

COVID-19 associated neurological complication and croup in children

臺北榮總 新生兒科 周佳穗

2024/1/9



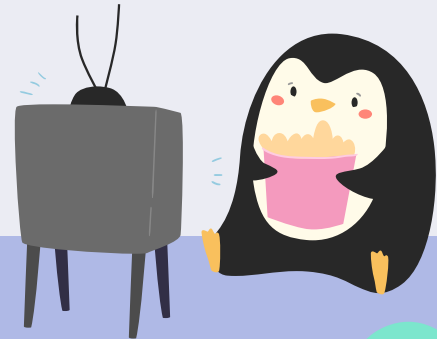
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01.

Introduction





Background

- Novel coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus
 - Taiwan has entered the community transmission stage of COVID-19 **Omicron variants since April 2022.**
 - Plenty of studies reported that SARS-CoV-2–positive pediatric upper airway disease rates increased during the Omicron surge.
 - We have encountered pediatric cases with neurological involvement during this pandemic.
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SARS-CoV-2感染的相關臨床表現分類

輕度	無併發症之輕症	非專一性的症狀
中度	肺炎	Room air > 94%
重度	嚴重肺炎	PaO ₂ /FiO ₂ < 300 Room air ≤ 94%
極重度	ARDS	PaO ₂ /FiO ₂ < 300, SpO ₂ /FiO ₂ ≤ 264 OI index or OSI index
	敗血症	有疑似或確認之感染，且符合SIRS其中兩指標
	敗血性休克	
	MIS-C	Fever > 3 days, ESR/CRP/PCT↑, 加上兩項臨床特徵

02.

Neurological complication





Case 1. 2 y/o boy (2022/5/14)

Chief complaint

- Spiking fever ($>42^{\circ}\text{C}$) with convulsion in the evening on 2022/5/13
- Consciousness disturbance after convulsion
- Known to have COVID-19 PCR positive (tested on 2022/5/12)

Past history

- Vaccination: as schedule
- Failure to thrive:
 - Endocrine study: no finding
 - Plan to PCV for evaluation
- Denied history of febrile convulsion



Present illness

- **Cough and rhinorrhea**
- **2022/5/12 Day time**
 - Contact a COVID-19 PCR (+) caregiver
 - Rapid screening: positive
 - Visit hospital
 - No toxic sign
 - Oral medication
 - COVID-19 PCR
- **2022/5/13 凌晨**
 - Fever, 39 °C
 - No seizure
- **2023/5/13 傍晚**
 - High fever again
 - **Seizure at home** (2-3 min)
- **At ER**
 - **High fever (42.4°C)**
 - Mycoplasma pneumonia (+)
 - Blood test: CBC, BS, CRP, electrolyte: WNL
 - CXR: no pneumonia patch
 - O2, iv, medication
- **Consultation and transfer: as soon as possible**

(+); Ct:18

After being transferred → in ICU

- Consciousness
 - Unresponsiveness
 - Coma (E1M1V1)
- Pupil: **dilated**, ou
- No oral ulcer
- Breathing
 - Irregular → gasping
- Skin: skinny, dry, cool, no rash
- Vomiting
 - Coffee ground

- On ETT+IMV
- Fluid resuscitation
- Hydrocortisone
- Norepinephrine
- Epinephrine infusion
- Antibiotics
- Decadron

- UGI bleeding
- **Pulmonary hemorrhage**
- Bradycardia
- Profound hypotension
- Anuria

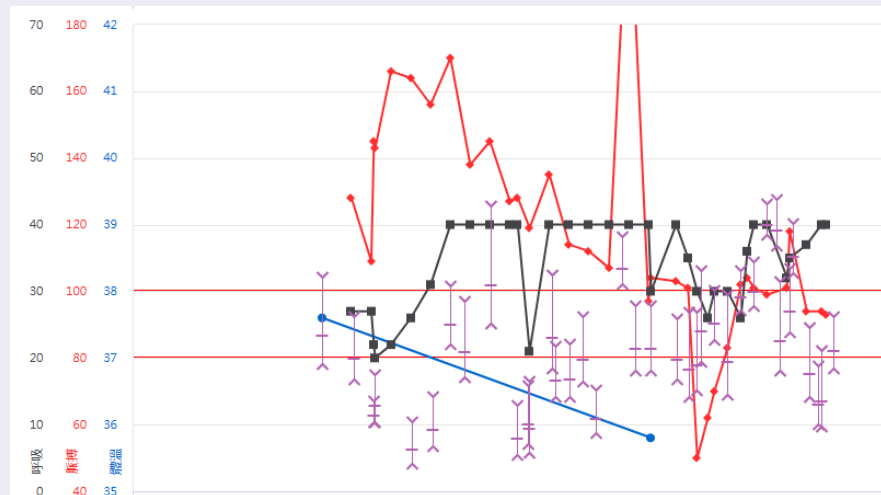
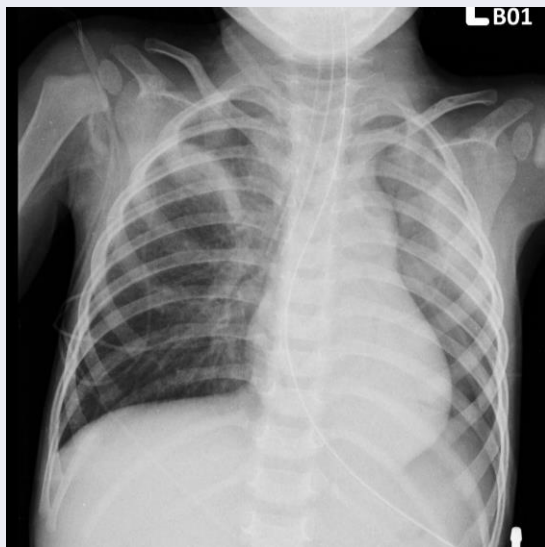
DNR
→ Palliative care
→ Expired

Coma & shock

CPR

DNR

Very rapid progression



日期	FIO2	PH	PO2	PCO2	HCO3	BE	O2SAT	HB	HCT	Na	K	iCa	Bun	Cr	BEB	SO2	TCO2
22-05-14 04:39		7.52	70	29	23.3		95.7										24.2

Ferritin: 1937 ng/ml

日期	WBC	RBC	HGB	HCT	MCV	MCH	MCHC	RDW	PLT	INR(PT)	PT	APTT	BAND	SEG	LYM	MONO	EOS	BASO	D-dimer	FDP	FIBRINOGEN
22-05-14 04:25	12760	5.17	13.9	43.6	84.3	26.9	31.9	14.3	189000	-	-	-	0.0	81.1	15.6	2.8	0.2	0.3	-	-	
22-05-14 04:41	-	-	-	-	-	-	-	-	-	2.45	26.7	48.3	-	-	-	-	-	-	14.207	-	227.4

日期	TP	ALB	CA	CHOL	BUN	UA	CREA	BILIT	ALKP	LDH	ALT	AST	NA	K	CL	GLU	IP	CK	TROP	CRP	lactate	procalcitonin(PCT)
22-05-14 04:36	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	87.10
22-05-14 04:36	-	-	-	-	31	-	0.97	-	-	684	170	347	141	5.5	-	74	-	225	0.20	0.32	54.1	-

Final diagnosis

- Convulsion with loss of consciousness, suspected **acute encephalitis/acute necrotizing encephalopathy of childhood (ANEC)**, **intracranial thrombi** can not be ruled out
- SARS-CoV-2 infection(COVID-19) with multiple organ involvements
- Systemic inflammatory response syndrome (SIRS) and septic shock-related to COVID-19
- Suspected combination of bacteria infection s/p vancomycin + mepem (meningitis dose)
- Disseminated intravascular coagulation(DIC)
- Upper GI bleeding
- Pulmonary hemorrhage
- Mycoplasma infection
- Liver function impairment
- Acute kidney injury with oliguria
- **Multi-organ organ failure s/p CPR 3:10-7:36 am father agree for DNR at 7:36 am**
- **Expired at 2022/5/14 8:55 am**

Case 2. 4 y/o girl (2022/6/3)

Chief complaint

- **Seizure** intermittently for more than one hour with **consciousness change** occurred this afternoon (since 5pm to arriving at ER)
- Mother: COVID-19 (+)



Past history

- Vaccination: as schedule
- Intractable epilepsy
 - since 4-month-old
 - under medication with Depakine 1cc Q8AM+Q8PM, Frisium 2.5mg Q8AM, Q8PM, Keppra 2cc Q8AM, Q8PM, Perampanel 2mg Q8PM
 - regular follow up at NTUH
- Developmental delay
 - under rehabilitation

Present illness

- **2022/6/3 5 PM**

- Generalized tonic-clonic seizure with impaired awareness
- Every episode last for 1 mins

- **2022/6/3 6 PM**

- Frequent seizure attack

- **2022/6/3 7 PM ER**

- Unresponsive (E1V1M1)
- Seizure
- Pupil size (4/3)
- Desaturation (SpO2<80%)
- **BT: 40.7°C, BP: 76/42, HR: 171**
- COVID-19 PCR **Ct: 16.6**

- **At ER 7PM~10PM**

- Fluid resuscitation
- Sodium bicarbonate
- **Intubation**
- **Brain CT**: slightly increased leptomeningeal enhancement along bilateral high frontoparietal region
- **Tocilizumab, dexamethazone (0.5mg/kg), mannitol**



2022/06/03

2022/06/04

2022/06/05

2022/06/06

2022/06/07

At ER

- Tocilizumab,
- Decadron 0.5mg/kg
- Mannitol

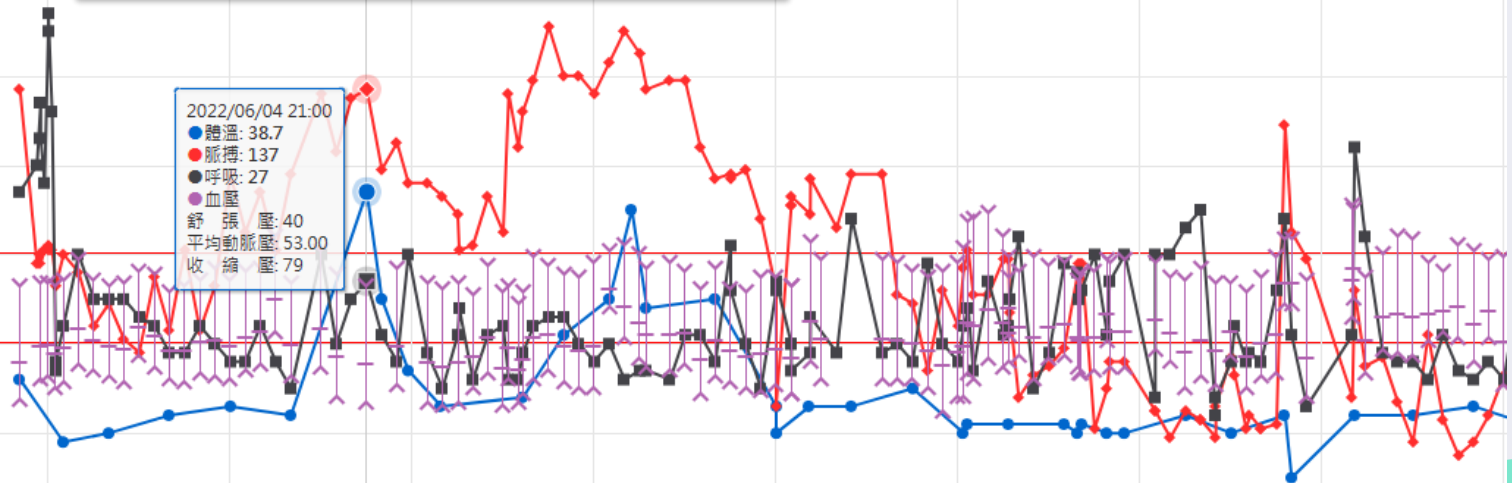
At ICU

- Keppra, mannitol
- IVIG 1g/kg
- Decadron 0.15mg/kg
- Dopamine
- Remdesivir 6/3-6/7
- Vancomycin + sintrix

4

At ICU

- Extubation



日期	<u>FIO2</u>	<u>PH</u>	<u>PO2</u>	<u>PCO2</u>	<u>HCO3</u>	<u>BE</u>	<u>O2SAT</u>	<u>HB</u>	<u>HCT</u>	<u>Na</u>	<u>K</u>	<u>iCa</u>	<u>Bun</u>	<u>Cr</u>	<u>BEB</u>	<u>SO2</u>	<u>TCO2</u>
22-06-03 19:19	21.00	7.148	29.1	53.3	18.1	-10.9										40.8	
22-06-03 21:21	100.00	7.291	48.2	47.5	22.4	-4.1										77.2	
22-06-04 00:17		7.55	59	20	16.9		93.6										17.5
22-06-04 05:43		7.35	67	44	23.4		91.8										24.8
22-06-04 08:18		7.31	66	52	25.6		90.2										27.2
22-06-04 16:04		7.37	71	48	26.5		93.5										28.0
22-06-04 23:18		7.40	73	42	25.6		94.4										26.9

日期	<u>WBC</u>	<u>RBC</u>	<u>HGB</u>	<u>HCT</u>	<u>MCV</u>	<u>MCH</u>	<u>MCHC</u>	<u>RDW</u>	<u>PLT</u>	<u>INR(PT)</u>	<u>PT</u>	<u>APTT</u>	<u>BAND</u>	<u>SEG</u>	<u>LYM</u>	<u>MONO</u>	<u>EOS</u>	<u>BASO</u>	<u>D-dimer</u>	<u>FDP</u>	<u>FIBRINOGEN</u>
22-06-03 19:33	28330	4.47	12.9	42.8	95.7	28.9	30.1	12.6	194000	-	-	-	1.9	51.4	30.5	12.4	0.0	0.0	-	-	
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22-06-04 04:59	9560	-	11.6	-	-	-	-	-	113000	-	-	-	0.0	85.9	4.5	6.1	3.3	0.2	-	-	
22-06-05 06:03	3720	-	10.5	-	-	-	-	-	85000	-	-	-	0.0	65.8	25.3	8.6	0.0	0.3	-	-	
22-06-06 03:10	3220	-	10.1	-	-	-	-	-	78000	-	-	-	0.0	47.8	41.3	10.6	0.0	0.3	-	-	
22-06-06 03:16	-	-	-	-	-	-	-	-	-	1.58	17.1	35.0	-	-	-	-	-	-	5.897	-	114.1
22-06-07 04:34	3680	-	9.1	-	-	-	-	-	203000	-	-	-	0.0	44.6	44.0	11.4	0.0	0.0	-	-	
22-06-07 11:23	-	-	-	-	-	-	-	-	-	1.08	11.6	33.1	-	-	-	-	-	-	1.640	-	167.3
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Ferritin: 209 ng/ml on 6/4

日期	TP	ALB	CA	CHOL	BUN	UA	CREA	BILT	ALKP	LDH	ALT	AST	NA	K	CL	GLU	IP	CK	GGT	CKMB	TROP	CRP	lactate	procalcitonin(PCT)	Free Ca++	Mg	Amonia(NH3)	NT-ProBNP
22-06-03 19:41	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1.06	-	-	-
22-06-03 19:41	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0.12	-	-	-	-
22-06-03 19:41	-	4.0	-	-	22	-	-	-	-	-	23	93	142	3.8	104	354	-	76	-	39	<0.10	<0.03	94.5	-	-	2.02	148	-
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22-06-04 05:16	-	-	-	-	16	-	0.31	-	-	-	26	97	143	3.7	108	-	4.8	184	-	-	-	0.38	17.5	-	-	1.94	95	-
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22-06-05 06:07	6.8	-	-	-	10	-	0.45	-	-	-	41	134	141	4.0	106	81	4.8	-	-	-	-	0.59	-	-	-	1.95	83	-
22-06-05 06:57	-	-	-	-	-	-	-	-	149	-	-	-	-	-	-	-	-	-	15	-	-	-	16.9	-	-	-	-	-
22-06-05 08:29	-	-	-	-	-	-	-	0.25	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
22-06-05 09:19	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	360.0
22-06-06 03:19	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	24.10	-	-	-	-
22-06-06 03:19	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	292.0
22-06-06 03:19	-	-	-	-	-	-	-	-	-	406	44	117	-	-	-	-	2448	-	49	<0.10	0.14	13.4	-	-	-	-	28	-
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22-06-06 09:16	-	2.7	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
22-06-06 11:52	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1.19	-	-	-
22-06-06 11:52	-	-	-	-	-	-	-	-	-	-	-	-	138	3.0	-	-	3.3	-	-	-	-	-	-	-	-	-	1.78	-
22-06-07 04:52	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1.22	-	-	-
22-06-07 04:52	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1893.0
22-06-07 04:52	-	-	-	-	12	-	0.33	0.59	-	346	31	84	143	4.1	-	92	3.6	1623	-	45	<0.10	-	10.0	-	-	1.80	-	-
22-06-07 09:08	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	13.60	-	-	-	-
22-06-08 05:48	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1.16	-	-	-
22-06-08 05:48	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	5.99	-	-	-	-
22-06-08 05:48	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	867.0
22-06-08 05:48	-	-	-	-	16	-	0.30	-	-	309	29	65	144	3.8	-	90	3.7	865	-	30	<0.10	0.04	17.5	-	-	2.04	-	-

Final diagnosis (6/24)

- SARS-CoV-2 infection with **hyperinflammation and status epilepticus**
 - s/p Tocilizumab on 6/3
 - s/p IVIG 1g/kg on 6/3-4
 - s/p remdesivir on 6/3-6/7
 - s/p dexamethasone on 6/3-12
 - s/p mannitol on 6/3-9
- Respiratory failure, SARS-CoV-2 infection related
 - s/p OETT on 6/3-6/7, HFNC on 6/7-6/14
 - s/p vancomycin on 6/4-6/11, sintrix on 6/4-6/8, mepem on 6/8-6/11.
- Shock, COVID-19 related
 - s/p dopamine 6/3-10
- Myositis, COVID-19 infection related, improved
- Intractable epilepsy since 4-month-old, chromosome 2q deletion related under AED
- Developmental delay, related to microdeletion in chromosome 2q24.3q31.1



5月21日(六)

兒童新冠肺炎併發急性腦炎之臨床處置與案例討論

2022.05.21 14:00-16:05

中央流行疫情指揮中心
Central Epidemic Command Center



兒童 COVID-19 併發急性腦炎
臨床治療暫行指引

臺灣兒科醫學會、台灣小兒神經醫學會、
臺灣兒童感染症醫學會、台灣兒童胸腔暨重症醫學會
台灣兒童急診醫學會、衛生福利部疾病管制署

共同編修

111 年 5 月 21 日訂定 (第一版)



兒童COVID-19併發急性腦炎

(疾病管制署兒童COVID-19併發急性腦炎臨床治療暫行指引)

- 兒童感染SARS-CoV-2病毒大多症狀輕微或無症狀，然自4月中起，陸續出現兒童新型冠狀病毒感染併發急性腦炎個案，且其病程變化十分快速，此現象於歐美國家較為少見。
- 關於兒童急性腦炎併發心血管功能的變化，因為目前還沒有很好的病生理機轉。
- 急性腦炎病生理，4種致病機轉導致腦部病變
 - 病毒直接侵犯腦部
 - 引起細胞激素風暴
 - 導致血管內皮細胞受傷
 - 因其他器官受損導致代謝異常

可能不只出現上述單一機制，而是好幾種機制同時出現

兒童COVID-19併發急性腦炎

(疾病管制署兒童COVID-19併發急性腦炎臨床治療暫行指引)

- 注意危險因子
 - 昏迷指數(Glasgow Coma Scale, GCS)
 - 抽搐發作(Seizures): focal seizure, repetitive seizure without consciousness recovery, status epilepticus)
 - 腦幹症狀(Brainstem signs):cranial nerve abnormalities
 - 高燒(High fever)
- **重症前驅症狀**
 - 體溫大於41度
 - 意識不佳($GCS \leq 12$)
 - 持續昏睡、持續頭痛、持續嘔吐
 - 肌躍型抽搐、抽搐、步態不穩



兒童腦炎重症前驅症狀

如家長觀察到兒童出現下述症狀，請立即就醫評估：

重症前驅症狀

- ★ 體溫大於41度
- ★ 意識不佳
- ★ 持續昏睡
- ★ 持續頭痛
- ★ 持續嘔吐
- ★ 肌躍型抽搐
- ★ 抽搐
- ★ 步態不穩

摘自「兒童新冠急性腦炎治療臨床指引」

2022/05/22

中央流行疫情指揮中心

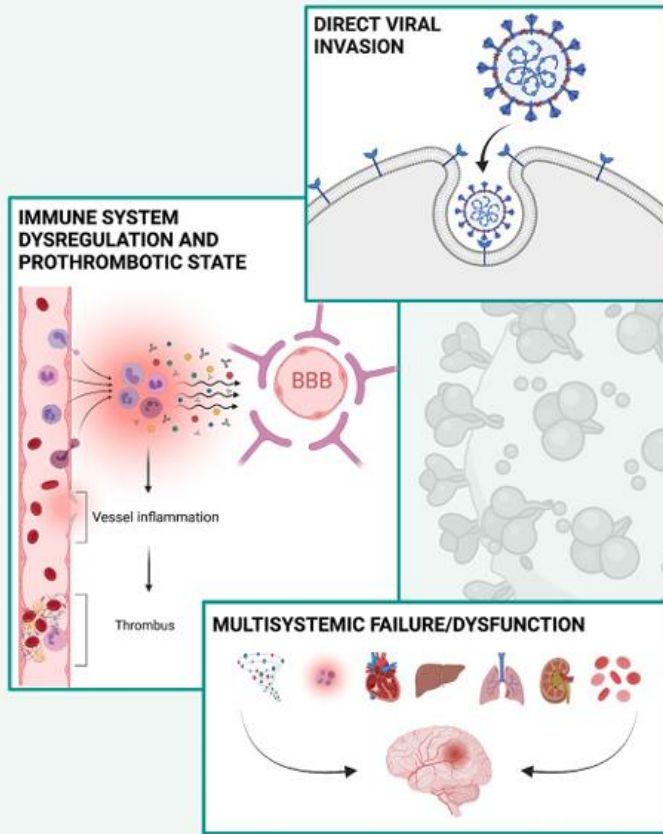


腦病變(Encephalopathy)

包含急性腦炎, 腦幹腦炎、腦脊髓炎等

- **臨床表徵**：意識或行為改變、精神混亂、肌躍型抽搐、抽搐、肢體麻痺、非自主性眼球動作(眼球往上看、眼球固定偏向一側、眼球亂轉、眼球震顫、鬥雞眼)、顱神經功能異常、凶門膨出、運動失調等。
- **上運動神經元症狀**：如Babinski sign, 垂足, 錐體外症候群(像EPS的表現), 角弓反張, 肌張力不全(dystonia)等。
- **需與兒童單純性熱性痙攣(常見年齡6個月至5歲)鑑別診斷**
- **重點式神經學檢查**，簡稱**REM-BR**: Respiratory pattern, Eye response (pupil size), Motor (decerebrate/decorticate posture, foot plantar flexion, Babinski sign), Brainstem Reflex: light reflex and corneal reflex)
- Lab：建議抽**ferritin, IL-6, LDH, DIC profile**(D-dimer)
- 需監測BP, HR, SpO2, sugar, troponin I, BNP or NT-proBNP
- **Brain CT**: impending herniation (suspected brainstem involvement)

NEURO-PATHOPHYSIOLOGICAL MECHANISMS



NEUROLOGIC MANIFESTATIONS

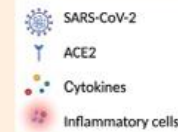
Anosmia
Ageusia

Headache
Seizures
Encephalopathy
Meningoencephalitis
Stroke
Autoimmune encephalitis
Long-COVID

ADEM

GBS
Polyneuropathy



Myalgia
Myositis



兒童神經急性照護

- 顱內壓升高照護
 - 適情況安排腦部電腦斷層檢查
 - 20% mannitol 0.5–1g/kg/dose (2.5–5ml/kg/dose) , 3% NaCl , Dexamethasone 0.15mg/kg/dose once治療(Max 6 mg/dose)
- 新冠病毒腦炎感染與免疫相關之治療
 - 抗病毒藥物
 - 抗發炎：考慮給予靜脈注射免疫球蛋白與IL-6 antagonist(Tocilizumab)
- 抽搐發作控制
- 兒童重症照護
- 合併自主神經失調(autonomic dysregulation)處置
- 合併心臟衰竭休克(cardiogenic shock)處置

表一、COVID-19 兒童參考用藥一覽表^{5,6,8,11,12,15,17,25,26} (更新日期: 2022/5/22)

	藥名	≥ 40 kg 且 ≥ 12 歲 (同成人用法與用量)	< 40 kg 孩童 (<12 歲孩童的實證有限，僅供參考)
抗病毒藥物	Remdesivir ^{6,8} 	Day 1: 200 mg/day, iv Day 2 以上: 100 mg/day, iv (依嚴重度用 3 或 5 天;必要時 10 天)	(需 ≥ 28 天 且 ≥ 3kg) Day 1: 5 mg/kg ^c Day 2 以上: 2.5 mg/kg, iv ^c (依嚴重度用 3 或 5 天;必要時 10 天)
	Paxlovid (Nirmatrelvir + Ritonavir)	Nirmatrelvir 300 mg + Ritonavir 100 mg, po, bid, 5 天	尚無建議
免疫調節劑: 皮質類固醇 ^{12,17} (使用期:最長 10 天或到出院為止)	Dexamethasone 	6mg, po/iv	0.15 mg/kg, po/iv (max. 6 mg)
	Prednisolone	40mg, po	1 mg/kg, po(max. 40 mg)
	Hydrocortisone	160 mg, iv	新生兒(<1 m): 0.5 mg/kg, iv, q12 h, 7 天 + 0.5 mg/kg, iv,qd,3 天 兒童(≥1 m): 1.3 mg/kg, iv, q8h (max. total: 150 mg/day)
	Methylprednisolone	32 mg,po/iv	0.8 mg/kg, po/iv qd (max 32 mg)
免疫調節劑: 皮質類固醇 ¹⁵ (有 MIS-C 時)	Methylprednisolone +/- Prednisolone		(嚴重 KD) methylprednisolone 0.8 mg/kg, iv, bid 5-7 天, 或 10-30 mg/kg, iv,qd 3 天, 接口服 prednisolone 2mg/kg,qd, 遞減劑量 2-3 週。 (SHLH) methylprednisolone 30 mg/kg, iv,qd3 天, 接 1 mg/kg q12h, 遞減劑量至停藥。

	藥名	≥ 40 kg 且 ≥ 12 歲 (同成人用法與用量)	< 40 kg 孩童 (<12 歲孩童的實證有限，僅供參考)
其他免疫調節劑 ⁶	免疫球蛋白 ^{15,25}  (IVIG)(有 MIS-C 時)		(符合 KD) 2 g/kg, iv, 通常給一次 (符合 sHLH) 1-2 g/kg, iv(14 天後可 repeat) (符合急性腦炎) 1 g/kg, iv, 共 2 天
	Tocilizumab ^{15,17 *}  (IL-6 單株抗體)	8 mg/kg, iv, max.: 800mg, 單次(需併用 Dexamethasone, 或 Dexamethasone + remdesivir)	(≥ 2 歲) < 30kg: 12 mg/kg, iv, 單次 > 30 kg: 8 mg/kg, iv, 單次 (需併用 Dexamethasone, 或 Dexamethasone + remdesivir)
	Baricitinib ^{17,23a,e} (JAK inhibitor)	4 mg/day, po, 14 天或出院(需併用 Dexamethasone, 或 Dexamethasone + remdesivir)	(≥ 2 且 < 9 歲) 2 mg/day, po, 14 天或出院 (≥ 9 歲) 4 mg/day, po, 14 天或出院 (需併用 Dexamethasone, 或 Dexamethasone + remdesivir)
	複合式單株抗體 ^{b*} (Casirivimab + imdevimab)或 *(Bamlanivimab + etesevimab)	600 mg casirivimab + 600 mg imdevimab, iv, 單次; 或 700 mg bamlanivimab + 1400mg etesevimab, iv, 單次	尚無建議
	Anakinra ^{2,15} (IL-1 單株抗體)	5 mg/kg/dose, iv/sc, bid	2-6 mg/kg/day, iv/sc
抗血栓或 抗凝劑 (有 MIS-C 時)	Enoxaparin(預防性) ²⁶	40 mg, sc, qd	< 2 m: 0.75 mg/kg/dose, sc, q12h ^d ≥ 2 m: 0.5 mg/kg/dose, sc, q12h
	Aspirin ¹⁵		(符合 KD) 30-50 mg/kg/day, po, 至退燒 48h 後 降為 3-5 mg/kg/day, po

Mild to Moderate

- Hallucination only
- Seizure, GTC(<15 m)
- No neurological sign
- Consciousness clear
- GCS=15

Severe

- Seizure>15 mins
- Focal seizures
- Consciousness change
- Abnormal eye movement
- Other neurological sign
- GCS: 13-14

Critical

- Seizure>20 mins, status
- Consciousness loss
- Abnormal eye movement
- **GCS ≤ 12**
- Abnormal breathing pattern
- Shock

- 抽血(全套)
- Admission
- Decadron 3d
- Remdesivir 3d

- 抽血(全套)
- 在ER就給1st decadron
- Brain CT
- Admission
- Decadron 5d
- Remdesivir 5d

如果是轉院個案：
請對方在等待時能
做的盡量先做

- 抽血(全套)
- 在ER就給1st decadron
- Mannitol, Remdesivir, Tocilizumab
- On ETT
- Treat shock(LR/NS)
- Brain CT
- Admission ICU
- IVIG: 1g/kg *2
- Decadron 2-5d (consider pulse therapy)
- Remdesivir 2-5d
- Mannitol
- L/P on 2nd day

COVID專責兒童ICU

PER藥物劑量

Dexamethasone(iv)	0.15mg/kg per day (max 6mg) 1 st 0.5mg/kg for brain edema (max 10mg)
Remdesivir (iv)	D1: 5mg/kg(max 200mg) D2-D5: 2.5mg/kg(max 100mg)
IVIG	1 g/kg, iv for 12 h*2d
Tocilizumab	($\geq 2y$) <30kg: 12mg/kg $\geq 30kg$: 8mg/kg, max 800mg
Mannitol	0.5-1g/kg for 30 mins
Fluid	70-80% of maintenance

檢驗項目

CBC/DC
PT/aPTT/D-dimer
BUN/Cr/Na/K
AST/ALT/ALKP/LDH
Total bilirubin/albumin
CK/CKMB/Troponin/NT-proBNP
Myoglobin
Glucose
CRP/ESR
IL-6
Serum ferritin
Procalcitonin
Blood gas
CXR
Urine routine

Hospitalized COVID-19 pediatric patients at TVGH
from April 1 to Sep 30, 2022.

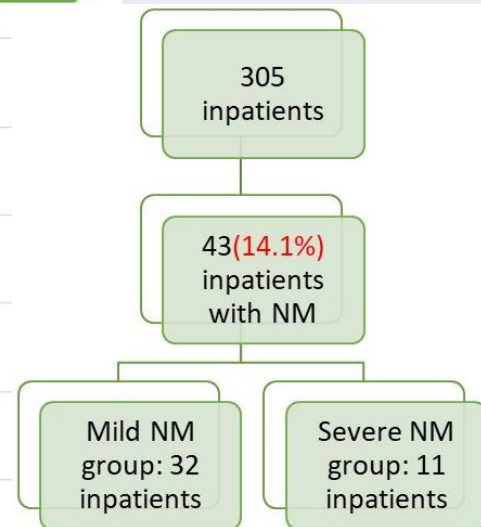
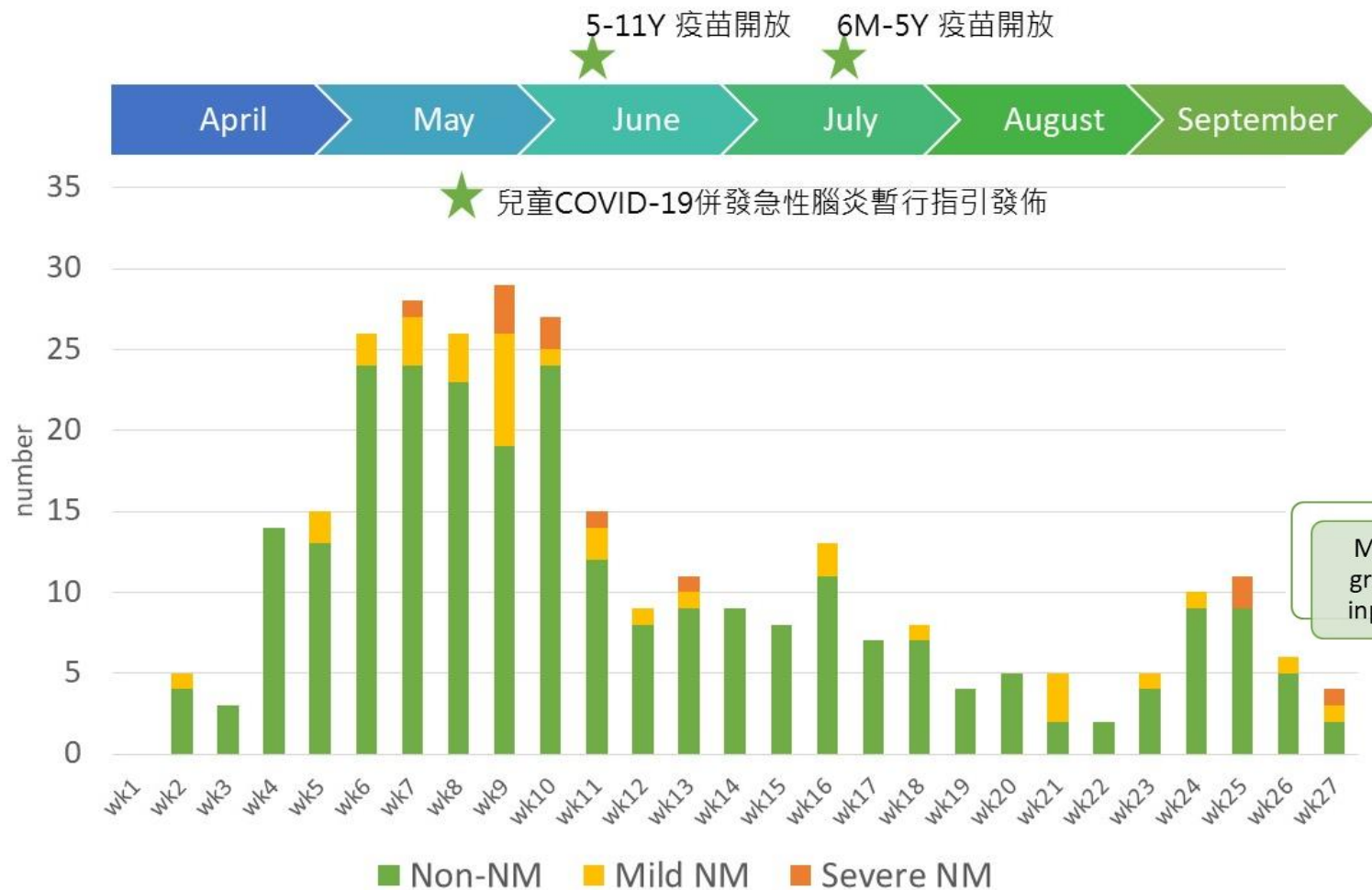
Patients with neurological manifestations(NMs)

Mild NM group

Severe NM group

Assess patient
characteristics, presenting
symptoms, laboratory test,
hospital course and outcome

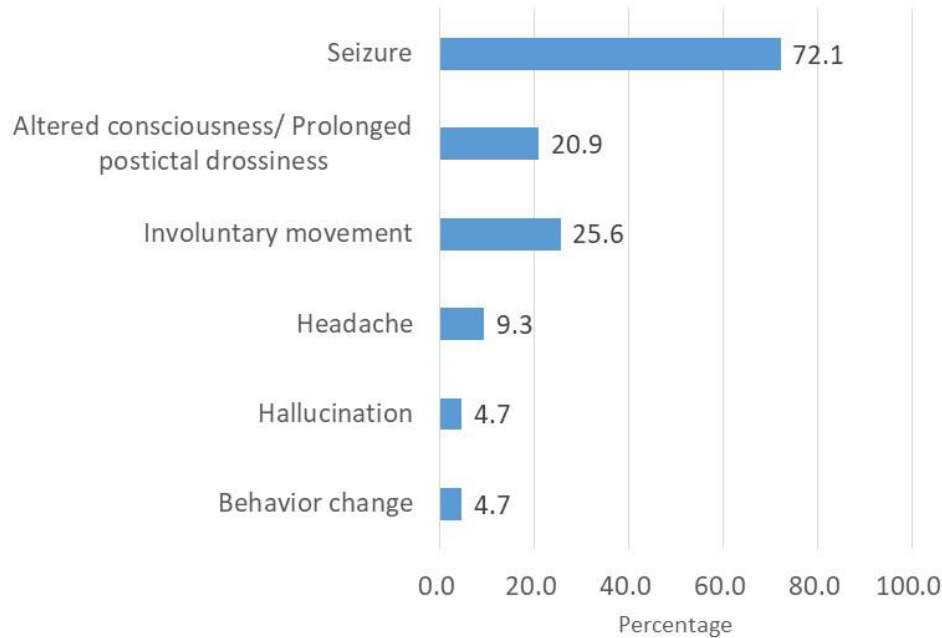
Altered mental status, prolonged
postictal drowsiness or behavior change



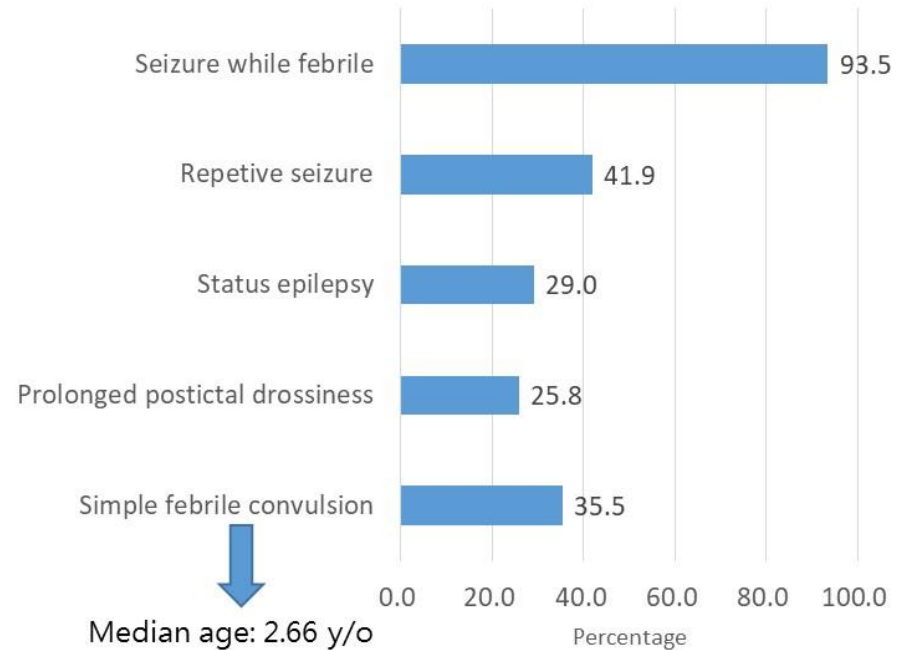
Patient characteristics

	N(%)			P-value
	Total	Mild NM	Severe NM	
Age (y) Median(IQR)	3.17(3.54)	1.83(4.34)	3.38(3.77)	0.989
Male sex	29(67.4)	23(71.9)	6(54.5)	0.29
COVID-19 vaccine	10(23.2)	7(21.9)	3(27.3)	0.715
Pre-existing condition				
Neurological or development except febrile convulsion	4(9.3)	1(3.12)	3(27.3)	0.017
Febrile convulsion	5(11.6)	5(15.6)	0	0.163
Cardiovascular	1(2.3)	0	1(9.1)	0.084
Respiratory	0	0	0	-
Gastrointestinal	0	0	0	-
Renal/urolgical	3(6.9)	2(6.3)	1(9.1)	0.75
Immunologic	2(4.7)	2(6.3)	0	0.396
Metabolic	0	0	0	-
Genetic defect	1(2.3)	0	1(9.1)	0.084
Hemalogical	0	0	0	-
Oncological	0	0	0	-
Premature	0	0	1(9.1)	0.084
Healthy	28(65.1)	23(71.9)	5(45.5)	0.113

Neurological manifestation



Seizure features



Non-neurological manifestation

		N(%)			p-value
		Total	Mild NM	Severe NM	
Fever		39(90.7)	29(90.6)	10(90.9)	0.978
From fever to NM onset(Day)		0(1)	0(1)	0(1)	0.519
Median(IQR)					
BT('C) Median(IQR)		39.2(1)	39.1(0.9)	39.5(0.7)	0.023
URI	Cough	18(41.9)	15(46.9)	3(27.3)	0.256
	Rhinorrhea	16(37.2)	14(43.8)	2(18.2)	0.13
	Sore throat	0	0	0	-
Dyspnea/ Respiratory insufficiency or failure		6(14)	2(6.3)	4(36.4)	0.013
Chest discomfort		1(2.3)	1(3.1)	0	0.553
GI	Vomiting	11(25.6)	8(25)	3(27.3)	0.882
	Diarrhea	3(7)	3(9.4)	0	0.292
	ABD pain	2(4.7)	0	2(18.2)	0.061
Skin rash		0	0	0	-
No non-NM symptom		17(40)	11(34.4)	6(54.5)	0.238

Laboratory test

	Median(IQR)		p-value
	Mild NM group	Severe NM group	
WBC (/μL)	6990(2935)	8330(5190)	0.032
Hb (g/dL)	12.6(1)	12.7(2.05)	0.837
Plt (10 ³ /μL)	221(62)	256(105)	0.516
Segment (%)	73.2(20.1)	72.7(17.1)	0.537
Lymphocytes (%)	16.3(16.15)	14.6(11.1)	0.537
BUN (mg/dL)	12(3)	15(10.5)	0.131
Cr (mg/dL)	0.37(0.14)	0.41(0.31)	0.124
ALT (U/L)	14(6.76)	21(15)	0.042
AST (U/L)	32.5(9.5)	41(46.5)	0.045
CK (U/L)	132(82.5)	105.5(122)	0.612
Lactate (mg/dL)	17.65(6)	39.45(41.75)	0.06
CRP (mg/dL)	0.18(0.25)	0.12(0.26)	0.288
PCT (ng/mL)	0.145(0.23)	0.33(3.4)	0.131
Ferritin (ng/mL)	73.4(28.6)	107(154.8)	0.154
LDH (U/L)	280.5(72.5)	392(195.25)	0.01
D-dimer (μg/mL)	0.38(0.27)	0.56(0.29)	0.794
PT _(s) Mean(SD)	12.32±0.97	13.84±4.2	0.386
APTT _(s)	35.95(5.35)	30.7(4.8)	0.017
Fibrinogen(mg/dL)	243.7(40.3)	216.8(52.25)	0.087
CT value	16(5.26)	16.6(4.73)	0.162

Other ancillary tests

- CSF analysis(N=10)
 - Both COVID-19 PCR and virus culture were negative for all patients.
 - Cell count, protein and glucose content were within normal range in all CSF samples, except 1 patient had high protein level(453.4mg/dL).
- Brain CT(N=20)
 - 15(75%) cases had no significant findings.
 - Most common finding was increased leptomeningeal enhancement(15%).






Outcome

	N(%)			p-value
	Total	Mild NM	Severe NM	
Hospital length of stay(D) Median(IQR)	9(20.9)	3(2.25)	6(10)	0.014
Mortality	1(2.3)	0	1(9.1)	0.084
Discharge with neurological symptoms	2(4.7)	0	2(18.2)	0.091
30-day readmission	1(2.3)	0	1(9.1)	0.084
MIS-C	0	0	0	-



Discussion




- COVID pediatric patients can present with **wide range** of neurological symptoms, such as **seizure(72.1%)**, altered consciousness and involuntary movement.
 - **Neurological comorbidities** were associated with more severe NMs in hospitalized COVID-19 pediatric patients.
 - Severe NM group showed higher values of **AST and LDH**.
 - Both COVID-19 PCR and virus culture **were negative** for all CSF samples.
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- 
- CSF analysis
 - Almost all the cases described worldwide had normal CSF analyses.
 - Lewis et al. : only a 6% positivity rate was found in CSF SARS-CoV-2 PCR testing of 304 patients with confirmed COVID-19 and neurologic symptoms.

Consistent with the hypothesis of SARS-CoV-2 induced hyperinflammation, rather than direct viral CNS invasion.



Conclusion

- **Neurological comorbidities** were associated with more severe neurological manifestations in hospitalized COVID-19 pediatric patients.
 - **Most patients(95.3%) were discharged without neurological symptoms regardless of initial disease severity.**
 - Long-term follow up is necessary for monitoring post-COVID-19 neurological sequelae.
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03.

Croup





Case 3. 8 m/o boy (6/7)

Chief complaint

- Barking cough and stridor for 1 day

Present illness

- Fever since yesterday
- Developed barking cough, hoarseness, and stridor today
- Suprasternal and subcostal retraction when irritable
- COVID-19 PCR test was **positive (Ct: 13)**

Past & personal history

- Vaccination: as schedule
- Nil

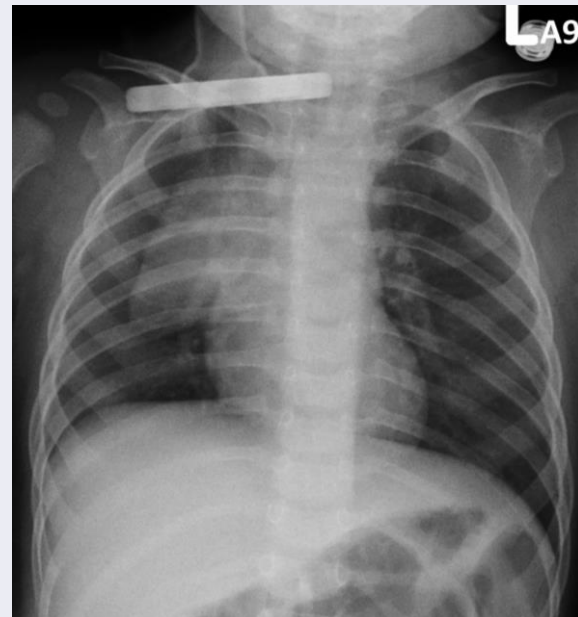
Hospital course

- Dexamethasone 5 mg at ER
- RDV and dexamethasone were given due to ventilator needed.
- Under HFNC since 6/7 and began tapering setting since 6/8



Final diagnosis (6/12)

- SARS-CoV-2 infection (COVID-19)
(2022/06/07 Ct value 13.4; 2022/6/11:21.49)
 - s/p Remdesivir on 6/7-6/11
 - s/p dexamethasone 0.6mg/kg on 6/7, 6/8-6/11
- Croup, COVID-19 infection related, improved
 - s/p HFNC on 6/7-6/11
- Dehydration, improved





Case 4. 9 m/o boy (9/12)

Chief complaint

- Stridor with subcostal retraction noted this morning

Present illness


- Fever up to 38.8°C on 9/11 3AM
- Cough with sputum, mild dyspnea, and some whitish RN
- ER on 9/11
 - Deteriorating dyspnea with poor activity and appetite
 - Stridor, barking cough, and subcostal retraction
 - COVID-19 PCR test was positive (Ct 17.1)



Past history

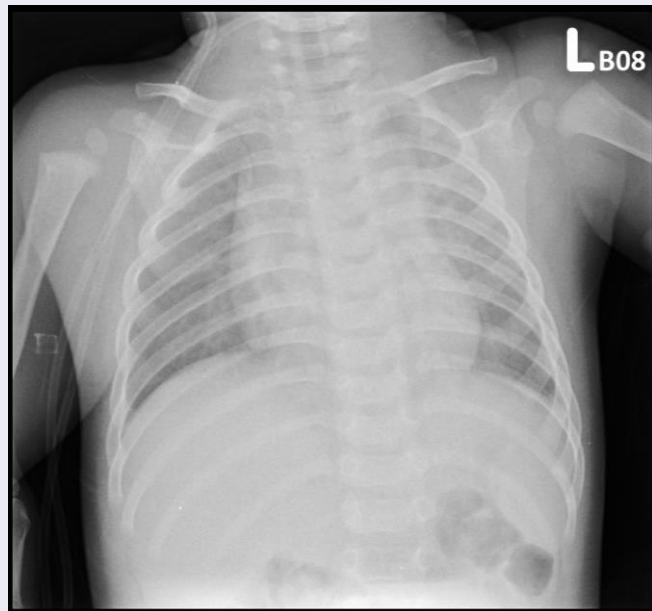
- Vaccination: as schedule
- Received single dose of BNT vaccination on 2022/08/31

Hospital course

- Dexamethasone 5 mg at ER
 - HFNC since 9/12
- 


Final diagnosis (9/15)

- Fever, SARS-CoV-2 infection (2022/09/12 Ct value 17.1)
- Croup
 - s/p Dexamethasone 5mg IM on 09/12
 - HFNC on 9/12 to 9/14
- Dehydration, improved






Croup

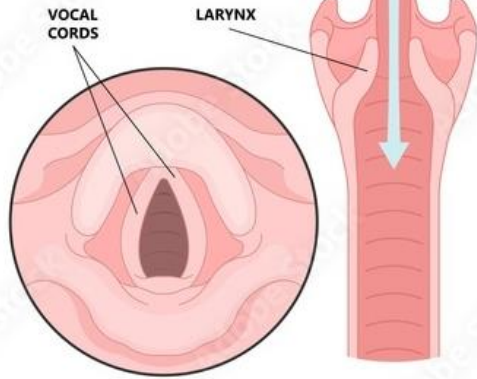
- Respiratory illness characterized by **inspiratory stridor**, **barking cough**, and **hoarseness**
 - Inflammation in the larynx and subglottic airway
 - Typically occurs in young children
 - Caused by viruses
 - **Parainfluenza virus**
 - Respiratory syncytial virus (RSV)
 - Adenoviruses, influenza
 - **Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)**
- 



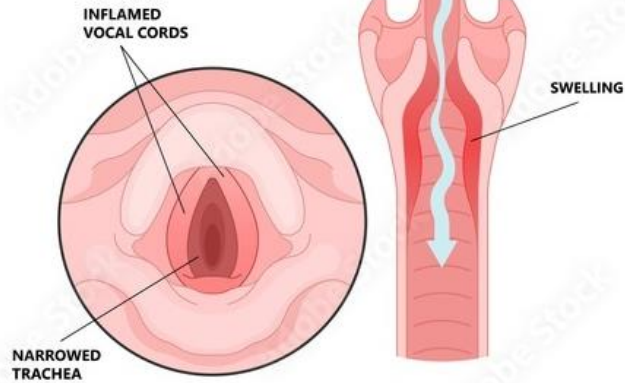
Croup-SARS-CoV-2 virus

- The SARS-CoV-2 virus has been reported to cause croup in case series and case reports.
 - Croup was a more common manifestation of infection with the **Omicron variant** than the earlier variants of SARS-CoV-2.
 - Children with croup caused by SARS-CoV-2 (primarily the Omicron variant) may have **more severe symptoms**, may require **more intense treatment** in the emergency department, and may be **more likely to need admission to the hospital** than children with croup caused by other viral etiologies.
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NORMAL LARYNX



CROUP

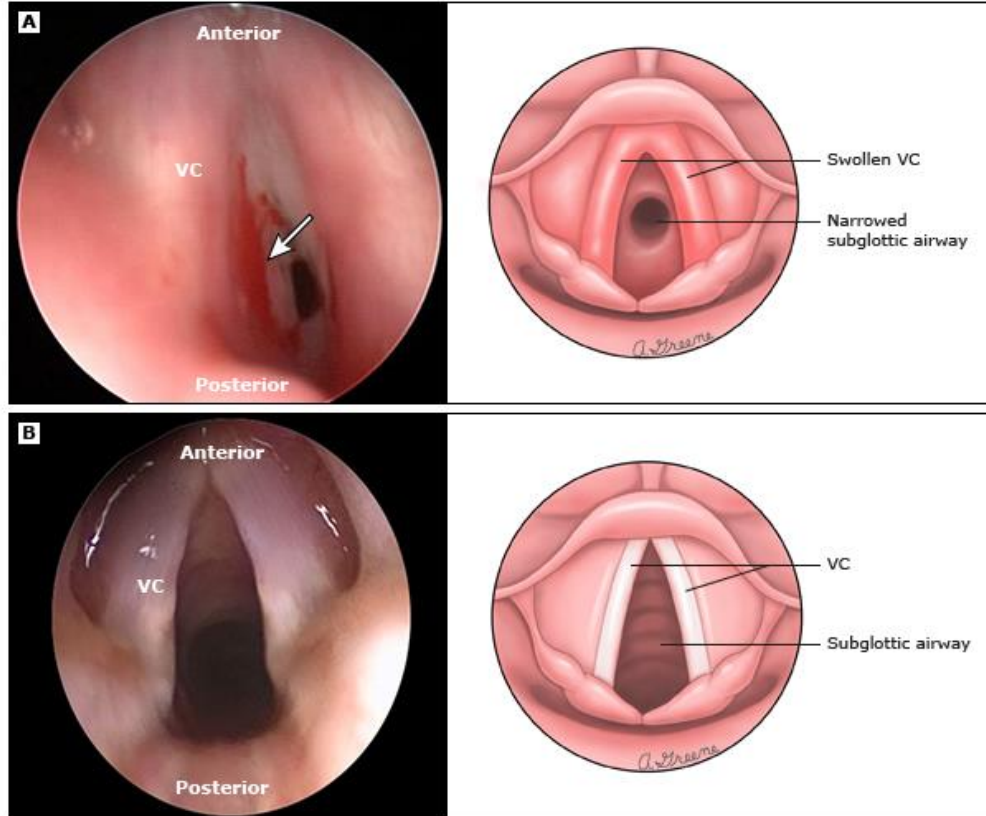


CROUP

LARYNGOTRACHEOBRONCHITIS



Laryngoscopy in a child with croup



Croup: Anteroposterior radiograph with "steep sign"



Westley croup severity score

Westley croup severity score

Clinical feature	Assigned score
Level of consciousness	
Normal, including sleep	0
Disoriented	5
Cyanosis	
None	0
With agitation	4
At rest	5
Stridor	
None	0
With agitation	1
At rest	2
Air entry	
Normal	0
Decreased	1
Markedly decreased	2
Retractions	
None	0
Mild	1
Moderate	2
Severe	3

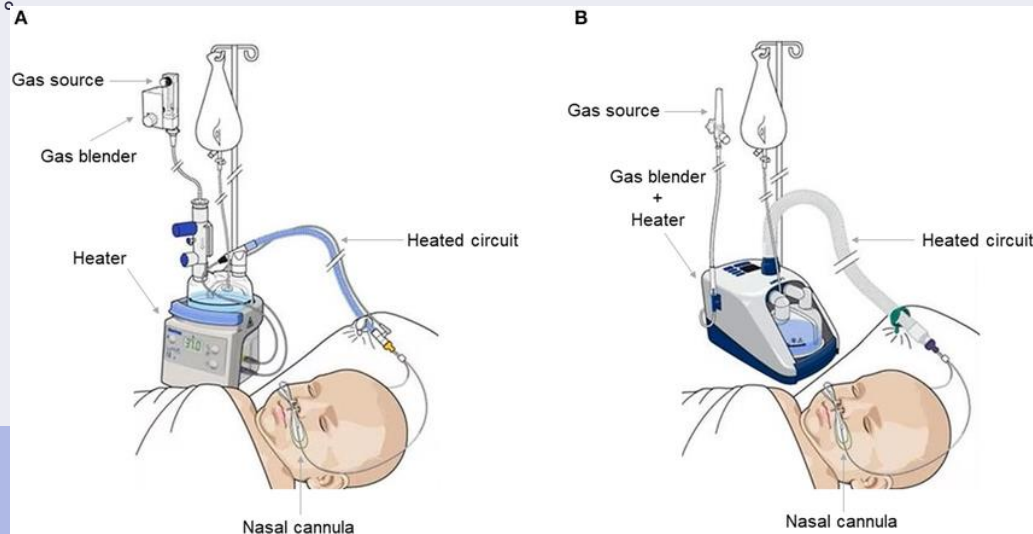
Score total	Severity	Description	Management
≤2	Mild	Occasional barking cough, no stridor at rest, mild or no retractions	<ul style="list-style-type: none"> Home treatment – Symptomatic care including antipyretics and oral fluids Outpatient treatment – <u>Single dose of oral dexamethasone* 0.15 to 0.6 mg/kg (maximum 16 mg) or oral prednisolone (1 mg/kg)</u>
3 to 7	Moderate	Frequent barking cough, stridor at rest, mild to moderate retractions	<ul style="list-style-type: none"> <u>Single dose of oral dexamethasone 0.6 mg/kg (maximum 16 mg)*</u> Nebulized epinephrine[†] Hospitalization is generally not needed but may be warranted for persistent or worsening symptoms after treatment with glucocorticoid and nebulized epinephrine
8 to 11	Severe	Frequent barking cough, stridor at rest, marked retractions, significant distress	<ul style="list-style-type: none"> <u>Single dose of oral/IM/IV dexamethasone 0.6 mg/kg (maximum 16 mg)*</u> <u>Repeated doses of nebulized epinephrine[†] may be needed</u> Inpatient admission is generally required unless marked improvement occurs after treatment with glucocorticoid and nebulized epinephrine
≥12	Impending respiratory failure	Depressed level of consciousness, stridor at rest, severe retractions, poor air entry, cyanosis or pallor	<ul style="list-style-type: none"> <u>Single dose of IM/IV dexamethasone 0.6 mg/kg (maximum 16 mg)</u> <u>Repeated doses of nebulized epinephrine[†] may be needed</u> Intensive care unit admission is generally required Consultation with anesthesiologist or ENT surgeon may be warranted to arrange for intubation in a controlled setting

Croup-treatment









- **Dexamethasone** –moderate to severe croup.
 - 0.6 mg/kg, maximum of 16 mg, oral, iv, im
- **Nebulized epinephrine**
 - **Racemic epinephrine: 0.05 mL/kg per dose(maximum of 0.5 mL)** of a 2.25% solution diluted to 3 mL total volume with normal saline.
 - L-epinephrine: 0.5 mL/kg per dose (maximum of 5 mL) of a 1 mg/mL (1:1000).
- **Supportive care**, including oxygen or humidified air as needed, antipyretics, and encouragement of fluid intake.
- **High-flow nasal cannula (HFNC)** (the most commonly used) and **noninvasive ventilation (NIV)**
- **Intubation:** rarely required
- **Repeated glucocorticoid dosing**
 - Not routinely necessary but may be reasonable for persistent symptoms

高流量鼻導管(High flow nasal cannula, HFNC)

- 提供 FiO_2 0.21-0.95，提供溫暖、濕化的氧氣,而高流量氣體亦可提供 PEEP。
- 兒科 COVID-19 建議，當病人使用氧氣治療下仍有呼吸窘迫情形時,可使用 HFNC。
- 因為會有飛沫微粒散播的疑慮，建議在負壓隔離病房執行。
- 成人使用氧氣流量為 60L/min，**兒科病人會因機型不同及體重不同，使用的鼻導管 size 不同，而選擇的流量也會不同**。



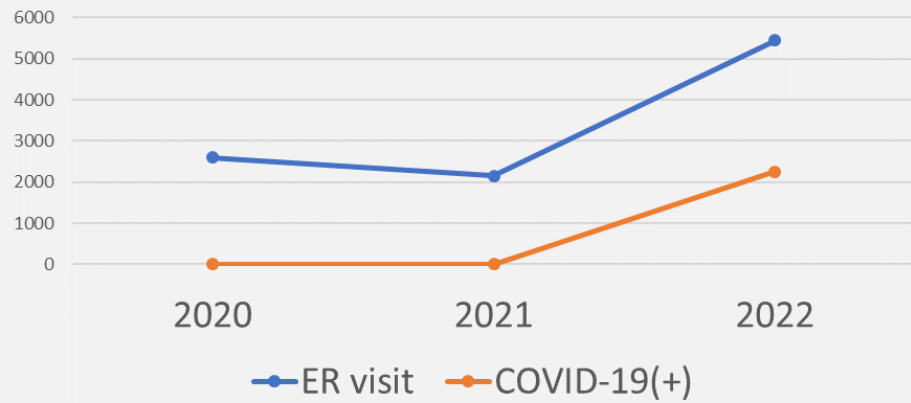
各機型的流量對照表

Cannula					
	 MR850				 AIRVO™ 2
	RT330	RT265	RT266	BCPAP	
	流量 LPM				
	OJR	OJR***VT	OJR***VT	OJR***B	
 XS OJR410	0.5-8	4-8	1-4	4-8	不適用
 S OJR412	0.5-9	4-9	1-4	4-9	
 M OJR414	0.5-10	4-10	1-4	4-10	
 L OJR416	0.5-23	4-15	1-4	4-15	2-20
 XL OJR418	0.5-25	4-15	1-4	4-15	2-25
 XXL OJR520	1-36	N/A			10-50

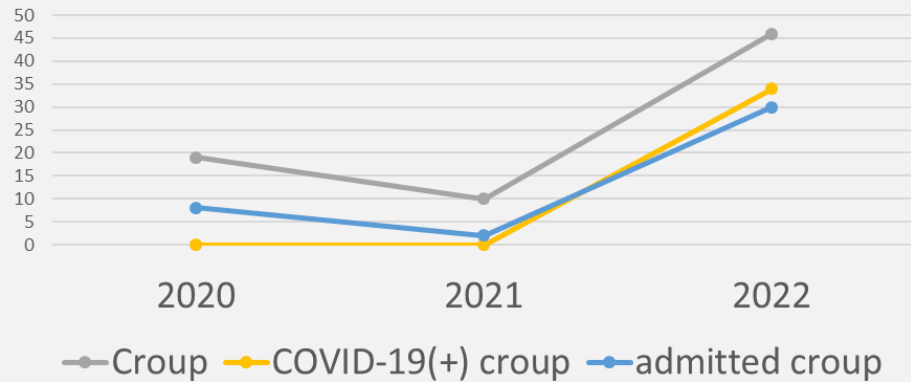
Characteristics of patient visiting ER with croup (2022/3~2022/9)

Characteristic	Total (n = 46)
Age (months)	22 ± 5.4
Sex	
Male	31 (67.4%)
Female	15 (32.6%)
COVID-19(+)	34 (73.9%)
COVID-19 PCR Ct value	17.9 ± 1.8
Ward admission	30 (65.2%)
Symptoms	
Barking cough	34 (73.9%)
Stridor	26 (56.5%)
Short of breath	29 (63.0%)
Chest retraction	19 (41.3%)
Laboratory examination	
pH ^a	7.34 ± 0.02
PCO ₂ ^a (mmHg)	39.0 ± 3.9
HCO ₃ ^a (mmol/L)	20.5 ± 1.1
BE ^a (mmol/L)	-4.7 ± 0.6

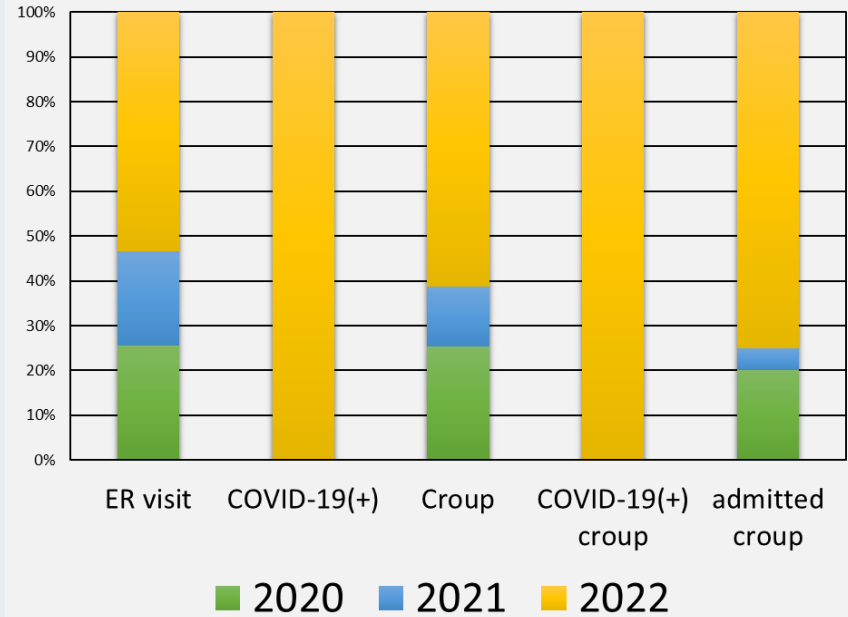
Characteristic	Total (n = 46)
WBC ^b (/μL)	11212 ± 1360
Band ^b (%)	0.7 ± 0.9
Seg ^b (%)	60.3 ± 8.2
Hb ^b (g/dL)	12.3 ± 0.3
Plt ^b (k/μL)	294.9 ± 35.8
CRP ^b (mg/dL)	1.3 ± 0.6
Procalcitonin ^c (ng/mL)	0.48 ± 0.22
Ferritin ^d (ng/mL)	203 ± 139
D-dimer ^e (μg/mL)	0.7 ± 0.1
X-ray steeple sign ^f	24 (64.9%)
Management at ER	
IM corticosteroid	32 (74.4%)
IH epinephrine	12 (26.1%)
IM/SC epinephrine	6 (13.0%)



Total ER visit and COVID-19(+) (Mar. to Sep. 2020-2022)



Croup, COVID-19(+) croup and admitted croup
(Mar. to Sep. 2022, 2021, and 2022)



Cumulative bar chart of left five parameters

Comparison of patients having croup visiting ER between 2022 and 2020-2021 (Mar. to Sep.)

Characteristic	2022 (n = 46)	2020-2021 (n = 29)	P value
Admission	30 (65.2%)	10 (34.5%)	0.017
Age (months)	22 ± 5.4	31.5 ± 6.5	0.106
Sex (male)	31 (67.4%)	19 (65.5%)	0.99
COVID-19(+)	34 (73.9%)	0	
Symptoms			
Barking cough	34 (73.9%)	19 (65.5%)	0.449
Stridor	26 (56.5%)	25 (86.2%)	0.01
Short of breath	29 (63.0%)	18 (62.1%)	0.99
Chest retraction	19 (41.3%)	3 (10.3%)	0.004
Laboratory examination			
WBC ^a	11212 ± 1360	13090 ± 2265	0.287
Seg ^a	60.3 ± 8.2	60.4 ± 8.9	0.944
CRP ^a	1.3 ± 0.6	0.8 ± 0.4	0.287
Management at ER			
IM corticosteroid	32 (74.4%)	22 (75.9%)	0.607
Inhaled epinephrine	12 (26.1%)	26 (89.7%)	<0.001
IM/SC epinephrine	6 (13.0%)	0	

Comparison of patients having Croup visiting ER with COVID-19(+) VS COVID-19(-) during Mar. to Sep. 2022

Characteristic	COVID-19(+) (n = 34)	COVID-19(-) (n = 12)	P value
Admission	25 (73.5%)	5 (41.7%)	0.019
Age (months)	18.9 ± 5.8	30.8 ± 11.5	0.057
Sex (male)	21 (61.7%)	10 (83.3%)	0.285
Symptoms			
Barking cough	24 (70.6%)	10 (83.3%)	0.472
Stridor	20 (58.8%)	6 (50%)	0.738
Short of breath	23 (67.6%)	6 (50%)	0.314
Chest retraction	15 (44.1%)	4 (33.3%)	0.735
Management			
IM corticosteroid at ER	23 (71.9%)	9 (75%)	0.698
IH epinephrine at ER	5 (14.7%)	7 (58.3%)	0.002
IM/SC epinephrine	4 (11.8%)	2 (16.7%)	0.862

Discussion

Rising incidence of croup was noted in omicron variant pandemic period.

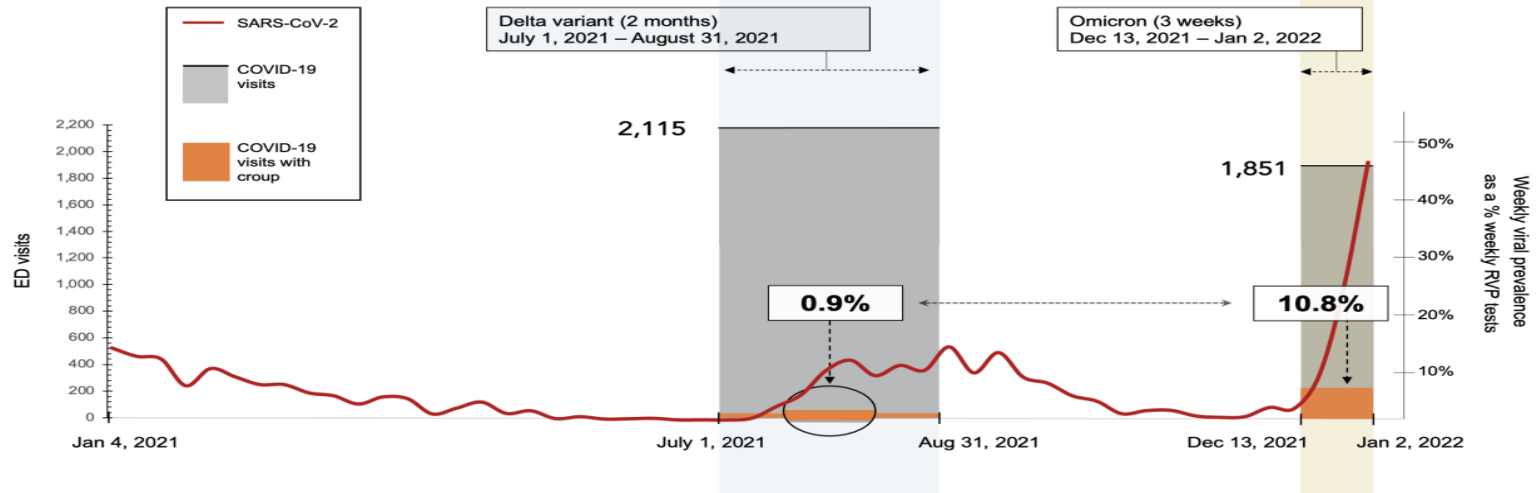



Figure 2. Frequency of laryngotracheitis (croup) among ED visits with COVID-19 diagnosis. Delta vs Omicron SARS-Cov-2 outbreaks within a pediatric quaternary care system. Abbreviation: ED, emergency department.

Sharma S, Agha B, Delgado C, et al. Croup Associated With SARS-CoV-2: Pediatric Laryngotracheitis During the Omicron Surge [published online ahead of print, 2022 May 5]. J Pediatric Infect Dis Soc. 2022;piac032.






Discussion

- Less epinephrine inhalation in COVID-19(+) croup
 - 新型冠狀病毒SARS-CoV-2感染臨床處置指引第二十版: 治療疑似或確診 SARS-CoV-2 感染病患時，應避免使用 Nebulizer 等氣霧式治療，可使用 Dry-powder inhaler 或 Metered-dose inhaler(MDI)
 - Not increased clinical severity in COVID-19(+) croup
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Conclusion

- Croup patient in spring and summer of 2022 had **increased overall incidence**, and were **mostly COVID-19 associated**. Higher proportion of admission, less inhalation of epinephrine in emergency room
 - **IM/SC epinephrine at ER** and **HFNC therapy** may be considered in COVID-19 associated croup patient
 - COVID-19 associated croup in spring and summer of 2022 had **fair clinical outcome**.
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04. Conclusion



- **Neurological comorbidities** were associated with more severe neurological manifestations in hospitalized COVID-19 pediatric patients.
- **Croup** was a more common manifestation of infection with the Omicron variant than the earlier variants of SARS-CoV-2.



OUR TEAM



THANKS!

Do you have any questions?

