized	
Severe or critical condition	9 (19)
Mild or moderate condition	6 (13)

Abbreviations: BiPAP, bilevel positive airways pressure; CPAP, continuous

- Finally, it is important to emphasize that the overall burden of COVID-19 infection in children remains relatively low compared with seasonal influenza.
- As of April 28, 2020, the CDC report 8 deaths in children 14 years or younger related to COVID-19 infection, whereas there have so far been 169 influenza-related deaths in children 14 years or younger during the 2019-2020 season, with 81 of these occurring in 2020.

The Impact of Coronavirus Disease 2019 Pandemic on U.S. and Canadian PICUs

- 2020.3.14-5.26, n=530 in 183 PICUs
- 30 deaths (5.7% case mortality rate)
- Most common mild comorbidity: obesity, asthma, hypertension
- Most common moderate to severe comorbidity: seizure, CP, CLD, requirement of NG, developmental delay.

TABLE 1. Admission Characteristics of 530 Coronavirus Disease 2019 Admissions to Date

Age, yr	Total admissions, *n* (%)
< 2	75 (14)
2–12	132 (25)
12–18	194 (37)
18–30	82 (15)
> 30	47 (9)
Comorbidities	
None	226 (42)
Mild	141 (27)
Moderate/severe	163 (31)
Respiratory support	Days of care to date (67% total days), *n* (%)
High-flow nasal cannula	371 (16)
Noninvasive ventilation	275 (12)
Conventional mechanical ventilation	1,598 (69)
High frequency oscillatory ventilation	12 (< 1)
Extracorporeal membrane oxygenation	60 (3)

TABLE 2. Characteristics of 284 Discharged Coronavirus Disease 2019 Patients

Characteristics	0–2 yr	2–12 yr	12–18 yr	18–30 yr	> 30 yr
n (% all)	42 (15)	70 (25)	106 (37)	36 (13)	30 (11)
Length of stay, median (interquartile range, 1st–3rd quartile) (range)	2.0 (2–4) (1–32)	5 (3–8) (1–25)	5 (2–9) (1–55)	6.5 (2–12) (1–32)	8 (4–15) (1–33)
Deaths (% age group)	1 (2)	2 (3)	4 (4)	2 (6)	12 (40)
Comorbidity moderate to severe (% age group)	12 (29)	16 (23)	32 (30)	21 (58)	13 (43)
Requiring conventional ventilation, high frequency oscillatory ventilation, or extracorporeal membrane oxygenation (% age group)	8 (19)	23 (33)	32 (30)	8 (22)	23 (76)

TABLE 3. Length of Stay, Ventilation, and Case Fatality Rate by Comorbidity of 284 Discharged Patients

Comorbidity	None	Mild	Moderate to Severe
n (% all approximately)	122 (43)	69 (24)	92 (32)
Conventional, high frequency oscillatory ventilation, and extracorporeal membrane oxygenation (% group)	32 (26)	24 (35)	39 (42)
Length of stay, median (interquartile range, 1st–3rd quartile) (range, d)	4 (2–7) (1–33)	5 (2–9) (1–26)	6 (2–11) (1–55)
Case fatalities (rate %)	1 (< 1)	5 (7)	15 (16)

Implications in PICU care

- Contrary to the typical PICU demographics, children less than 2 years comprised of only 14.2% of the population.
- Important comorbidities include obesity, asthma, and hypertension along with developmental delay.
  - Requiring longer stays, more ventilatory support than usual PICU admissions.
- 67% of patients required advanced respiratory support. Preparing for this surge number of ventilator cases and their safe management is crucial

Coronavirus Disease 2019–Associated PICU Admissions: A Report From the Society of Critical Care Medicine Discovery Network Viral Infection and Respiratory Illness Universal Study Registry

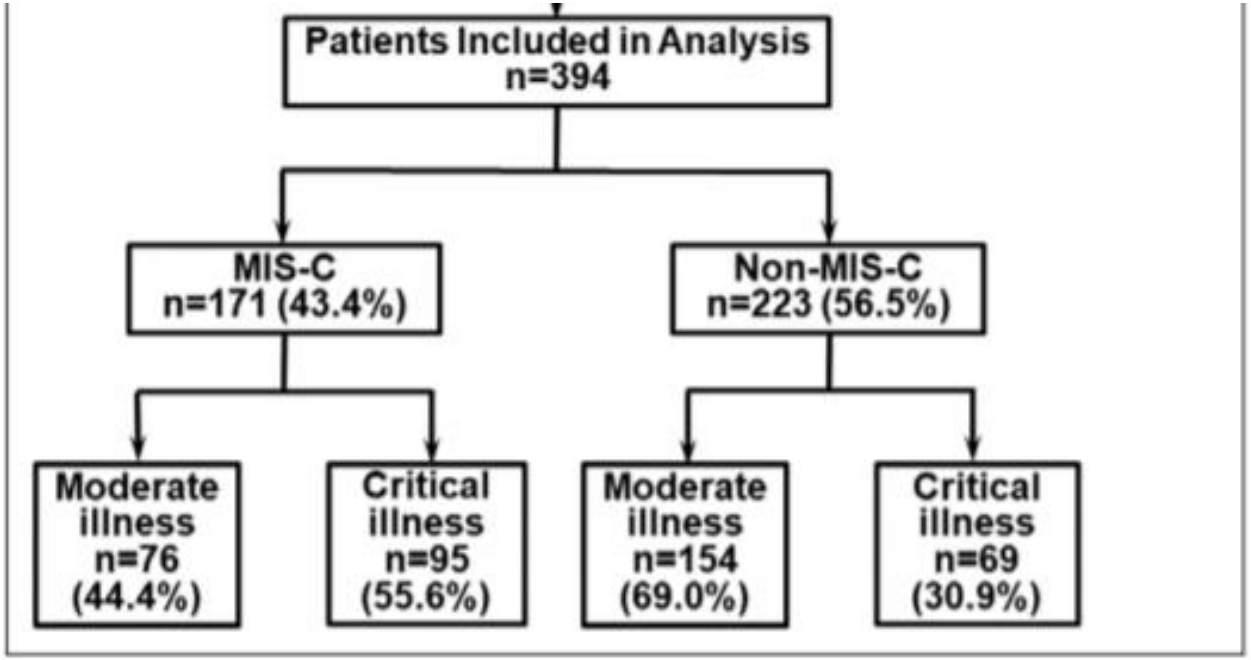
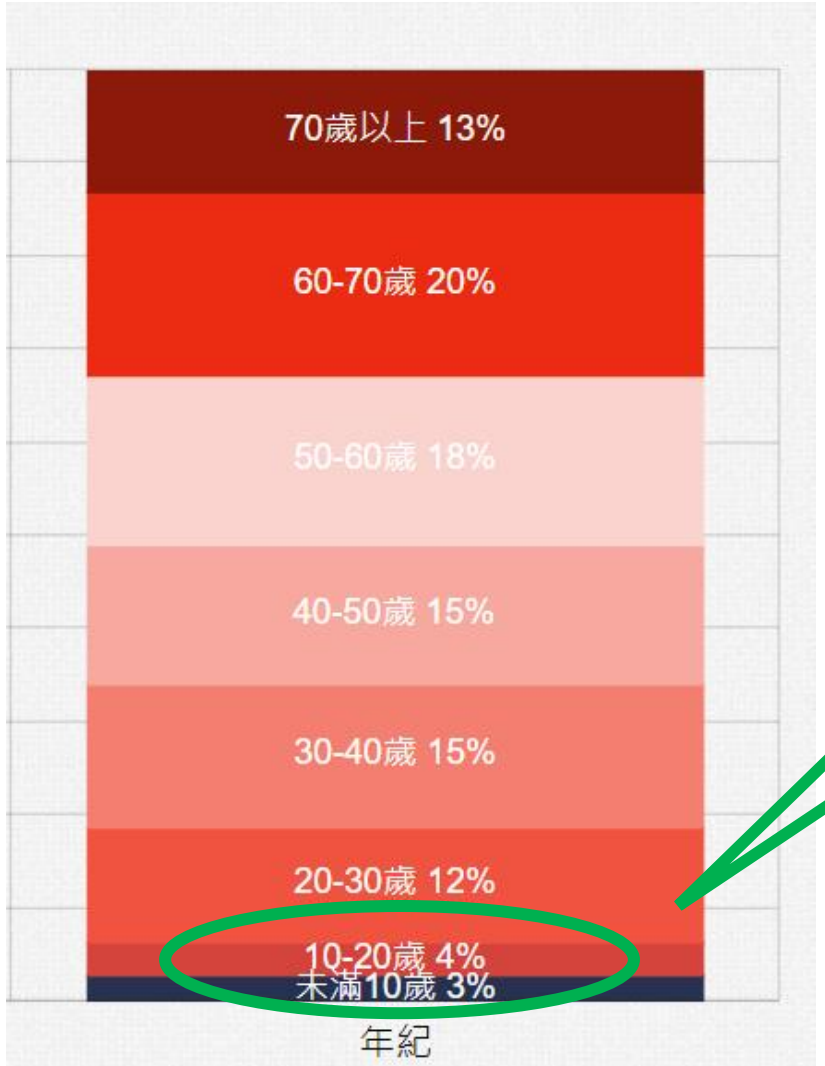


Figure 1. Patient recruitment consort diagram. MIS-C = multisystem inflammatory syndrome in children, VIRUS = Viral Infection and Respiratory Illness Universal Study.

- Children with MISC: younger (2-12 vs adolescents), fever/abdominal pain >> cough/dyspnea, less likely to have comorbidities (33.3% vs 61.9%).
- Inflammatory markers, use of vasopressors, corticosteroids, anticoagulants: more in MISC
- Overall mortality: 3.8%
- MISC: longer hospitalization.

累計確診	新增確診	累計死亡
13,771	+188	518
	+1.38%	+21 (死亡率: 3.76%)



How many % need PICU??
Mortality:0

聯合報 即時 要聞 娛樂 運動 全球 社會 產經 股市 房市 健康 生活 文教 評論 地方 兩岸 數位 旅

美疫情翻轉 新確診兒童占22% 年輕人重症比率提高

2021-05-04 14:27 世界日報 / 編譯林梅婕／綜合3日電

No vaccine for children
School and group activity restarted
children may play a major role in community-based viral transmission

Data on pediatric COVID-19 (updated)

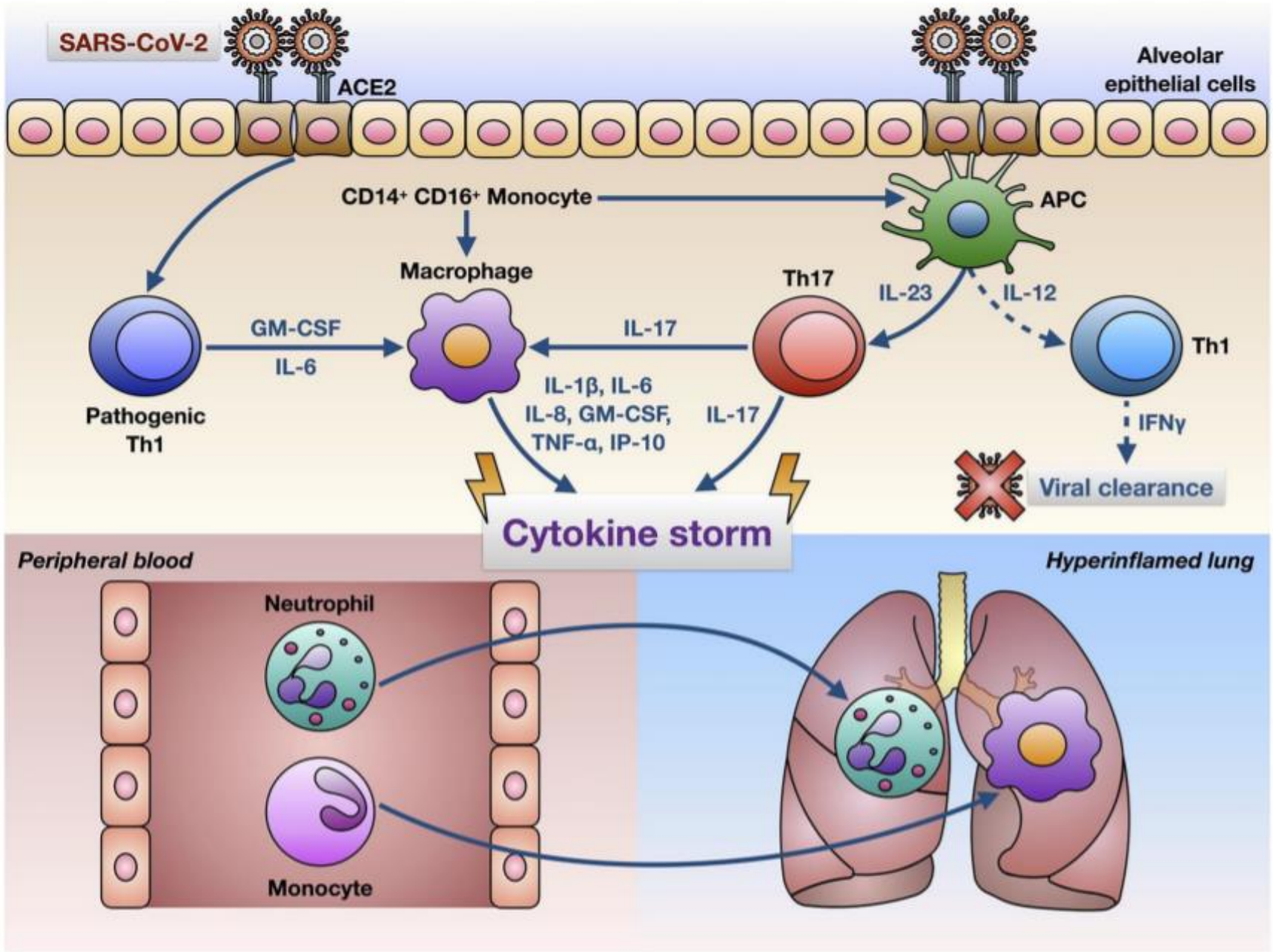
- As of May 6, 2021, more than 3.85 million children in the US have tested positive for COVID-19, accounting for 14% of all cases in the US.
- For the week ending May 6, children were 24% of new reported weekly COVID-19 cases.
- Children and adolescents generally have a milder COVID-19 disease course as compared to adults.
- Available data indicate that COVID-19 associated hospitalization and death is uncommon in children
  - Children were 1.2%-3.1% of total reported hospitalizations, and between 0.1-1.9% of all child COVID-19 cases resulted in hospitalization
  - Children were 0.00-0.21% of all COVID-19 deaths
  - Ranks in the 2019 top 10 causes of death in children.

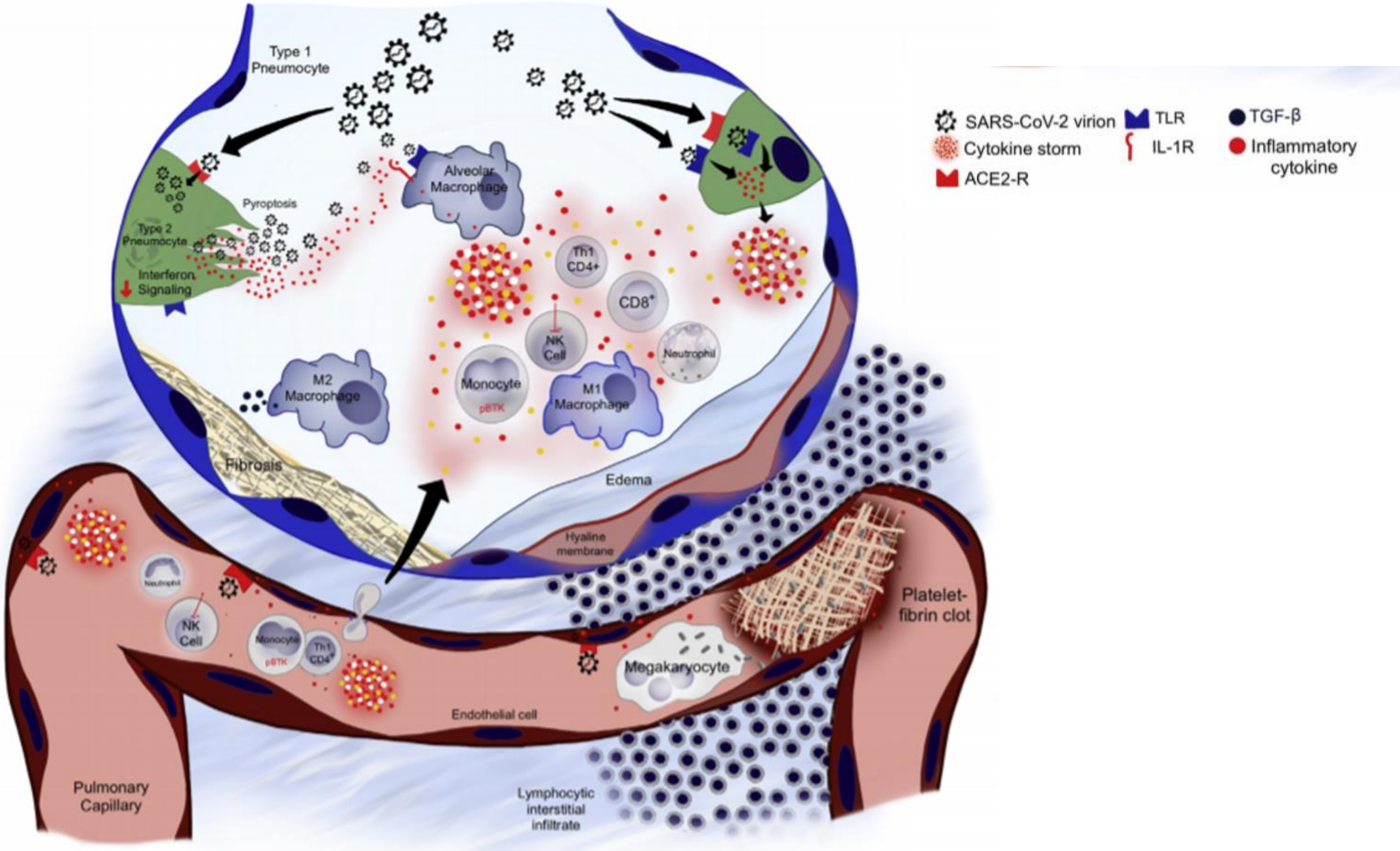
Risk factors

- Attentions has now shifted to the vulnerability of children for two reasons.
  - First, the degree of which children transmit COVID-19 is key to how countries reopen communities after lockdown
  - Second, new concerns about a novel severe Kawasaki – like disease in children related to COVID-19 now referred as multisystem inflammatory syndrome in children (MIS-C)

PICU indications

- ARDS
  - Type L COVID-19 ARDS: intrapulmonary shunting, preserved compliance, less potential for lung recruitability, increased alveolar dead space due to pulmonary micro-thrombi formation.
  - Type H : “traditional ARDS”
- Shock, MOF
- MIS-C
- Lack of caregivers
- Isolation


SARS-CoV-2
ACE2
Alveolar epithelial cells
CD14+ CD16+ Monocyte
APC
Macrophage
Th17
IL-23
IL-12
GM-CSF
IL-6
IL-17
Th1
Pathogenic Th1
IL-1β, IL-6
IL-8, GM-CSF,
TNF-α, IP-10
IL-17
IFNγ
Viral clearance
Cytokine storm
Peripheral blood
Hyperinflamed lung
Neutrophil
Monocyte


SARS-CoV-2 virion
Cytokine storm
ACE2-R
TLR
IL-1R
TGF-β
Inflammatory cytokine
Type 1 Pneumocyte
Alveolar Macrophage
Pyroptosis
Type 2 Pneumocyte
Interferon Signaling
Th1 CD4+
CD8+
NK Cell
Neutrophil
Monocyte
pBTK
M1 Macrophage
M2 Macrophage
Fibrosis
Edema
Hyaline membrane
Platelet-fibrin clot
Megakaryocyte
Endothelial cell
Pulmonary Capillary
Lymphocytic interstitial infiltrate

PICU guidelines for COVID-19??

OPEN

Caring for Critically Ill Children With Suspected or Proven Coronavirus Disease 2019 Infection: Recommendations by the Scientific Sections' Collaborative of the European Society of Pediatric and Neonatal Intensive Care*

PCCM January 2021 • Volume 22 • Number 1

(Pediatr Crit Care Med 2020; 21:e1031–e1037)

Perspective of the Surviving Sepsis Campaign on the Management of Pediatric Sepsis in the Era of Coronavirus Disease 2019*

www.nature.com/pr

Pediatric RESEARCH

SPECIAL ARTICLE OPEN

COVID-19 PICU guidelines: for high- and limited-resource settings

Pediatric Research (2020) 88:705–716

Basic rules --Protect Yourself and Your Team

- Full personal protective equipment (PPE) should always be worn when caring for COVID-19 (+) or suspected children.
- Aerosol generating procedures (AGPs) are high-risk interventions and must be reduced to an absolute minimum.

TABLE 1.
Common Aerosol-Generating Events

High-flow nasal cannula.
Continuous positive airway pressure or noninvasive ventilation without an adequate seal.
Bag-mask ventilation.
Intubation.
Any advertent or inadvertent circuit or endotracheal tube disconnection.
Tracheal suction (without a closed system).
Extubation.
Coughing/sneezing or any procedure inducing this.
Chest physiotherapy.
Delivery of nebulized medications (unless via closed circuit).
Cardiopulmonary resuscitation (prior to intubation).

SPECIAL ARTICLE OPEN

COVID-19 PICU guidelines: for high- and limited-resource settings

Saraswati Kache[1], Mohammod Jobayer Chisti[2], Felicity Gumbo[3], Ezekiel Mupere[4], Xia Zhi[5], Karthi Nallasamy[6], Satoshi Nakagawa[7], Jan Hau Lee[8], Matteo Di Nardo[9], Pedro de la Oliva[10], Chhavi Katyal[11], Kanwaljeet J. S. Anand[12], Daniela Carla de Souza[13], Vanessa Soares Lanziotti[14] and Joseph Carcillo[15]

- Respiratory support
- Hemodynamic support
- Adjuvant therapy
- CPR
- ECMO considerations
- MIS-C

Pediatric Research (2020) 88:705–716;

Grading of recommendation

- strong recommendation
- weak recommendation (suggestions)
- best practice statement
- in our practice statement (insufficient evidence recommendation)

(Paucity of relevant evidence regarding COVID-19 in pediatric patients and the rapidly changing landscape of this disease)

Respiratory support

	Recommendation	Strength
1	In children with COVID-19 infection and hypoxemia, begin supplemental oxygen therapy by low-flow nasal cannula when oxygen saturations (SpO2) are <90%. If the patient continues with hypoxemia, oxygen delivery via a face mask with reservoir bag should be initiated	Strong
2	Children with COVID-19 that remain with increased work of breathing and hypoxemia should be escalated to high flow nasal cannula (HFNC) if available. Patients with progressive respiratory distress or where HFNC is unavailable can be escalated to noninvasive positive pressure ventilation (NIPPV), bubble continuous positive airway pressure (bCPAP) or bilevel positive airway pressure (BiPAP).	Strong
3	Children with COVID-19 failing NIPPV should be escalated to mechanical ventilation.	Strong

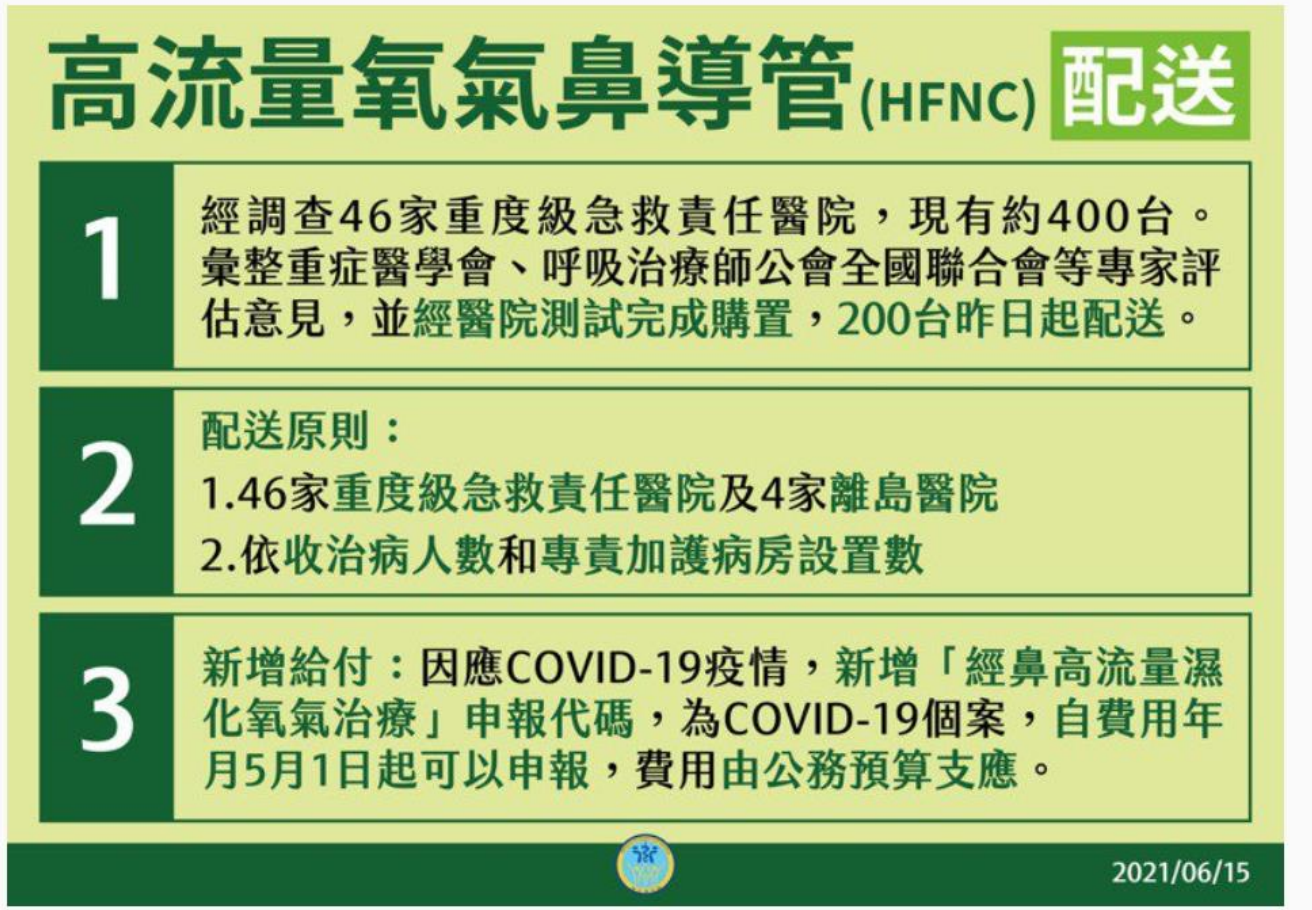
	Recommendation	Strength
4	In children with COVID-19 requiring intubation, the procedure should be done by a trained and skilled health-care provider.	Strong
5	Children with COVID-19 requiring intubation should be intubated with a cuffed endotracheal tube.	Strong
6	For children with COVID-19 requiring intubation, use of video laryngoscopy should be considered for intubation	Weak
7	Personal protective equipment (PPE) should be worn for intubation and extubation of all children with COVID-19.	strong
8	For children with COVID-19 requiring mechanical ventilation, tidal volumes should be limited to 6 ml/kg	Weak

Multiple intubation attempts can result in poorer outcomes for the patients and place the provider at greater risk of exposure to COVID-19.

9	For children with COVID-19 requiring mechanical ventilation, positive end expiratory pressure (PEEP) titration should be individualized to each patient and their phase of ARDS.	Weak
10	For children with COVID-19 requiring mechanical ventilation, prone position should be considered in patients with ARDS and severe hypoxemia.	Weak
11	For children with COVID-19 requiring mechanical ventilation with refractory hypoxemia, use of Inhaled nitric oxide is not recommended.	Insufficient evidence
12	For children with COVID-19 requiring mechanical ventilation, high-frequency oscillatory ventilation (HFOV) is not recommended for routine application but may be considered in select cases.	Insufficient evidence

「救命神器」為何醫院不敢買　醫師曝真實原因！網緊張：小心被出征

22小時前



Hemodynamic support

- **There is no change to the 2020 surviving sepsis campaign (SSC) “pediatric septic shock guidance” recommended in children with COVID-19.**
- **Of note, hypovolemia is common following the vomiting and diarrheal prodrome with reduced fluid intake before ICU admission.**

Hemodynamic support

	Recommendation	strength
13	For children with COVID-19 and shock admitted to health systems with PICU availability (ventilatory support and access to vasoactives), administer bolus fluids, 10–20 ml/kg per bolus up to 40–60 ml/kg, over the first hour of resuscitation.	Weak
14	For children with COVID-19 and shock admitted to health systems without PICU	
	a. Patients without hypotension, no fluid bolus should be administered, and maintenance fluids should be initiated	Strong
	b. Patients with hypotension, administer bolus fluids, 10–20 ml/kg per bolus up to 40 ml/kg, over the first hour of resuscitation.	Weak
15	In children with COVID-19 and shock, crystalloid solutions should be administered, instead of colloids, for the initial fluid resuscitation. Specifically, we recommend use of balanced solutions over 0.9% saline.	Weak
16	In children with COVID-19 and shock, age-appropriate mean arterial pressure (MAP) should be targeted. In settings where accurate MAPs cannot be easily obtained, systolic blood pressure is an acceptable option.	Strong

	Recommendations	Strength
17	In children with COVID-19 and shock, consider the use of advanced hemodynamic variables, when available (measurements of cardiac index, systemic vascular resistance, and central venous oxygen saturation); these along with clinical variables at the bedside can guide resuscitation	Weak
18	In children with COVID-19 and shock, in addition to clinical evaluation, trends in blood lactate levels can help guide resuscitation.	Weak
19	In children with COVID-19 and shock, epinephrine or norepinephrine should be administered, instead of dopamine. Diluted solution can be initiated through a peripheral intravenous catheter if central venous access is not available.	Best practice
20	In children with COVID-19 and shock who need high doses of catecholamines, consider initiating vasopressin.	Best practice
21	In children with COVID-19 and shock, recommendations regarding the use of inodilators cannot be made. But in clinical practice, inodilators such as milrinone, dobutamine or levosimendan could be used when there are signs of tissue hypoperfusion and cardiac dysfunction, despite high doses of catecholamines	Best practice

	Recommendations	Strength
22	In children with COVID-19 and refractory shock, consider anti-inflammatory doses of glucocorticoids.	Insufficient evidences
23	In a pediatric patient with COVID-19 and severe disease, a thorough cardiac evaluation should be conducted including an EKG, echocardiography and cardiac biomarker levels (troponin, CK and CK MB).	Strong
24	Glucocorticoid anti-inflammatory therapy and intravenous immunoglobulin (IVIG) are potential suggested treatments for children with COVID-19-related myocarditis.	Insufficient evidences

Adjuvant therapy

	Recommendations	Strength
25	Consider anticoagulation therapy in children with COVID-19 with:	Weak
	a. Mild risk of venous thromboembolism (VTE) (i.e. those with indwelling central or peripheral central venous catheters or severely ill with no hyperinflammatory status and with no risk of thrombosis), consider:	
	i. Subcutaneous enoxaparin < 2 months: 0.75 mg/kg/dose q12 h; ≥2 months: 0.5 mg/kg/dose q12 h	
	ii. Anti-Xa factor target: 0.3–0.5 IU/ml	
	b. Children with COVID-19 with high risk of VTE (i.e. critically ill, hyperinflammatory state—C-reactive protein > 150 mg/l, D-dimer > 1500 ng/ml, IL-6 > 100 pg/ml, ferritin > 500 ng/ml, or past history of thromboembolic events) consider:	
	i. Subcutaneous enoxaparin < 2 months: 1.5 mg/kg/dose q12 h; ≥2 months: 1 mg/kg/dose q12 h	
	ii. Anti-Xa factor target: 0.5–1 IU/ml	

	Recommendations	
26	In critically ill children with COVID-19, thrombocytopenia-associated multiple organ failure (TAMOF: platelet counts of less than 100 × 109/L and two or more failing organs) and acquired ADAMTS-13 deficiency could indicate a thrombotic microangiopathic process. For such patients, therapeutic plasma exchange may be beneficial in controlling the hyperinflammatory and thrombotic state and reversing organ dysfunction.	Weak
27	For critically ill children with COVID-19, we suggest convalescent plasma treatment be offered only within a research framework or on a compassionate basis.	Insufficient evidence
28	For children with COVID-19 admitted to the PICU, initiate enteral nutrition for patients with no contraindications, but parenteral nutrition need not be initiated in the first 7 days of PICU admission.	Weak
29	For children with COVID-19 that develop fluid overload or renal dysfunction and are unresponsive to diuretic therapy consider renal replacement therapy.	Weak

AKI and RRT

- Unless there is a situation such as severe sepsis where CRRT is clearly superior to PD allowing hemodynamic stability and more accurate fluid removal, both methods are equally efficacious.
- Other extracorporeal therapies (e.g. hemoperfusion and cytoabsorption) have been proposed to remove proinflammatory cytokines, thereby reducing cytokine storm induced organ damage.
  - With minimal supportive data and the risk of therapeutic drug removal, as well as poor availability, we do not currently recommend them.

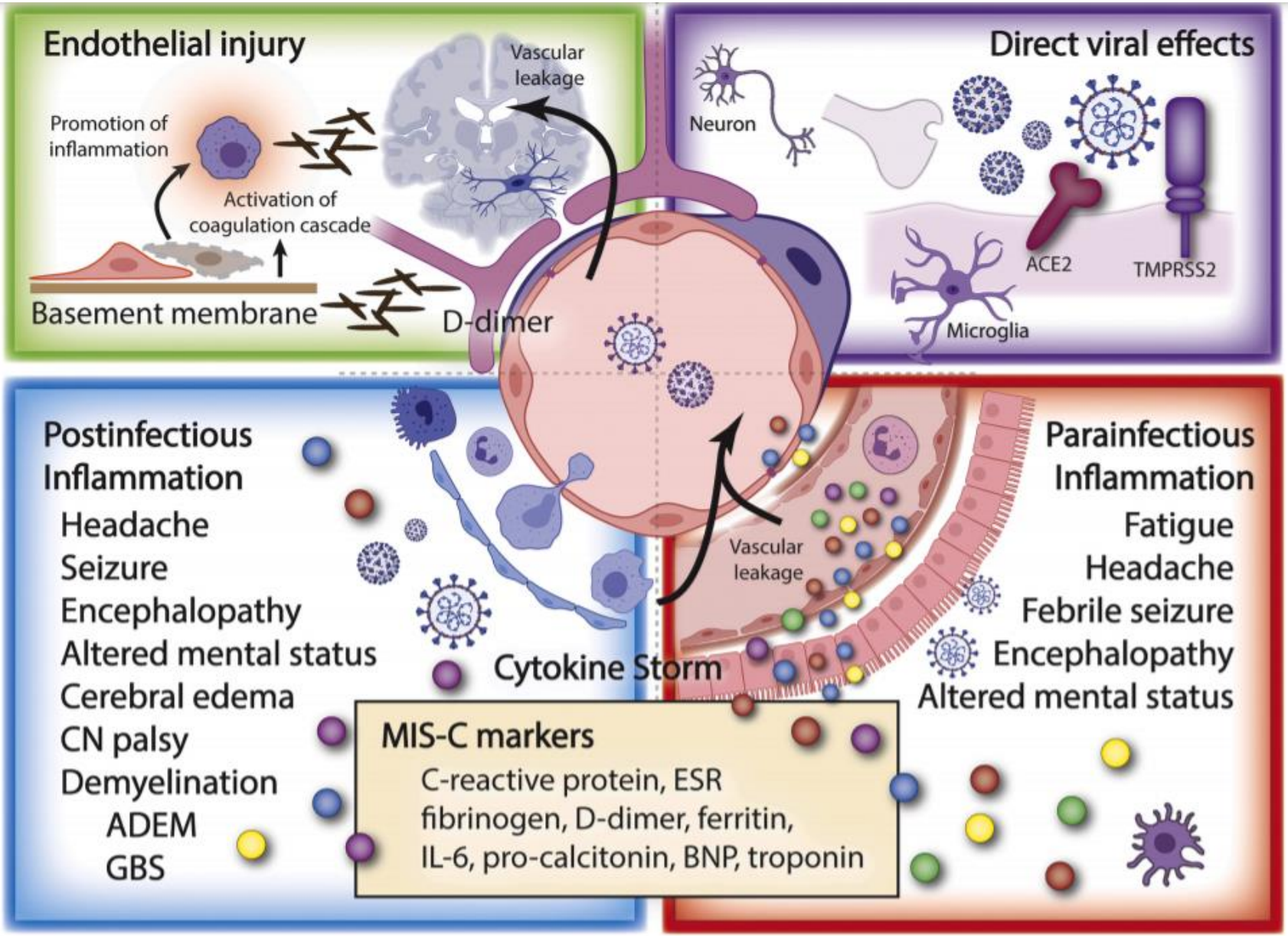
Adaptation of RRT Regimens With Resource Limitation

- With resource limitations, RRT regimens can be adapted.
  - 1) Single machine use for two or more patients by increasing exchange rates to compensate for decreased RRT time
  - 2) Use of lower rates after achieving metabolic control to limit consumable waste
  - 3) If CRRT unavailable, PD may be used

Risks of Filter Clotting During CRRT.

- The hypercoagulable COVID-19 state means frequent filter clotting, and vascular thrombosis can be an issue, so the usual approach of prefilter heparin is recommended
- Many adults with COVID-19 have had deranged liver function tests (LFTs), so citrate has been relatively contraindicated. Cautious use in children is permitted, Alternatively, a combination of prostacyclin and unfractionated heparin (both pre filter) can be used.

Neurologic involvement



- Anti-bacterial treatment
  - Follow the principals of antimicrobial stewardship as SSC guidelines.
  - 1 hour bundle : blood culture collection before administering antibiotics, administration of broad-spectrum antibiotics, and completion of a 20-mL/kg fluid bolus.
  - Daily assessment of de-escalation

- Nutritional support
  - Enteral feeding tube placement and aspiration are potential AGP
  - Decrease exposure by quicker gastric tube placement rather than postpyloric tubes
  - Avoid measuring gastric residual volumes (no evidence)

ECMO

	Recommendations	Strength
	ECMO considerations	
35	**ECMO should be considered in COVID-19-infected pediatric patients to manage ARDS and/or cardiac failure (myocarditis, arrhythmias, pulmonary embolism).**	**Strong**
36	**Strict selection criteria for both Veno-Arterial (VA) and Veno-Venous (VV) ECMO should be applied in order to utilize ECMO for those patients most likely to benefit from the procedure.**	**Strong**

Sepsis/shock in covid-19 pandemic

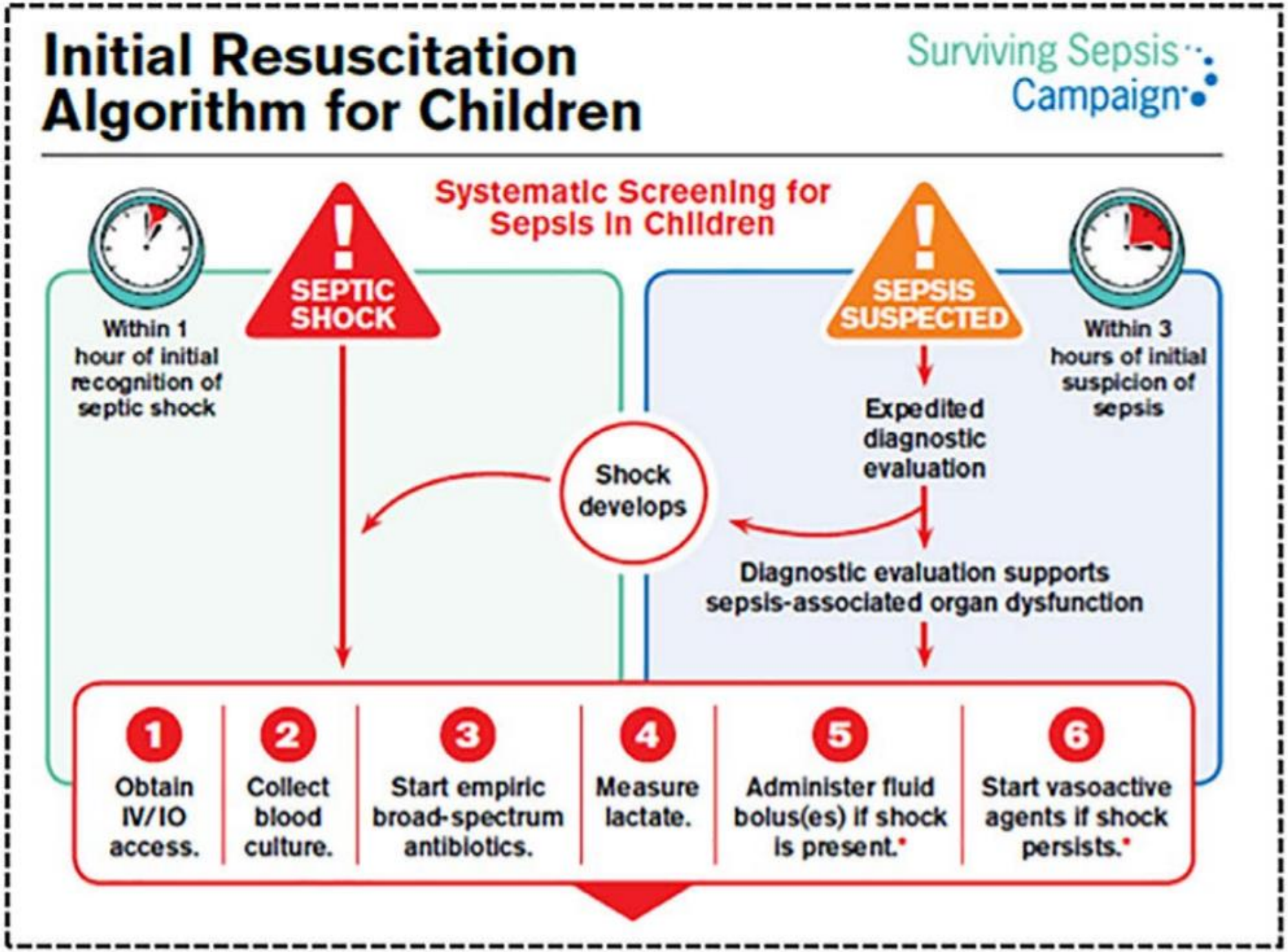
- Even if social distancing reduced the incidence of sepsis by up to 50% by limiting transmission of more typical pathogens, the number of children hospitalized for sepsis in the US would have remained at least 10-fold higher than COVID-19.
- Fear to seek medical attention, lack of accessible transportation, overwhelmed local resources, and disrupted supply chains risk delaying sepsis recognition and exacerbation inequities in health.
- Not all septic shock is COVID-19 related.

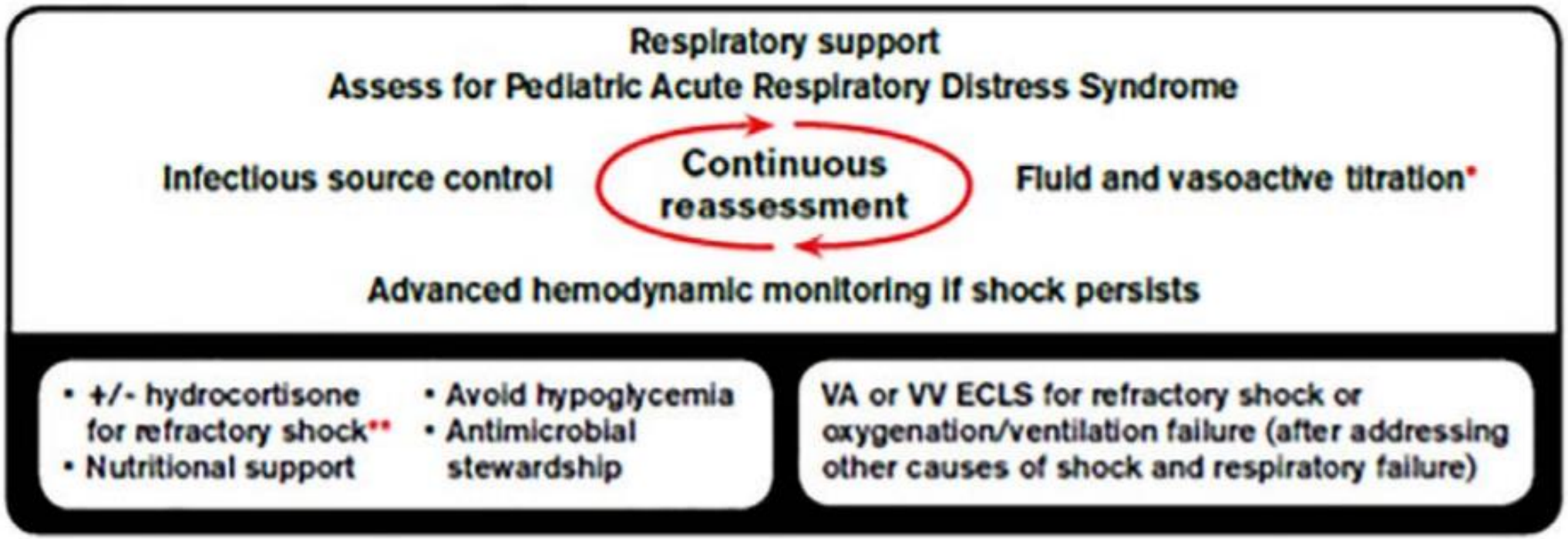
TABLE 1. Characteristics of Non-Coronavirus Disease 2019 Sepsis, Acute Coronavirus Disease 2019 Illness, and Pediatric Inflammatory Multisystem Syndrome Temporally Associated With Severe Acute Respiratory Syndrome Coronavirus 2 Infection/ Multisystem Inflammatory Syndrome in Children

Characteristic	Non-COVID-19 Sepsis	Acute COVID-19 Illness	Pediatric Inflammatory Multisystem Syndrome Temporally Associated With Severe Acute Respiratory Syndrome Coronavirus 2 Infection/Multisystem Inflammatory Syndrome in Children
Initial symptoms			
Fever	Common	Common	Common (typically persistent for days)
Cough	Possible	Common	Uncommon
Shortness of breath	Common	Common	Uncommon
Rhinorrhea	Possible	Possible	Uncommon
Gastrointestinal[a]	Possible	Possible	Common
Tachypnea	Common	Common	Possible
Tachycardia	Common	Common	Common
Myalgia	Possible	Common	Uncommon
Sore throat	Possible	Possible	Uncommon
Fatigue	Common	Common	Common
Headache	Possible	Common	Uncommon
Conjunctival erythema	Uncommon	Uncommon	Common
Cervical lymphadenopathy	Possible	Not reported	Possible
Dried, cracked lips, or "strawberry tongue"	Uncommon	Uncommon	Common
Rash	Possible	Uncommon	Common
Anosmia	Uncommon	Possible	Not reported
Dysgeusia	Uncommon	Possible	Not reported

Characteristic	Non-COVID-19 Sepsis	Acute COVID-19 Illness	Pediatric Inflammatory Multisystem Syndrome Temporally Associated With Severe Acute Respiratory Syndrome Coronavirus 2 Infection/Multisystem Inflammatory Syndrome in Children
Laboratory results			
WBCs	Low, normal, or high	Low, normal, or high	Low, normal, or high
Absolute lymphocytes	Low to normal	Very low	Very low
Platelets	Low to normal	Normal to high	Normal to high
Sodium	Low, normal, or high	Normal	Low
Alanine aminotransferase, aspartate aminotransferase	Normal to high	Normal to high	High
Creatinine	Normal to high	Normal to high	Normal to high
C-reactive protein	High	High	High
Procalcitonin	High	Normal to high	Normal to high
Erythrocyte sedimentation rate	High		Low to normal
Ferritin	Normal to high	High	Very high
Fibrinogen	Low (with disseminated intravascular coagulation or macrophage activation syndrome), normal, or high	High	Usually high (but can be low)
D-dimer	Normal to high	Very high	Very high
Troponin	Often normal	Often high	High
Brain natriuretic peptide	Normal to high	Normal to high	Very high
Triglyceride	Normal	High	High
Microbiology			
Blood culture	± Positive	Negative[b]	Negative[b]
SARS-CoV-2 polymerase chain reaction	Negative	Positive	± Positive (often with high cycle time)[c]
SARS-CoV-2 immunoglobulin G	Negative	Unknown	Positive

A


Initial Resuscitation Algorithm for Children
Surviving Sepsis Campaign
Systematic Screening for Sepsis in Children
SEPTIC SHOCK
SEPSIS SUSPECTED
Within 1 hour of initial recognition of septic shock
Within 3 hours of initial suspicion of sepsis
Expedited diagnostic evaluation
Shock develops
Diagnostic evaluation supports sepsis-associated organ dysfunction
1 Obtain IV/IO access.
2 Collect blood culture.
3 Start empiric broad-spectrum antibiotics.
4 Measure lactate.
5 Administer fluid bolus(es) if shock is present.*
6 Start vasoactive agents if shock persists.*



*See fluid and vasoactive algorithm. Note: Fluid bolus should be omitted from bundle if a) fluid overload is present or b) it is a low-resource setting without hypotension. Fluid in mL/kg should be dosed as ideal body weight.

**Hydrocortisone may produce benefit or harm.

ECMO for COVID-19 pediatric patients

- Indications: not different from other disease
- Limited resources vs best effects??
- Risk of staff?

- Ethical dilemmas”
  - Prioritization of children over adults for ECMO use
  - Institution of DNR orders
  - ECPR for COVID-19 patients

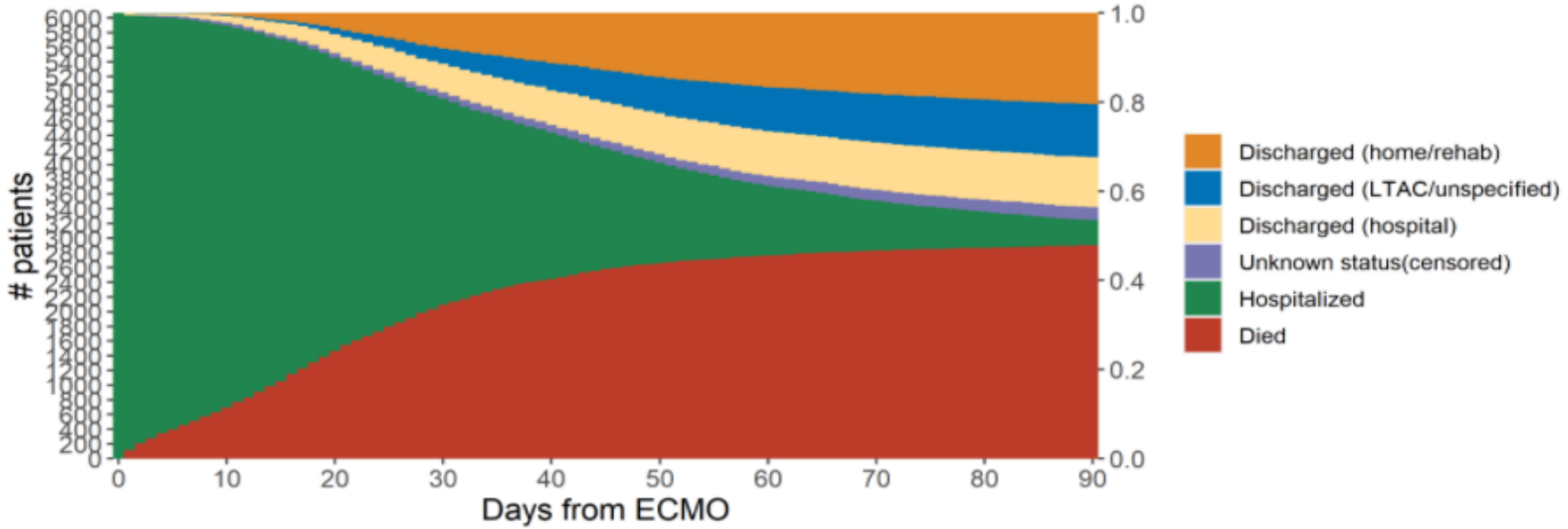
COVID-19 Cases on ECMO in the ELSO Registry

Total COVID-19 Cases	COVID-19 Suspected or Confirmed	COVID-19 Confirmed Cases
	7315	7288

Total counts of COVID-19 confirmed patients and count of COVID-19 suspected but not confirmed by testing.

Patients who initiated ECMO at least 90 days ago	COVID-19 Confirmed	COVID-19 In-hospital Mortality
	6072	49%

Outcomes



Age 50 y/o
FiO2 100%
PEEP 14
PIP 34
PF ratio 70
Prone 60%
NMB 75%
Steroid 70%
Remdesivir 49%
anti-cytokine 19%
ECPR 0%

COVID-19 ECMO counts by ELSO Chapter

	Still on ECMO	Still Hospitalized at ELSO Center	Total (n)
All ELSO	774	1013	7315
North America	375	501	4586
Europe	224	278	1657
Asia Pacific	22	23	79
Latin America	78	127	498
SWAAC	75	84	495

Reports counts of ECMO-supported suspected or confirmed COVID-19 cases by ELSO Chapter

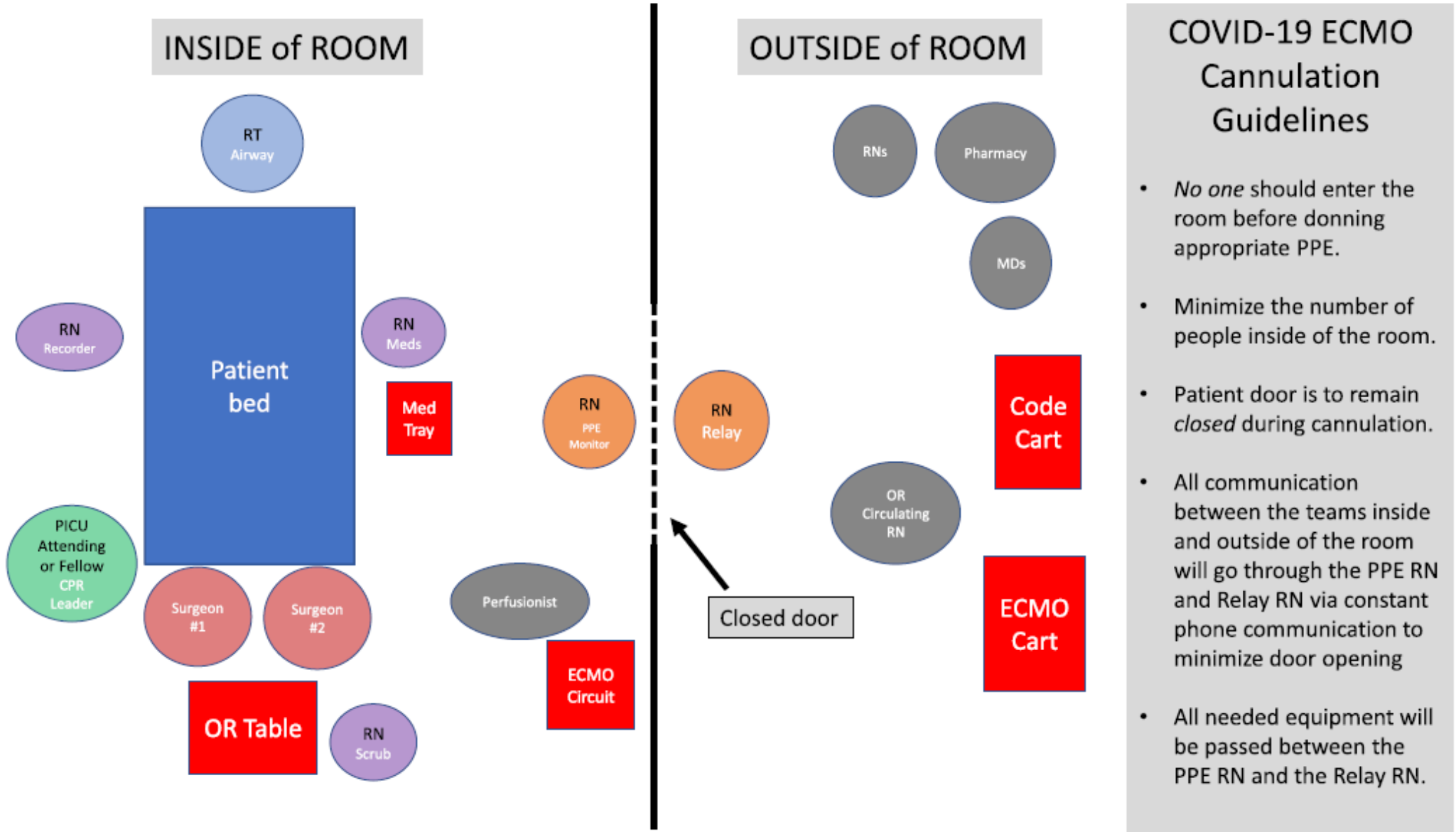
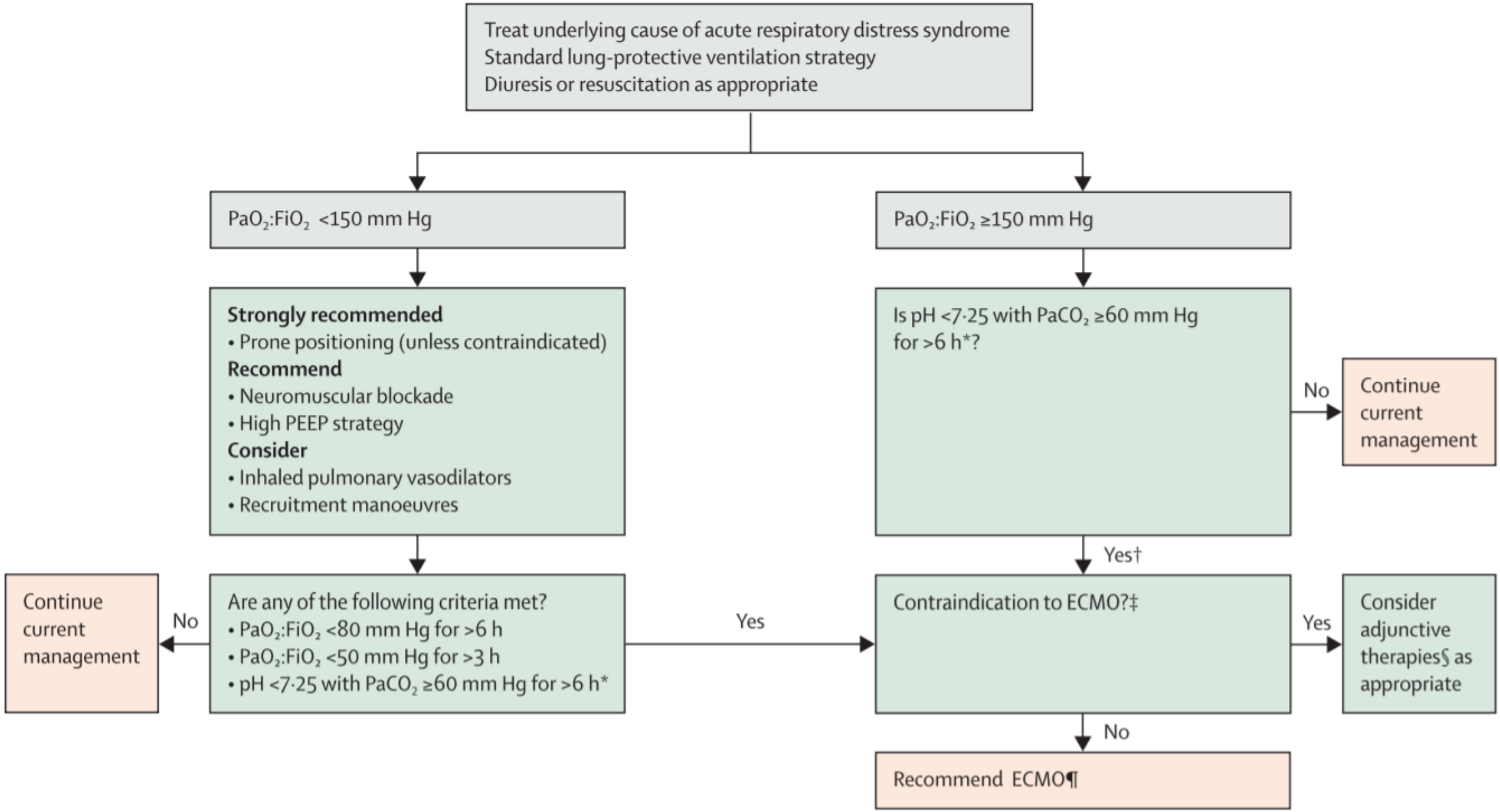
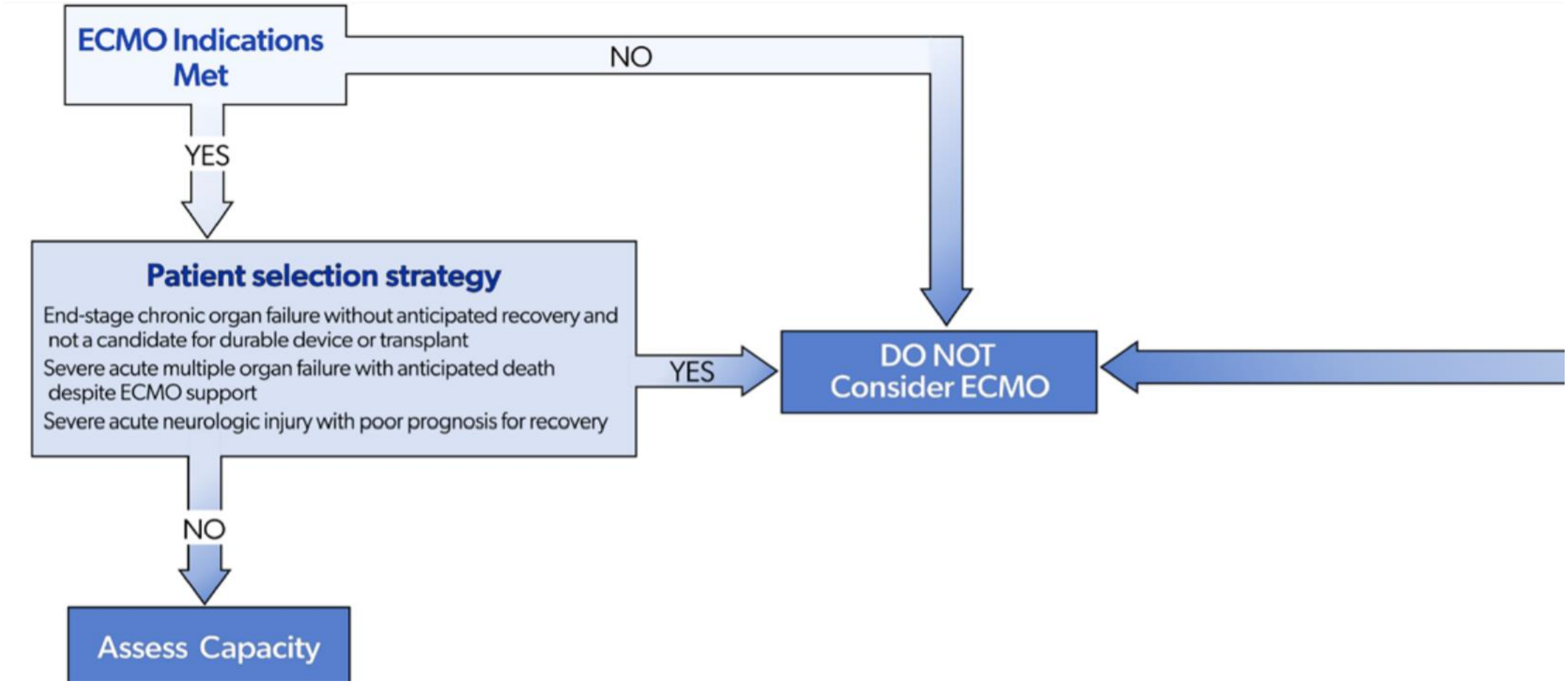
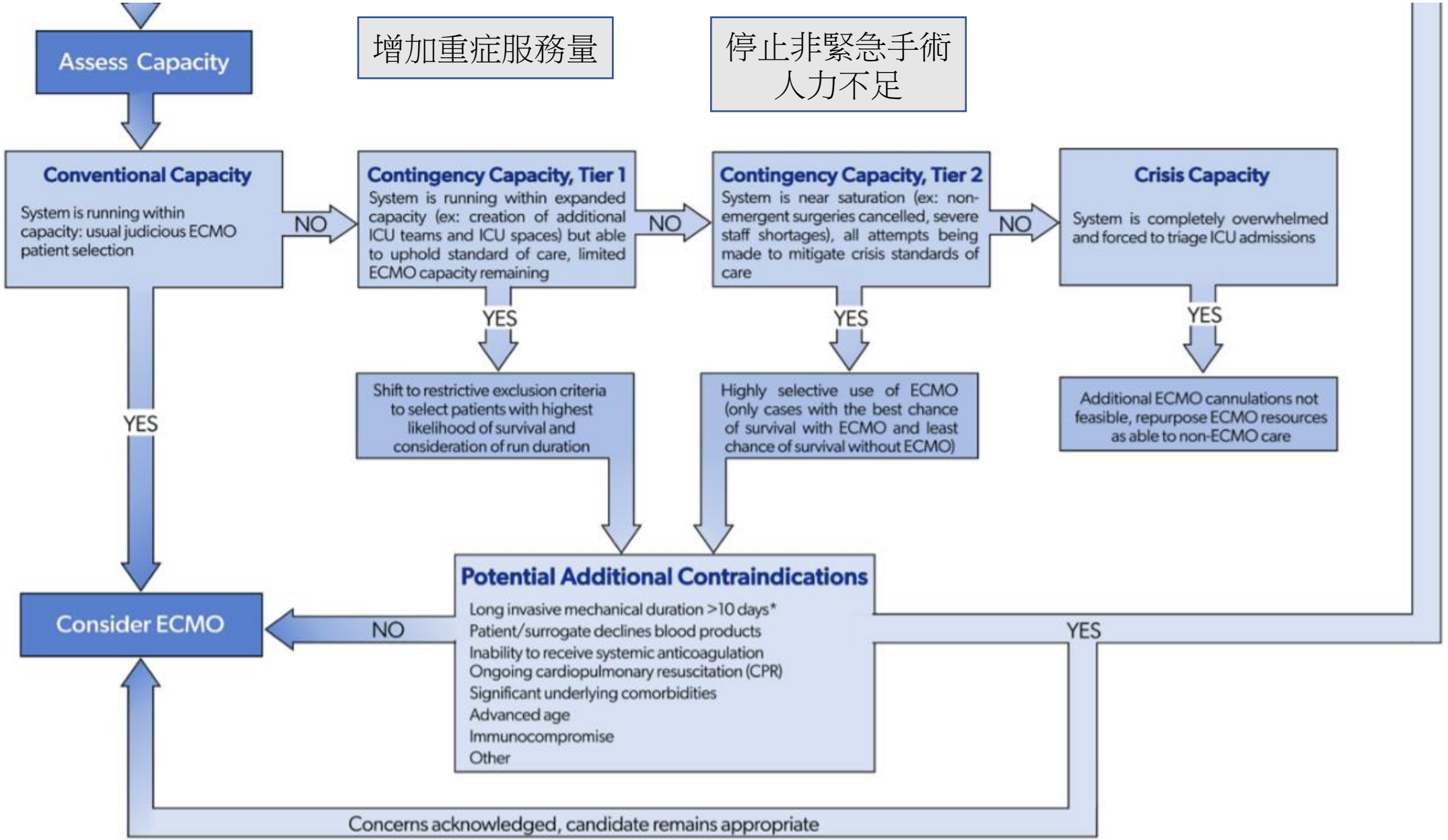


Fig. 2. Schematic for ECMO Cannulation of COVID-19 Positive Patients and Patients Under Investigation. (Credit: Anita Sen, MD).


Treat underlying cause of acute respiratory distress syndrome
Standard lung-protective ventilation strategy
Diuresis or resuscitation as appropriate
PaO2:FiO2 <150 mm Hg
PaO2:FiO2 ≥150 mm Hg
Strongly recommended
• Prone positioning (unless contraindicated)
Recommend
• Neuromuscular blockade
• High PEEP strategy
Consider
• Inhaled pulmonary vasodilators
• Recruitment manoeuvres
Is pH <7·25 with PaCO2 ≥60 mm Hg for >6 h*?
No
Continue current management
Yes†
Are any of the following criteria met?
• PaO2:FiO2 <80 mm Hg for >6 h
• PaO2:FiO2 <50 mm Hg for >3 h
• pH <7·25 with PaCO2 ≥60 mm Hg for >6 h*
No
Continue current management
Yes
Contraindication to ECMO?‡
Yes
Consider adjunctive therapies§ as appropriate
No
Recommend ECMO¶


ECMO Indications Met
NO
YES
Patient selection strategy
End-stage chronic organ failure without anticipated recovery and not a candidate for durable device or transplant
Severe acute multiple organ failure with anticipated death despite ECMO support
Severe acute neurologic injury with poor prognosis for recovery
YES
DO NOT Consider ECMO
NO
Assess Capacity


Assess Capacity
增加重症服務量
停止非緊急手術
人力不足
Conventional Capacity
System is running within capacity: usual judicious ECMO patient selection
NO
Contingency Capacity, Tier 1
System is running within expanded capacity (ex: creation of additional ICU teams and ICU spaces) but able to uphold standard of care, limited ECMO capacity remaining
NO
Contingency Capacity, Tier 2
System is near saturation (ex: non-emergent surgeries cancelled, severe staff shortages), all attempts being made to mitigate crisis standards of care
NO
Crisis Capacity
System is completely overwhelmed and forced to triage ICU admissions
YES
YES
YES
Shift to restrictive exclusion criteria to select patients with highest likelihood of survival and consideration of run duration
Highly selective use of ECMO (only cases with the best chance of survival with ECMO and least chance of survival without ECMO)
Additional ECMO cannulations not feasible, repurpose ECMO resources as able to non-ECMO care
YES
Potential Additional Contraindications
Long invasive mechanical duration >10 days*
Patient/surrogate declines blood products
Inability to receive systemic anticoagulation
Ongoing cardiopulmonary resuscitation (CPR)
Significant underlying comorbidities
Advanced age
Immunocompromise
Other
NO
Consider ECMO
YES
Concerns acknowledged, candidate remains appropriate

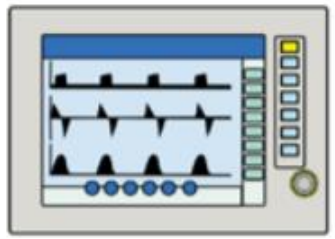
疫情期間葉克膜使用建議

1、葉克膜之使用，在許多疾病上，療效並無定論。
2、葉克膜之使用，應視個案狀況、醫院資源、人力而定。
3、目前國內具有合格葉克膜體外維生系統支持之訓練及操作人員配置仍有不足，因此須審慎。
4、心跳停止之葉克膜急救，並非急救之標準治療。應謹慎選擇。在成功率低或是無法保障醫療從業人員安全之情況下，建議暫停。
5、已經證實**COVID**為陽性者，**ECPR**在全球指引視為禁忌症。”除非已經證實非**COVID**者，才可考慮**ECPR”**
6、呼吸衰竭之葉克膜使用，應由跨科部團隊，專業討論後決定。對於預期治療無效或反應不佳之個案，應考慮緩和醫療。

台灣體外維生系統學會

Management strategy or procedure

Pulmonary

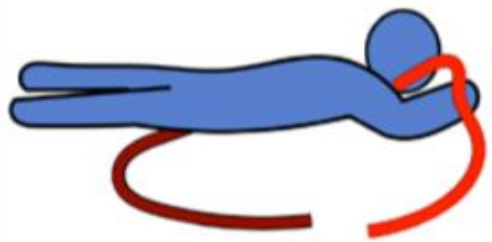


Mechanical Ventilation

No data to suggest deviation from commonly performed low-volume, low-pressure ventilator management for COVID-19 patients receiving ECMO for pulmonary support.

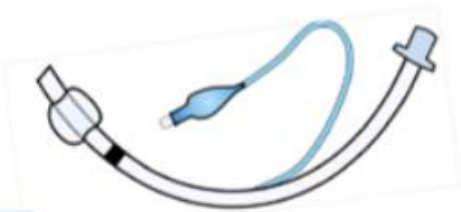
Tracheostomy

Percutaneous tracheostomy appears to be safe and feasible for patients with COVID-19.



Prone positioning

Prone positioning during ECMO is feasible, data are preliminary (demonstrate a potential association with lower mortality) but a recommendation cannot be offered at this time.



Awake ECMO

Early extubation strategy with awake ECMO may be feasible in COVID-19, but insufficient evidence to support recommendation.

Hematologic & Hemodynamics

Coagulopathy

COVID-19-induced coagulopathy appears to increase risk of both thrombotic and hemorrhagic events; however, normalized to run duration, rates of bleeding and circuit clotting similar to historical data: insufficient data to suggest deviation from usual anticoagulation practices on ECMO.

Deep Venous Thrombosis

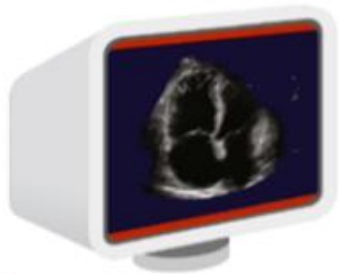
There may be a propensity for clotting with COVID-19 and ECMO: low threshold to pursue imaging for suspected DVT suggested, but insufficient data to recommend routine surveillance for DVT.

Cytokine Removal

Elevated cytokine profiles have been observed in COVID-19, but seem to be lower than in other causes of ARDS, sepsis and CAR T-cell-mediated cytokine release syndrome: extracorporeal hemadsorption or elimination therapies can only be recommended within the context of clinical trials.

Blood Transfusions

There is no evidence to deviate from usual institutional practice for blood transfusion thresholds during ECMO.



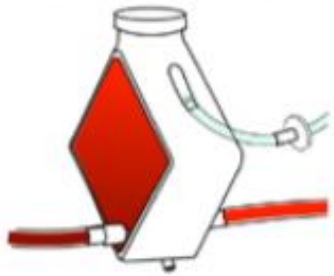
Hemodynamic Monitoring

Cardiac complications of COVID-19 have been reported, e.g., myocarditis, stress cardiomyopathy, acute right ventricular failure, pulmonary embolism, or acute coronary syndrome. Remaining vigilant to detect evidence of acute hemodynamic deterioration on V-V ECMO recommended.

General

PPE

Refer to local institutional policies and prior interim ELSO COVID-19 guidelines for recommendations on methods for PPE use and conservation when facing inadequate supply.

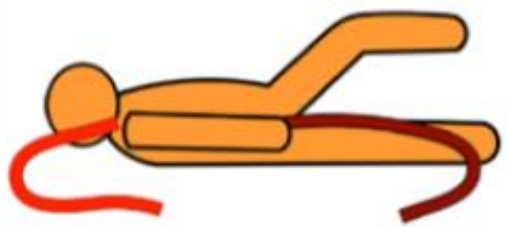


Membrane Lung

Limited evidence suggests SARS-CoV-2 does not spread from the blood to the gas side of polymethylpentene membrane lungs (MLs); to date, routine scavenging of ML gas outlet or use of viral filter is not recommended.

Co-infections

High rates of ventilator associated pneumonia and bacteremia observed, recommend remaining vigilant.



Rehabilitation

Mobilization is feasible, and may improve outcomes for extended runs and in ECMO as bridge to transplant, but current data do not refute or support rehabilitation on ECMO.

PICU challenges caused by indirect effects of COVID-19 pandemic

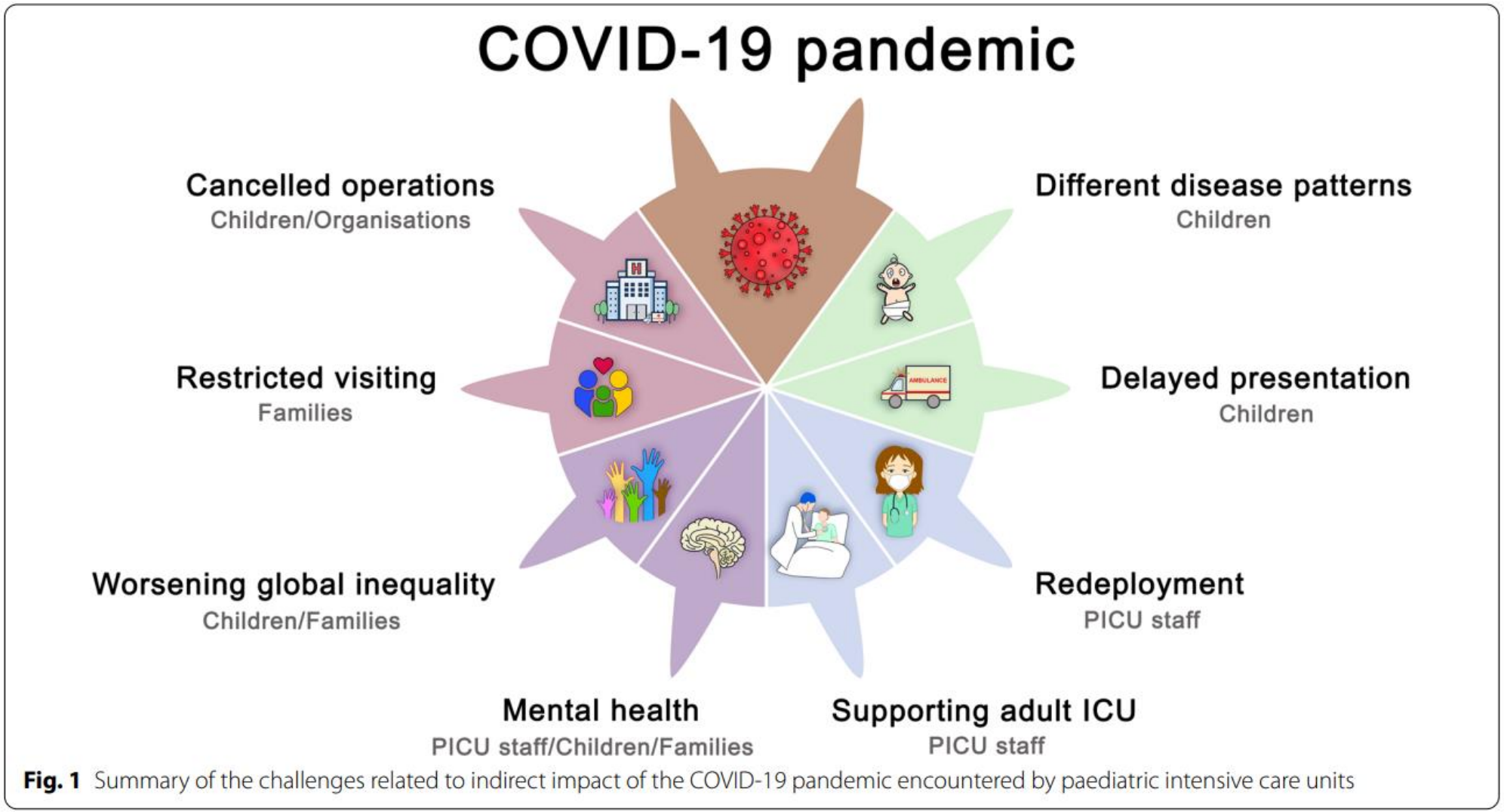
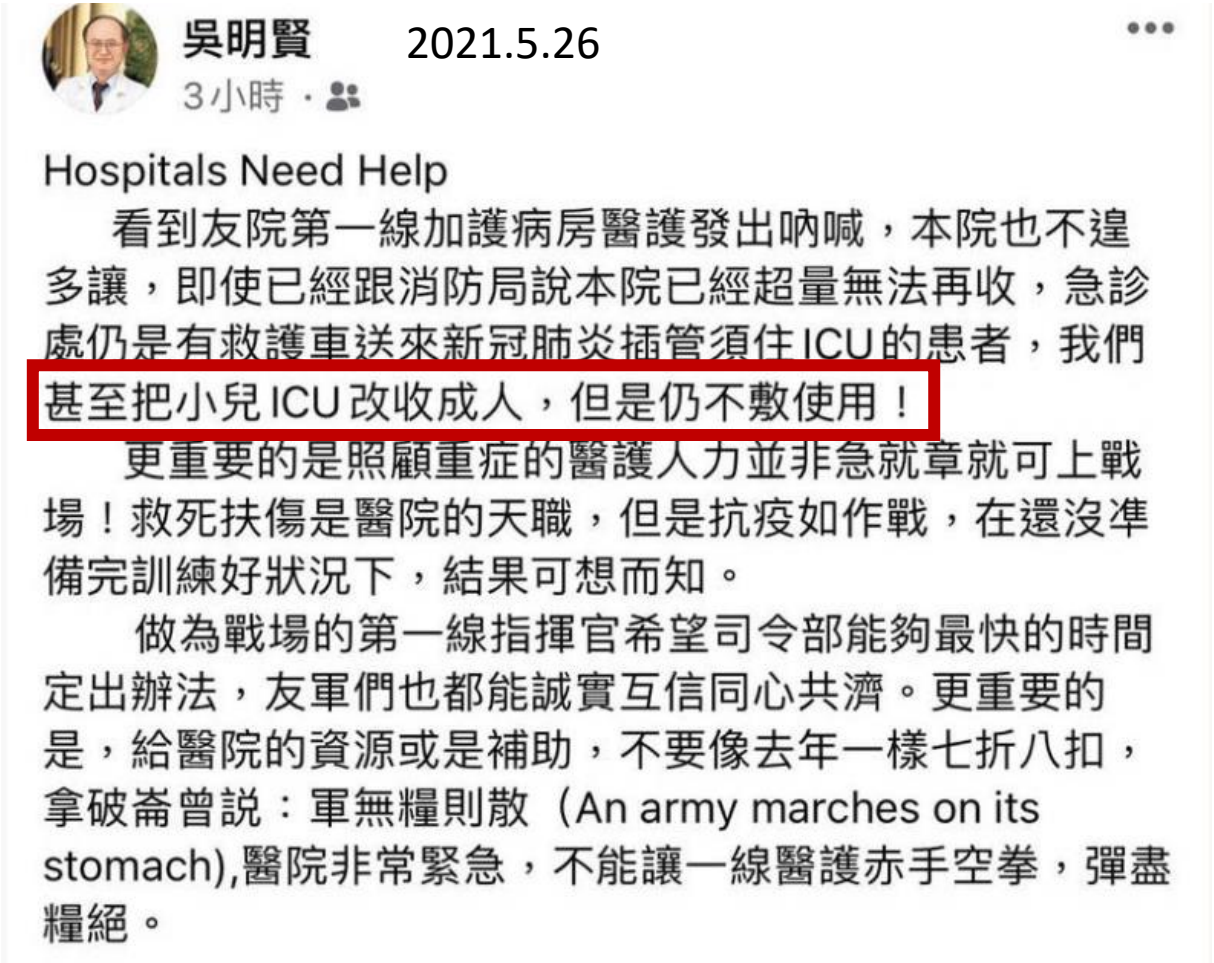


Fig. 1 Summary of the challenges related to indirect impact of the COVID-19 pandemic encountered by paediatric intensive care units

Rapid transition of a PICU to adult COVID-19 ICU care



吳明賢 2021.5.26

3小時 ·

Hospitals Need Help

看到友院第一線加護病房醫護發出吶喊，本院也不遑多讓，即使已經跟消防局說本院已經超量無法再收，急診處仍是有救護車送來新冠肺炎插管須住ICU的患者，我們甚至把小兒ICU改收成人，但是仍不敷使用！

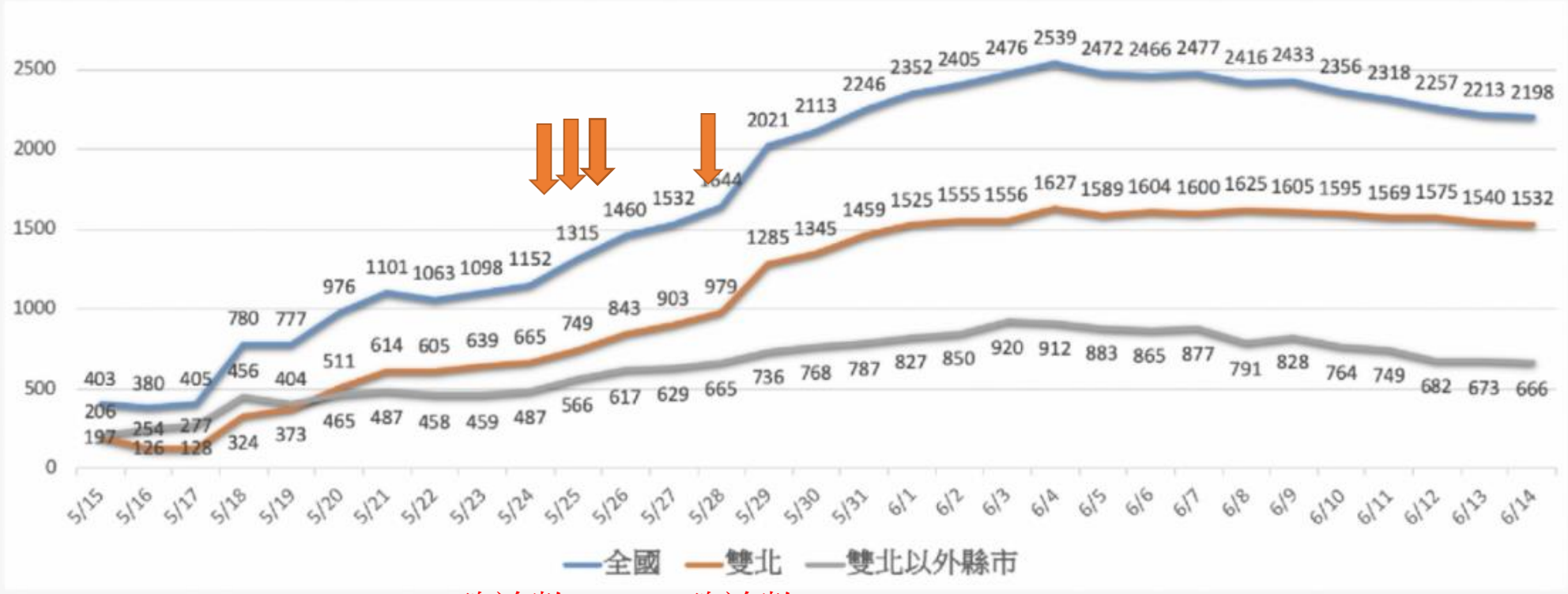
更重要的是照顧重症的醫護人力並非急就章就可上戰場！救死扶傷是醫院的天職，但是抗疫如作戰，在還沒準備完訓練好狀況下，結果可想而知。

做為戰場的第一線指揮官希望司令部能夠最快的時間定出辦法，友軍們也都能誠實互信同心共濟。更重要的是，給醫院的資源或是補助，不要像去年一樣七折八扣，拿破崙曾說：軍無糧則散（An army marches on its stomach),醫院非常緊急，不能讓一線醫護赤手空拳，彈盡糧絕。

- Preserving the internal PICU team ensured a rapid transition and boosted morale.
- Renovation of physical space:
  - Safely transferring and discharging pediatric patients, then transforming into COVID-19 MICU.
  - Restriction of regular PICU admission
- Staff training and support
  - Prior to the pandemic, we cared lots of adult patients
  - PALS vs ACLS

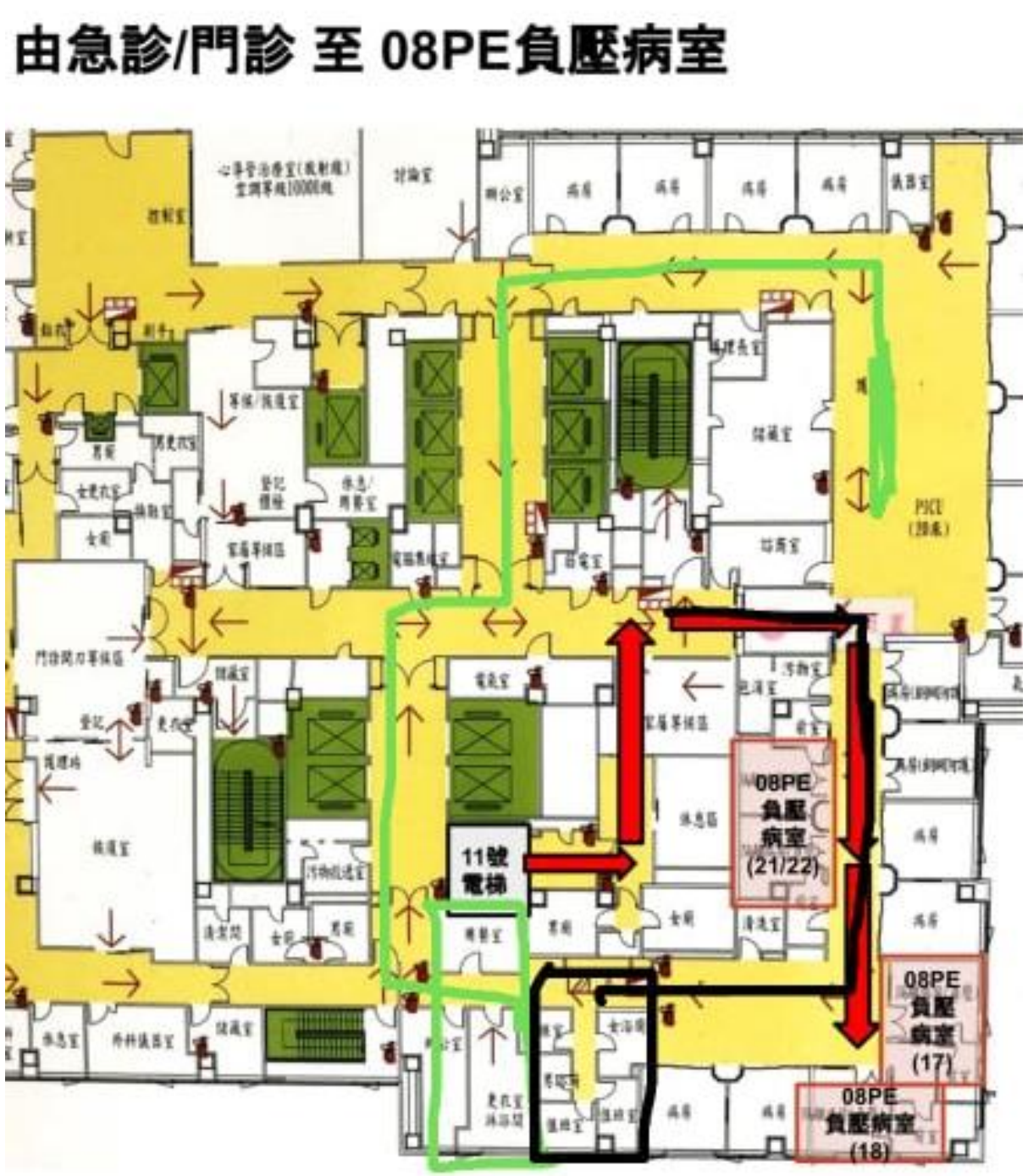
全國及雙北專責病房收治人數趨勢圖

0515-0614



確診數5450　確診數7315

Identifying potential surge capacity in the form of extra beds, staff, and equipment should also be anticipated and published guidance on early planning for pandemics is already available.



- **Hybrid model of pediatric and adult critical care**
  - Catering to the different physical, emotional, and social needs of both children and adults by the same PICU team was challenging.
  - Adult critical care vs essential services for critically ill children.
- Clean area vs contaminated area
- Fixed staff
- Total bed capacity 20-→12+
- Strict infection control

A hybrid model of pediatric and adult critical care during the coronavirus disease 2019 surge: the experience of two tertiary hospitals in London ands New York

TABLE 2.
Characteristics of Pediatric and Adult Patients Admitted During the Coronavirus Disease 2019 Surge With Performance Indicators

	King's College Hospital		Morgan Stanley Children's Hospital	
Characteristics	**Adults**	**Children**	**Adults**	**Children**
Admissions, *n*	23	25	46	149
Mortality, *n* (%)	4 (17.3)	4 (16.7)	1 (2.2)	8 (5.4)
Male: female	1.5:1	1.75:1	2.3:1	0.91:1
Median age, yr (range)	53 (19–77)	3.0 (0.5–17)	24.4 (18–52)	3 (0-17)
Median PICU length of stay, d (range)	3 (1–40)	2.5 (0.8–21.5)	8 (1–61)	4 (1–78)
Diagnosis	Respiratory 6 Neurology 6 Sepsis 4 Post liver transplant 2 Neurosurgery 8	Respiratory 8 Neurology 5 Neurosurgery 5 Liver/GI 11 Sepsis 6 Hematology/ oncology 2 Other 1	Respiratory 32 Cardiac 4 Liver/GI 1 Endocrine 2 Sepsis 1 Hematology/ oncology 4 Ingestion 1 Other 1	Respiratory 40 Cardiac 40 Neurology 8 Neurosurgery 4 Liver/GI 8 Endocrine 2 Renal 3 Sepsis 6 Hematology/ oncology 7 Ingestion 2 C-MIS 26 Other 3
Number of COVID polymerase chain reaction+	0	4	30	29

Over a 6-week period, PICU at KCH was converted to accommodate non-COVID adult ICU patients

While MSCH admitted COVID-19 adults into PICU

Retention of critical specialists such as transplantation services allowed for nine and four solid organ transplants occurs in London and NY, respectively.

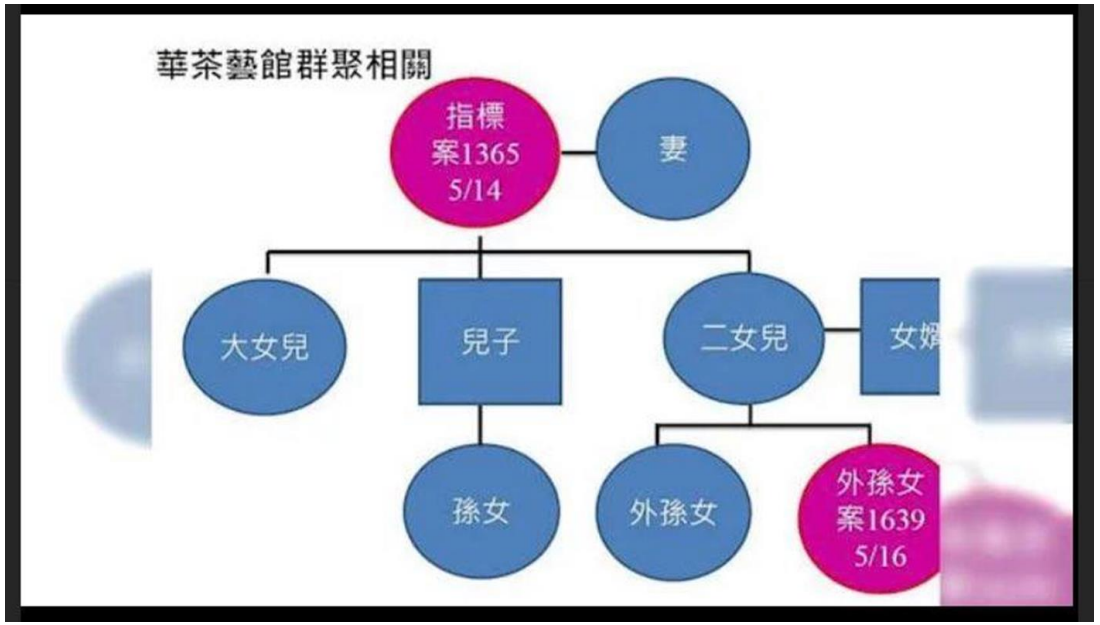
TABLE 3.

Characteristics of Coronavirus Disease Positive (Viral and Serologic) Pediatric and Adult Patients at Morgan Stanley Children's Hospital

Characteristics	Adults	Children
Number of admissions	30	40
Patients still admitted, *n*	6	2
Mortality, *n* (%)	0 (0)	1 (2.5)
Male:female	23:7	20:20
Median age, yr(range)	32 (18–52)	9 (0.16–17)
Median PICU length of stay, d (range)	14 (1–41)	5 (1–43)
Remains hospitalized	13	6
Transferred to medical ICU	6	NA
Readmitted	1	0
Diagnosis	ARDS–26 Acute on chronic respiratory failure–1 Diabetic ketoacidosis–2 Hypoxic ischemic encephalopathy post arrest–1	ARDS–5 Acute on chronic respiratory failure–3 Hyperkalemia–1 Heart failure–3 Tracheal stenosis–1 Progressive brain tumor–1 Coronavirus disease–related multi-system inflammatory syndrome–26
Illness severity	IMV–26 CRRT–6 ECMO–3	IMV–8 CRRT–1 ECMO–1

A 6-month-old girl presented with diarrhea

- Birth history and growth: non-remarkable
- Vaccination: as scheduled until BCG, no self-paid Rota
- Feeding: IF 150ml Q4H+ some soft diet
- TOCC: close contact with maternal grandfather (COVID P’t #1365), cared at home by grandmother



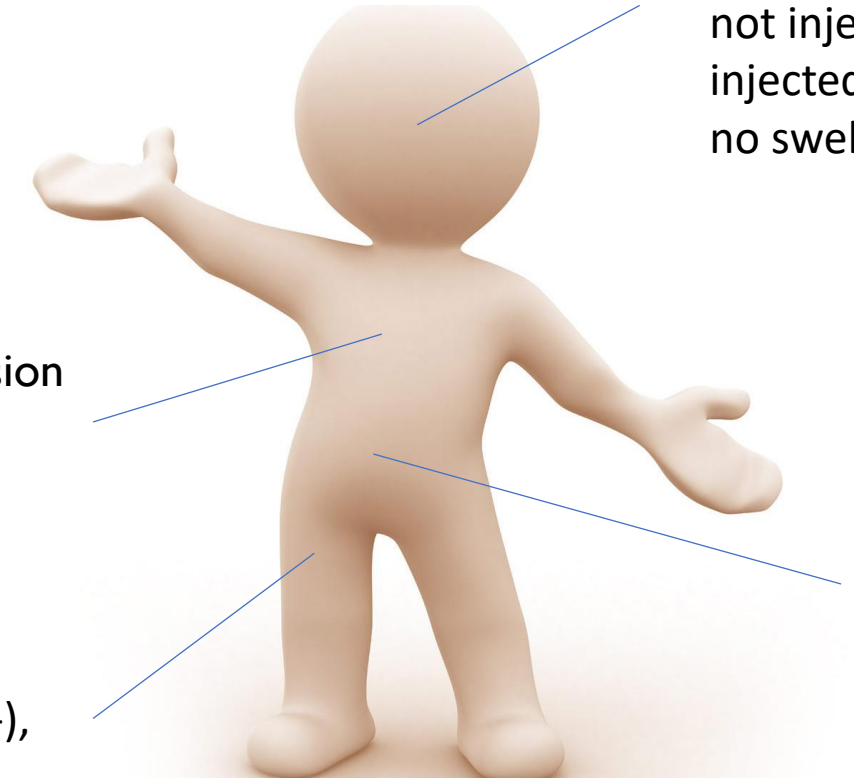
Past History (#1639, Our patient)

05/04	BCG vaccination (close contact with # 1365 for 2-3hrs)
05/08	Family gathering (close contact with # 1365)
05/12	Mild fever 37.8’C, resolved spontaneously, nasal stiffness(+)
05/14	# 1365 confirmed COVID(+) ⇒Family members all taken to XX H for COVID testing
05/15	Loose stool twice/day (no bloody or mucus content)
05/16	COVID(+, Ct: 27), decreased appetite (90ml Q4H), activity and U/O ⇒Admitted to PICU

Physical Examination

Consciousness: alert and agitated
TPR: 37.3/135/26; SpO2 99%
BP 90/70 mmHg, pain score: 0
Activity: fair

[HEENT]
Grossly normal, conjunctivae not pale, not injected, sclera anicteric, throat not injected, pus(-), ulcer(-), tonsils bilateral no swelling, bilateral ED intact, AF sunken



[Chest]
Bil clear BS; symmetric expansion
Regular heart beat; Murmur(-)

[Abd]
Soft, flat, normoactive BoS, no tenderness, muscle guarding(-), rebound tenderness(-), splenomegaly(-)

[Extremities, Back and Skin]
Freely movable, Icteric(-), ecchymosis(-), petechiae(-), CRT < 2s, warm

Lab data (05/16)

CBC D/C		
Hb	10.3	g/dL
HCT	32.0	%
MCV	60.4	fL
PLT	466	K/μL
WBC	9.08	K/μL
Blast	0.0	%
Band	0.0	%
Seg	13.5	%
Lym	79.8	%

BCS		
AST	68	U/L
ALT	59	U/L
LDH	478	U/L
BUN	9.2	mg/dL
Cre	0. 3	mg/dL
Na	137	mmol/L
K	4.3	mmol/L
Procalcitonin	0.083	ng/mL
CRP	0.04	mg/dL

ABG: 7.409/27.0/123.4/16.7, BE -8.0

Lab data (05/16)

科室:VH No:210516004764 THROAT SWAB 採檢:2021

檢驗項目	檢驗值
Influenza virus type B RNA PCR (qualitative test)	!
Influenza virus type A RNA PCR (qualitative test)	!

科室:VH No:210516004761 Nasopharyngeal Swab 採

檢驗項目	檢驗值
SARS-CoV-2 RNA PCR(Qualitative test)	Positive Ct: 23.4

科室:VF No:210516004760 NASAL SWAB 採檢:2021/

檢驗項目	檢驗值
Influenza A+B Rapid Screening Test	Negative

科室:OP No:210516004997 STOOL 採檢:2021/05/16 21:52 登入:2021/05/17 15:35 最後

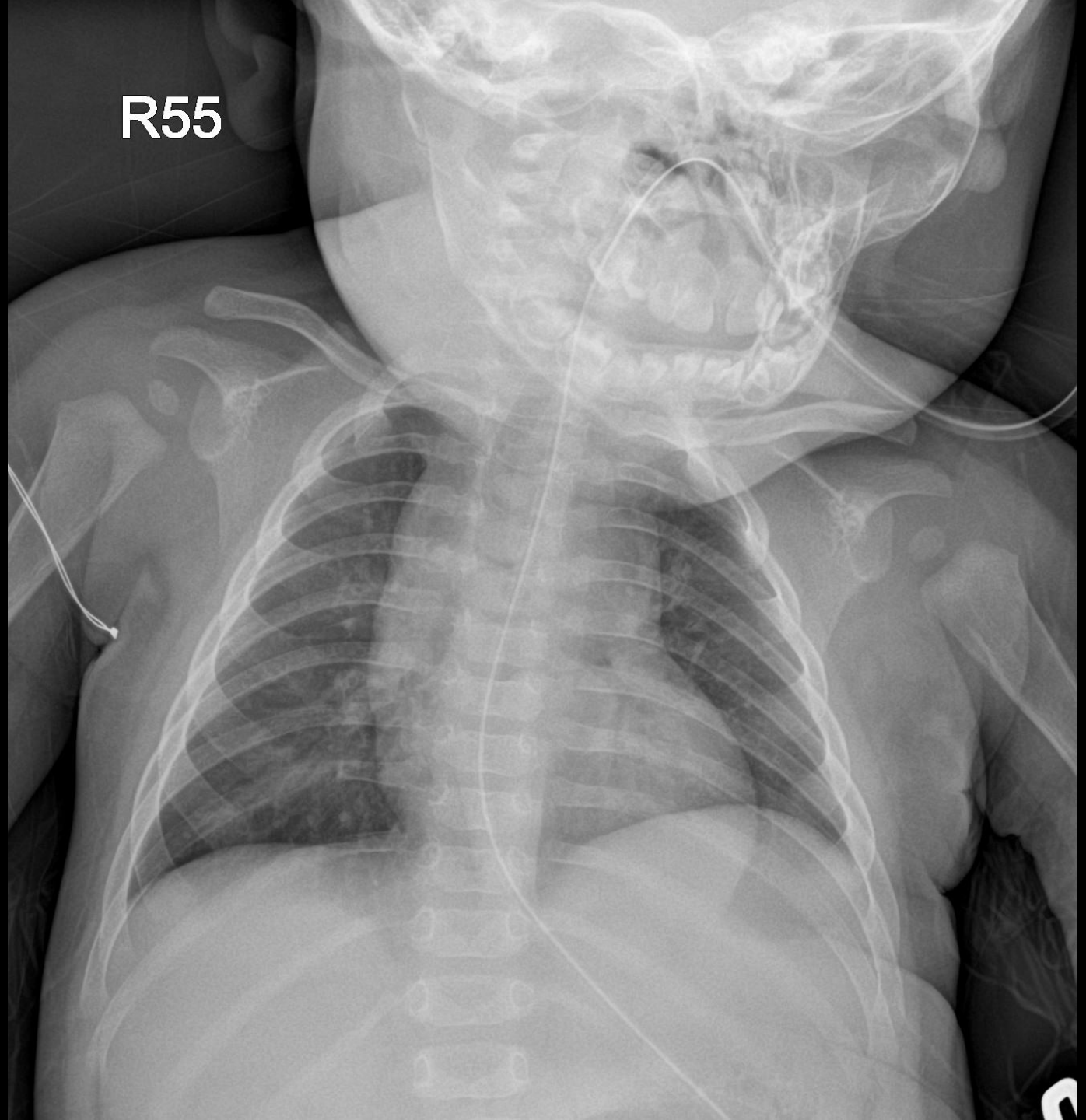
檢驗項目	檢驗值	單位	參考值
O.B.	2+	*	-
Stool WBC	Not found	/HPF	< 3 cells / HPF

科室:VR No:210516004996 STOOL 採檢:2021/05/16 21:52 登入:2021/05/17 13:43 最後

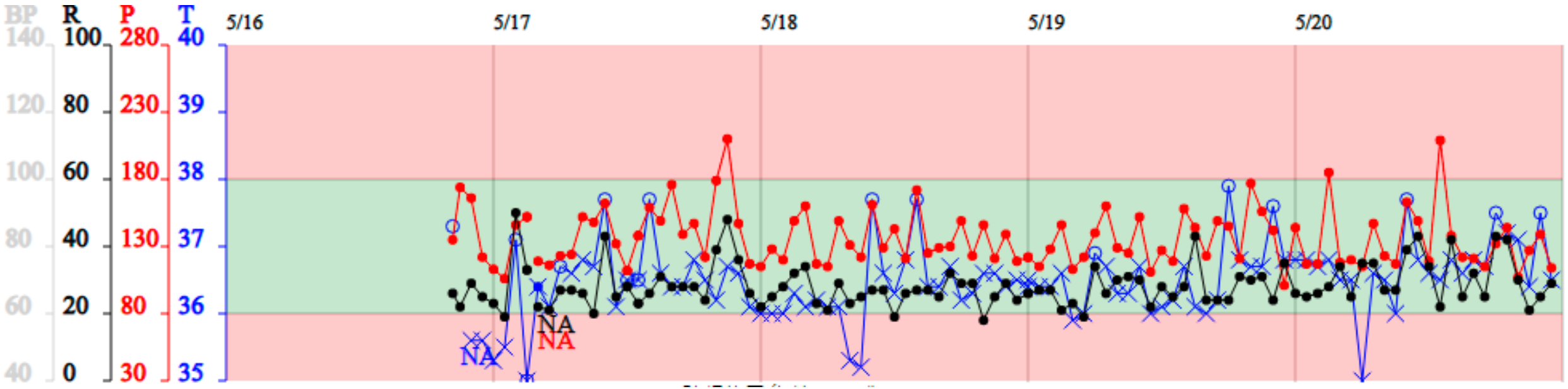
檢驗項目	檢驗值	單位	參考值
Rotavirus Antigen	Negative		Negative

科室:B1 No:210516004995 STOOL 採檢:2021/05/16 21:52 登入:2021/05/17 10:02 最後

檢驗項目	檢驗值	單位	參考值
ID+DS Sal. SHI#1	No Salmonella & Shigella	*	
ID+DS Intesti.#1	No Vibrio,Aeromonas	*	
ID+DS Intesti.#2	No Plesiomonas shigelloides	*	No Plesiomonas shigelloides
ID Campy.#1	No Campylobacter	*	



05/17

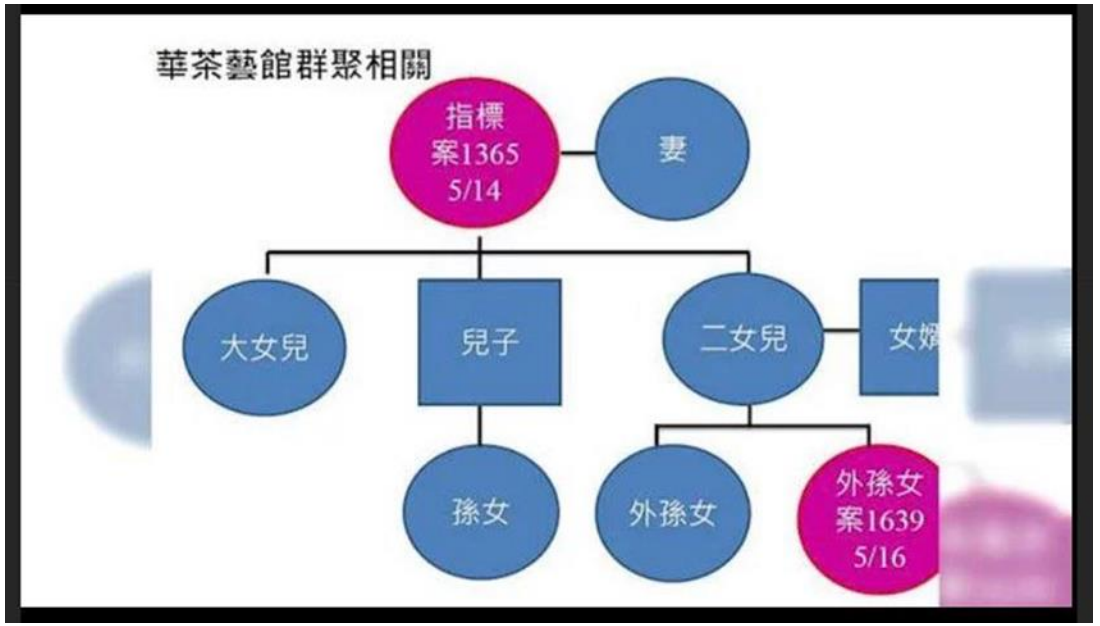


PICU

DC IVF

General ward

Who’s going to take care of her in general ward?



60 y/o man PICU stay 21 days, Remdesivir 3 days
HFNC 5/31-?

70 y/o man, PICU stay 20 days, Remdesivir 3 days
HFNC 5/31-6/12

- **“We don’t know when we will stop admitting adults, but this experience will undoubtedly have lasting effects and will allow us to practice with increased empathy for all members of our patients’ families.”**

May 15, 2020, at NEJM.org.

Conclusions

- Critical COVID-19 in pediatric groups requiring PICU care is very rare
  - Mortality is very low, except in patients with chronic illness
- PICU care guidelines: following SCC
- ECMO indication as other diseases, but source allocation should be considered
- Impact of COVID-19 on PICU care: complex and challenging
  - Change in disease epidemiology
  - Supporting adult critical patients
  - Infection control