



三軍總醫院

Tri-Service General Hospital

Analgesia and Sedation Strategies in COVID-19 Patients

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COVID-19 pneumonia with sepsis with endotracheal intubation



- 陳先生
- 67 years old
- Admission date: 2021/05/27
- TOCC 曾去萬華找朋友喝茶 (5/19 Ct 19)
- 5/21 COVID-19 infection, Stay at 防疫旅館
- 5/27 23:40 Fever and dyspnea for one day.

Physical examinations

Lab data

Image

Admission diagnose

Vital sign: TPR:38.3/81/25, BP:108/70, NRM full SpO2: 95%

General appearance: ill-looking

Conscious: alert, **Mentality:** intact to JOMAC

HEENT: no pale conjunctiva, no icteric sclera
no congestion, no enlargement of tonsils

Chest: coarse breathing sound, bilateral, no wheezing, no rhonchi, no crackles

Abdomen: flat, no Cullen's sign, no Turner sign, no tenderness, no rebounding pain

Extremities: no pitting edema

Physical examinations

Lab data

Image

Admission diagnose

檢驗代碼	結果	單位
WBC	5.94	10 ³ /uL
Hb	14.4	g/dL
PLT	L 84	10 ³ /uL
Neutrophil	H 89.6	%
Lymphocyte	L 4.0	%
VBGA PH	H 7.490	
VBGA PvCO2	L 33.4	mmHg
VBGA PvO2	63.9	mmHg
VBGA so2	94.1	%
BUN	20	mg/dL
Creatinine	0.9	mg/dL
AST	38	U/L

檢驗代碼	結果	單位
Na	L 132	mmol/L
K	4.2	mmol/L
Lactate	1.4	mmol/L
CRP	H 6.81	mg/dL
CK	103	U/L
Troponin I	31	pg/mL
PT (pt)	14.6	sec.
INR	1.1	
Aptt patient	H 47.5	sec.
D-dimer	H 0.68	mg/L

檢驗代碼	結果
Urine Test Panel	
STRIP Glucose	-
Urine Protein	+
Urine Bilirubin	-
Urobilinogen	<1.5mg/dL
pH	6.0
Occult Blood	1+
Acetone Urine	-
Nitrite	-
Strip WBC	-
CLARITY	CLEAR
Specific Gravity	1.024

檢驗代碼	結果
Sediments	
Urine RBC	2-5
Urine WBC	2-5
epith.cells	0-2
Urine Cast	Not Found
Bacteria	+/-
Crystal	Not Found
Yeast	Not Found
Spermatozoa	Not Found
Sediments	
Urine RBC	2-5
Urine WBC	2-5

**Physical
examinations**

Lab data

Image

**Admission
diagnose**



Physical
examinations

Lab data

Image

Admission
impression

Plan

- Impression
 - **COVID-19 pneumonia, bilateral, with sepsis**
 - **Hypertension**
- Plan
 - Follow up the microbiological culture for pathogen identification.
 - Conservative treatment with adequate fluid supplement and symptom control
 - Keep respiratory tract hygiene and isolation care
 - Empiric antimicrobial therapy **with Cravit 750mg IV QD and Methasone 6mg QD.**
 - Explain the present condition and following treatment direction to the patient and patient's family in detail

5/28

Isolation care in ward 65
Levofloxacin 750mg IV QD (5/28-6/3)
Dexamethasone 6mg IV QD (5/28-6/6)
Herbal medicine 清冠一號 (5/28-)
DNR except drug

5/29

Remdesivir (5/29-6/2)

5/31

Still on NRM full, RR > 40/min
Transfer to SICU and endotracheal intubation(ETT)

6/01

Enoxaparin 4000U SC QD (6/1-) D-dimer 19.5 mg/dL
Self-paid IL-6 inhibitor, tocilizumab 600 mg CRP 1.35 mg/dL

Hospital
course

Nutrition

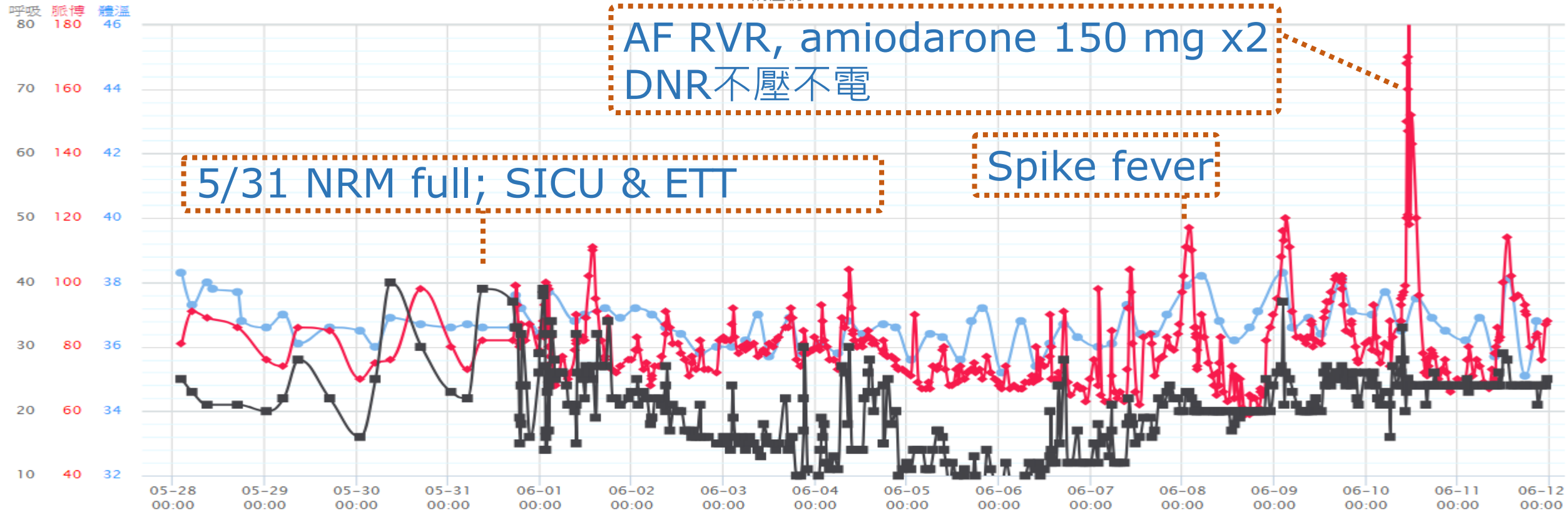
Sedation

Ventilation

Infection

Perfusion

Final
diagnosis



Levofloxacin 750mg IV QD (5/28-6/3)

Ceftazidime 2G Q8H
(6/3-6/7)

(6/8)

Meropenem 1G Q8H
(6/8-6/15)

Dexamethasone 6mg QD (5/28-6/6)

6/3, 6/8, 6/13 Tracheal Aspiration: *Candida albicans*

Full diet

Polymeric enteral diets (1.0S) 30 → 40 → 50 → 60 → 65 ml/hr

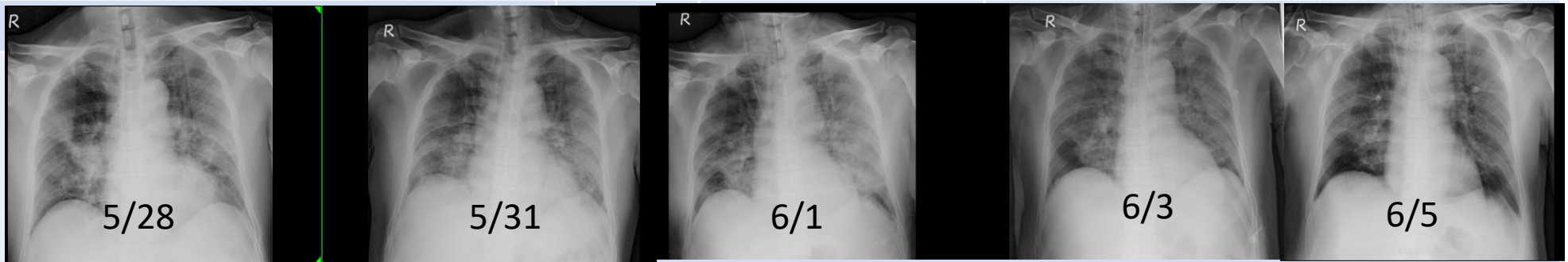


	0527	0528	0529	0530	0531	0601	0602	0603	0604	0605	0606
Blood pressure	Within normal range										
	No inotropic agent										
Albumin									Q12H		

	0607	0608	0609	0610	0611	0612	0613	0614	0615	0616	0617
Blood pressure	MAP < 65 mmHg								MAP<65		
Norepinephrine	8	0	1.6	2.13	0				1.07	0	
Albumin	QD				Q12H	QD					

Norepinephrine 單位 mcg/min, Epinephrine 單位 0.032mg/mL, Hydrocortisone 3.33mg/mL

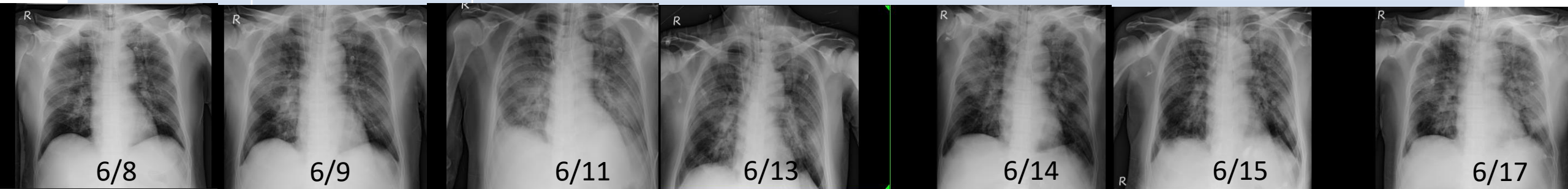


		0527	0528	0529	0530	0531	0601	0602	0603	0604	0605	0606
GCS												
Midazolam												
Fentanyl												
Cisatracurium												
RASS												
Mode	NRM full				PC					PSIMV+PS		
Pressure					12	14	12			12		
PEEP					8	10			12	12		
FIO2(%)					90	60		55	50	45		
pH					7.35-7.45							
CO2					46.4	45.8	44.7	49.5	59.1	60.9	60.2	
O2					133.8	210.1	61.1	61.4	141	102.8	330.2	
HCO3					28	29	27.9	32.6	39.7	38.5	39.3	
P/F					148.7	300.1	122.2	171.1	282	228.4	733.8	
SpO2(%)	95	95	94	91	82	>95						


Midazolam單位 mg/hr, Fentanyl 單位 mcg/hr, Cisatracurium mg/hr, Propofol單位 mg/hr



	0607	0608	0609	0610	0611	0612	0613	0614	0615	0616	0617
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Mode	PSIMV+PS	PC								PSIMV+PS	PC
Pressure	18	16		20							
PEEP	10										
FIO2	60						55		50	55	
pH	7.35-7.45			7.47	7.363	7.314	7.35	7.31	7.409	7.166	7.408
CO2	56.7	66.1	54.1	46.8	59.1	72.2	64.3	76.5	59.9	123.4	62.7
O2	100.9	72.4	96.5	98.5	96.5	129.9	104.2	130.8	86.1	124.6	129.3
HCO3	33.2	39.4	34.8	34.3	33.9	37	35.8	38.9	38.3	45	39.9
P/F	168.2	144.8	160.8	164.2	160.8	216.5	189.5	237.8	172.2	207.7	235.1
SpO2	<div>↓</div> >95										


 6/8 Dyspnea, SpO2 83-88%; PSIMV+PS -> PC

Hospital
course

Nutrition

Sedation

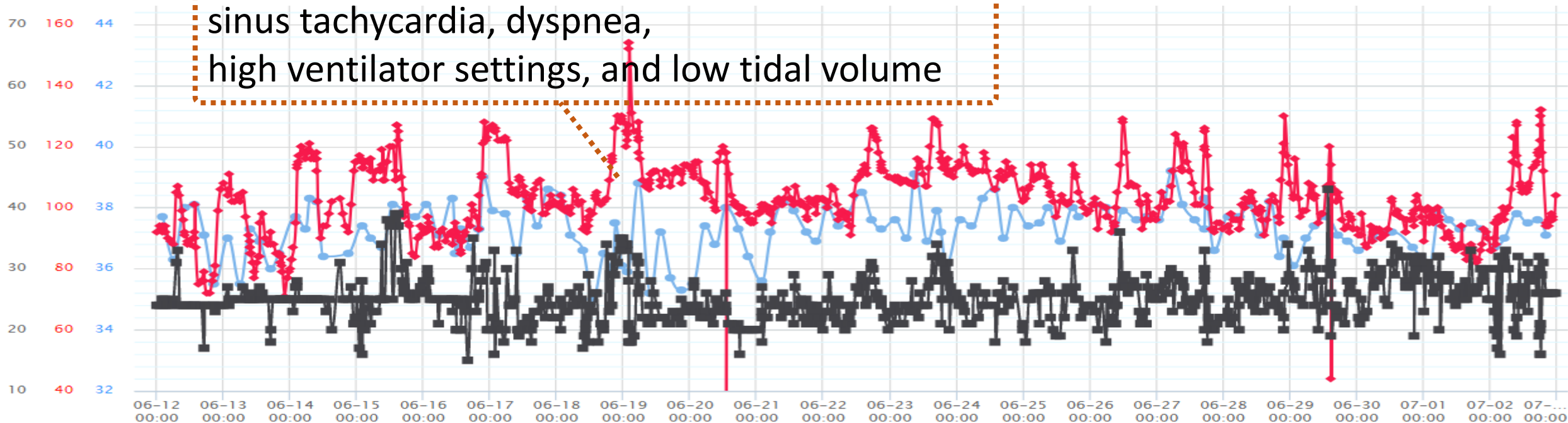
Ventilation

Infection

Perfusion

Final
diagnosis

sinus tachycardia, dyspnea,
high ventilator settings, and low tidal volume



Meropenem 1G IV Q8H (6/8-6/15) (6/15-6/22)

Levofloxacin 750mg IV QN (6/22-6/29) (6/29-7/6)

Teicoplanin 600 MG Q12H (6/14)
Teicoplanin 400 MG QD (6/15-6/22)

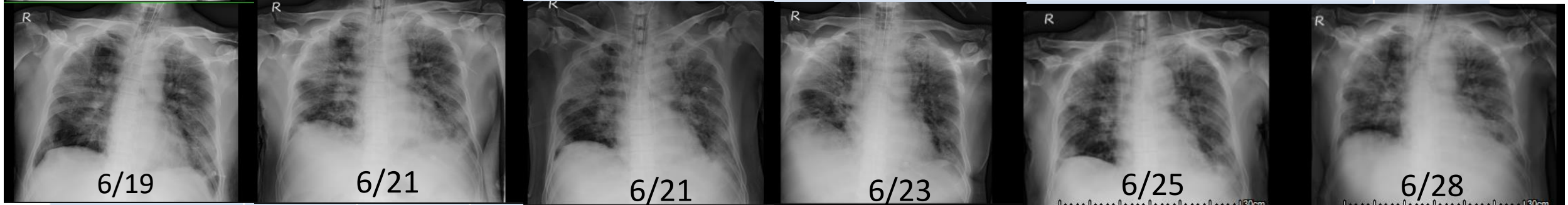
Ceftazidime 2G IV
Q8H (6/29-7/6)

6/17 Tracheal Aspiration: Elizabethkingia miricola (S to levofloxacin)
6/24 Tracheal Aspiration: Elizabethkingia miricola (S to levofloxacin);
Serratia marcescens(S to ceftazidime); Stenotroph. maltophil(R to all)

Polymeric enteral diets (1.0S) 65 ml/hr



	0618	0619	0620	0621	0622	0623	0624	0625	0626	0627	0628
--	------	------	------	------	------	------	------	------	------	------	------



RASS		-4							-3	-4	
Mode	PC			PSIMV+PS					PC		
Pressure	18	16	18			22			24		22
PEEP	10		8								
FIO2	55			50	55	50				45	
pH	7.223	7.482	7.35-7.45			7.312	7.436	7.443	7.459	7.445	7.394
CO2	106.6	48.1	59.8	65.6	75.2	91.3	61.2	54	47	55.6	64.7
O2	150.2	109.4	97.3	115.6	262.7	112.2	161.1	136.6	148.5	146.1	142.8
HCO3	44.3	36.3	40.5	39.2	43.1	46.6	41.5	37.3	33.7	38.6	39.9
P/F	250.3	198.9	176.9	210.2	477.6	224.4	322.2	273.2	297	292.2	317.3
SpO2	↓6/19 Endotracheal tube exchange >95										

suspected endotracheal tube obstruction caused by sputum

Hospital
course

Nutrition

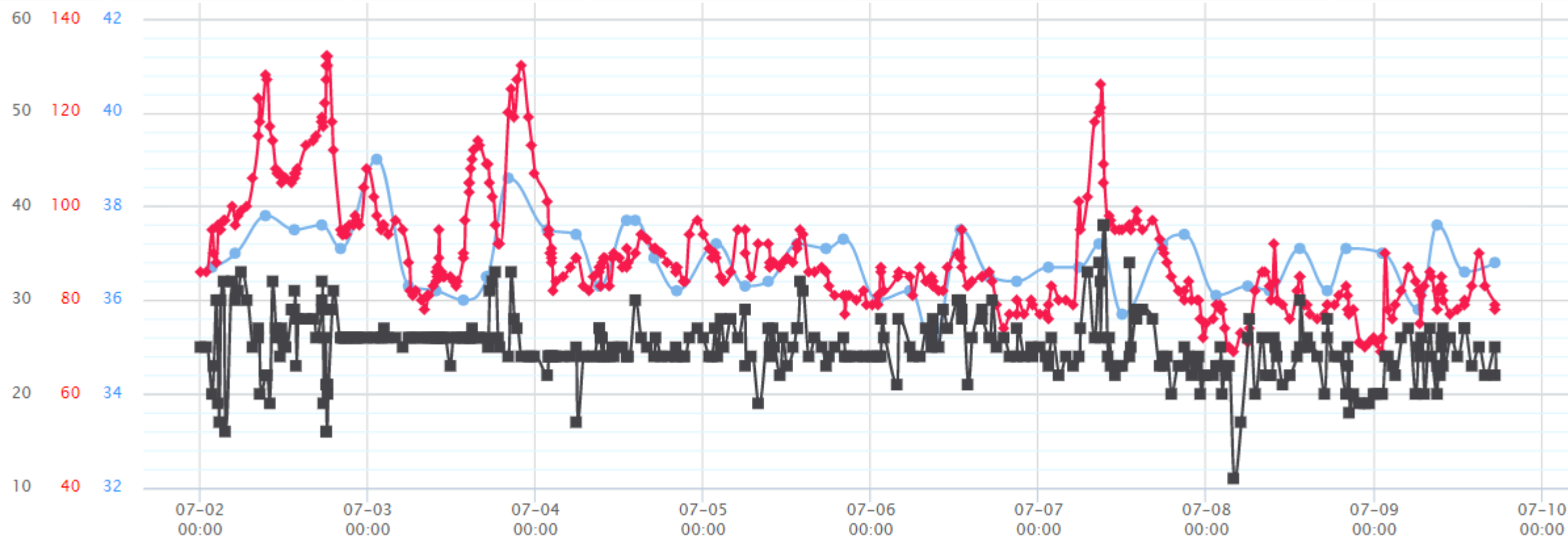
Sedation

Ventilation

Infection

Perfusion

Final
diagnosis



Levofloxacin 750mg IV QN (6/29-7/6)(7/6-7/13)

Ceftazidime 2G IV Q8H (6/29-7/6)(7/6-7/13)

Hydrocortisone 100 MG IV Q12H (7/6-7/7), QD (7/7-7/8)

Prednisolone 10 MG PO QD (7/9-)



	0618	0619	0620	0621	0622	0623	0624	0625	0626	0627	0628
Blood pressure	stable									MAP<65	
Norepinephrine										2.67	2.67
Albumin											
Hydrocortisone											Q12H

	0629	0630	0701	0702	0703	0704	0705	0706	0707	0708	0709
Blood pressure				MAP <65					stable		
Norepinephrine				1.07	5.33	1.87	1.07	off			
Albumin		QD					QD				
Midorine							5 mg Q8H				
Hydrocortisone								Q12H	QD	QD	P 2#QD

Norepinephrine 單位 mcg/min, Epinephrine 單位 0.032mg/mL, Hydrocortisone 100 mg

- COVID-19 PCR
 - 5/21 swab: (+) ct = 19
 - 6/9 swab: (+) ct < 30
 - 6/24 swab: (+) ct < 30
 - 7/1 swab: (+) ct ≥ 30
 - 7/3 swab: (+) ct < 30; sputum: (-)
 - 7/8 swab: (+) ct ≥ 30

Hospital
course

Nutrition

Sedation

Ventilation

Infection

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diagnosis

RASS -1 ~ +2 ; Pain 0-1;

Pressure support ~ BIPAP (PEEP 6, FiO2 30%, MV 14-10, SpO2 98%)

- 7/14 Tracheostomy
- 7/21 Spiriva respimat (tiotropium) 2.5 mcg/puff, 2 puff QD
- 7/21 Berodual N MDI 20 mcg/50 mcg/dose 4 puff QIDPRN
- 6/19 Quetiapine 25mg - 50 mg - 100 mg - 50 mg - 25 mg QD – QN -Q12H
- 7/5 Alprazolam 0.5 mg TID – Q8H – BID – QD
- 7/23 Sertraline 25 mg - 50mg QD



- 選擇 COVID-19 ARDS 之止痛鎮靜
- 調整 COVID-19 ARDS 之止痛鎮靜
- 停止 COVID-19 ARDS 之止痛鎮靜

COVID 19 → 130,295 results

 **National Library of Medicine**
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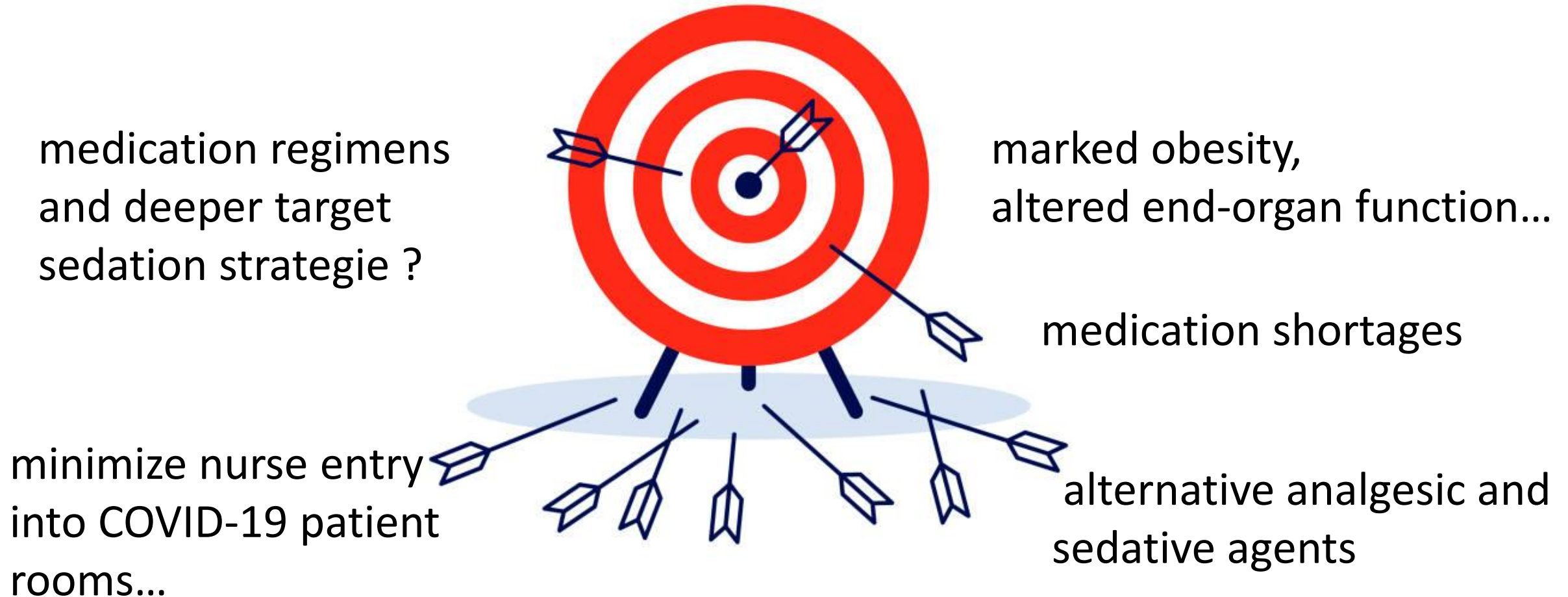
COVID 19 and sedation → 184 results

 **National Library of Medicine**
National Center for Biotechnology Information



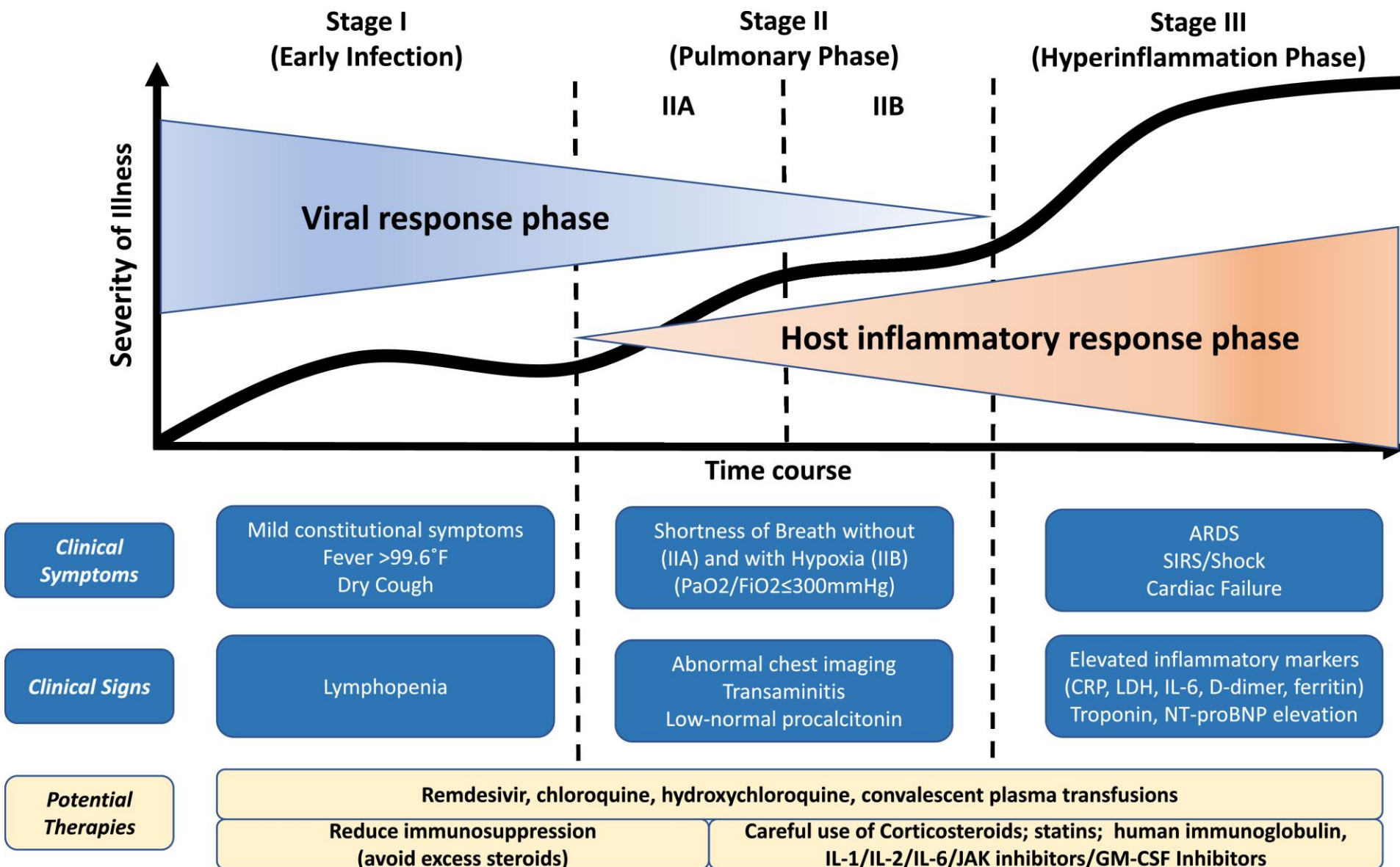
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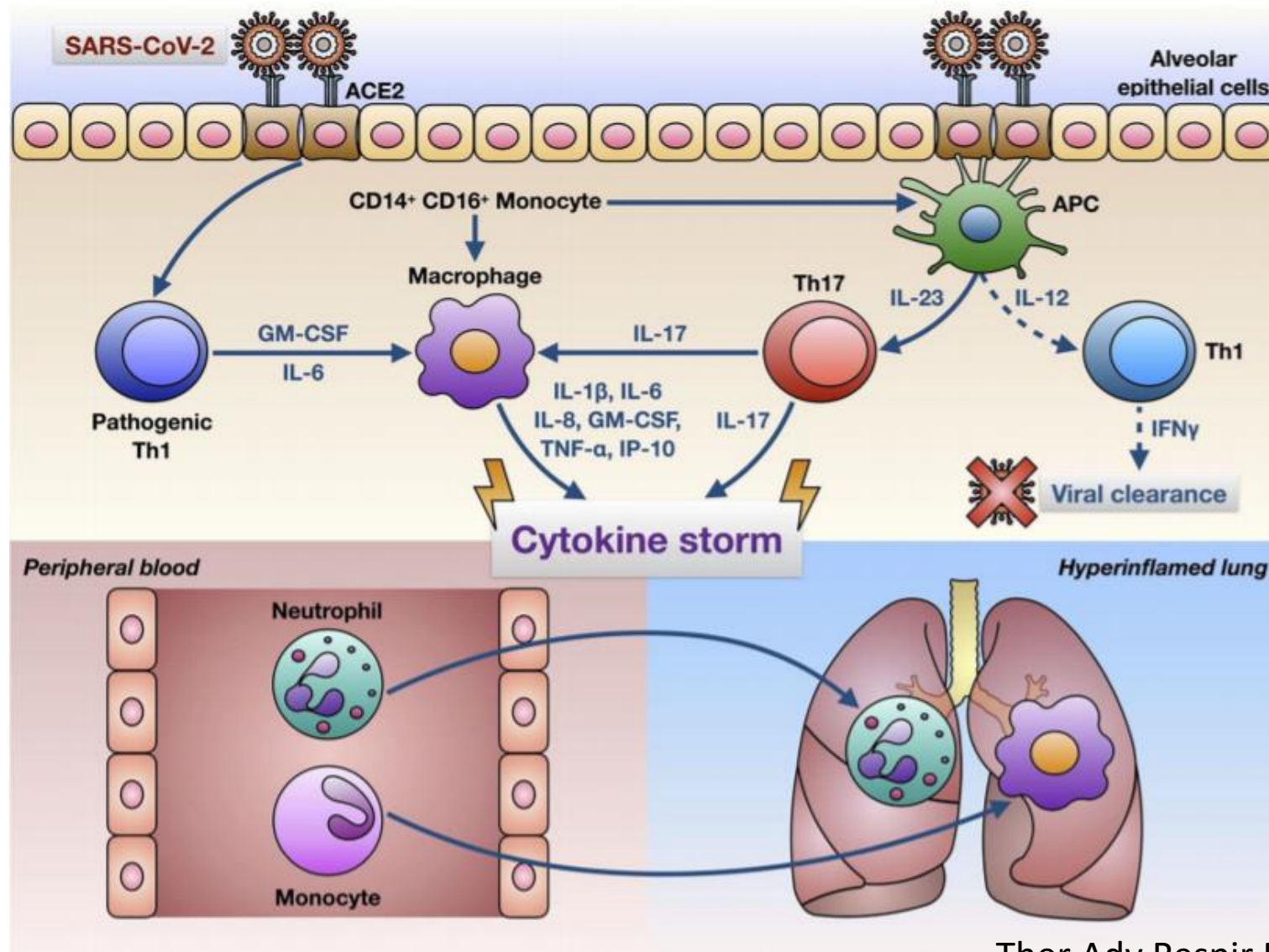
Why more analgesia and sedation in ventilated patients with COVID-19 ?

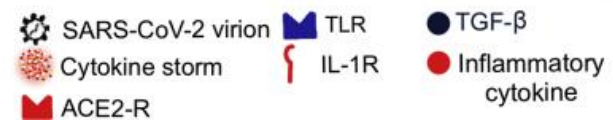
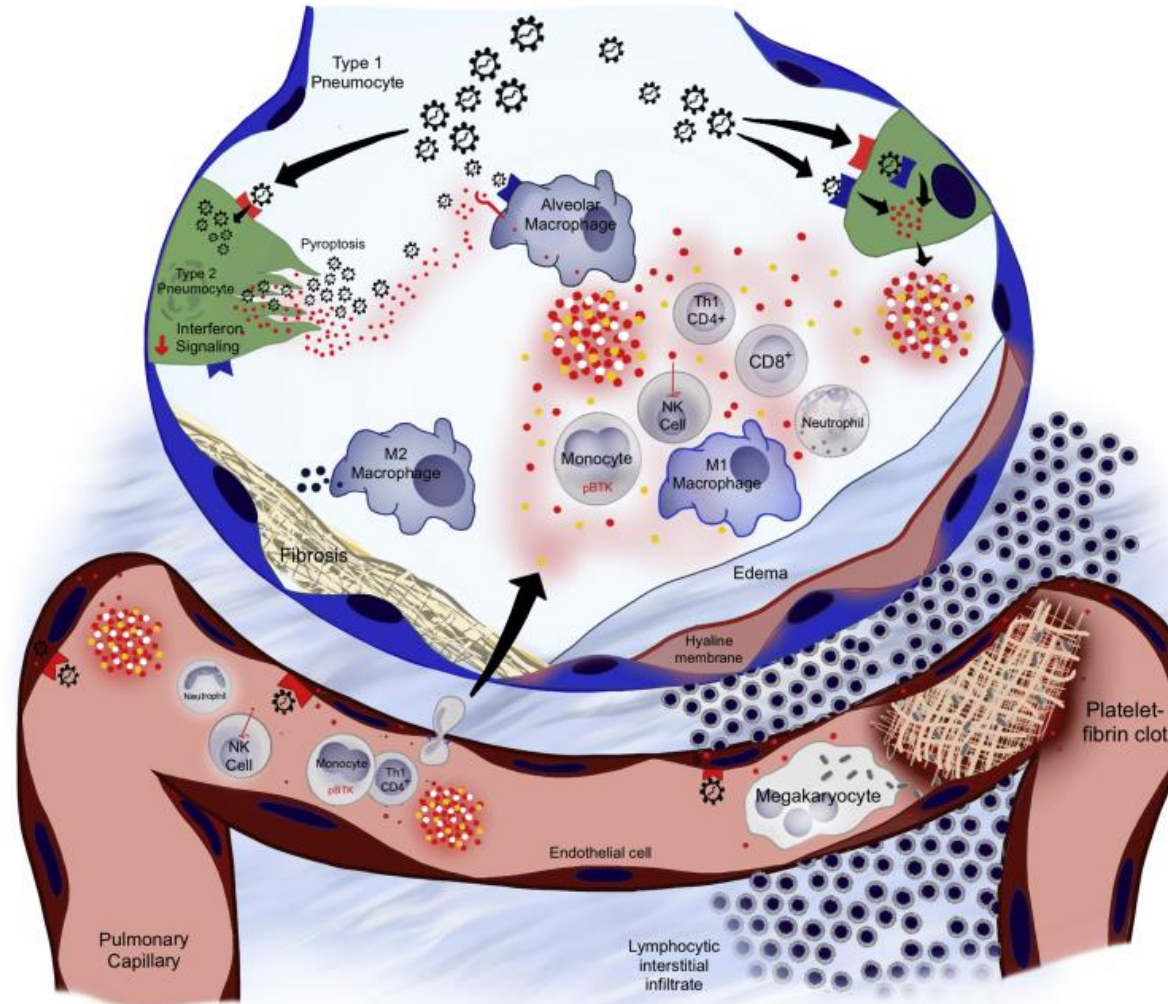


Definitions of Critical and Severe COVID-19

Category	Definition
Severe	Clinical signs of pneumonia (fever, cough, dyspnea, fast breathing) and one of the following: <ul style="list-style-type: none">• Respiratory rate > 30 breaths/min;• Severe respiratory distress; or• Oxygen saturation < 90% on room air
Critical	Presence of acute respiratory distress syndrome or respiratory failure requiring ventilation, sepsis, or septic shock

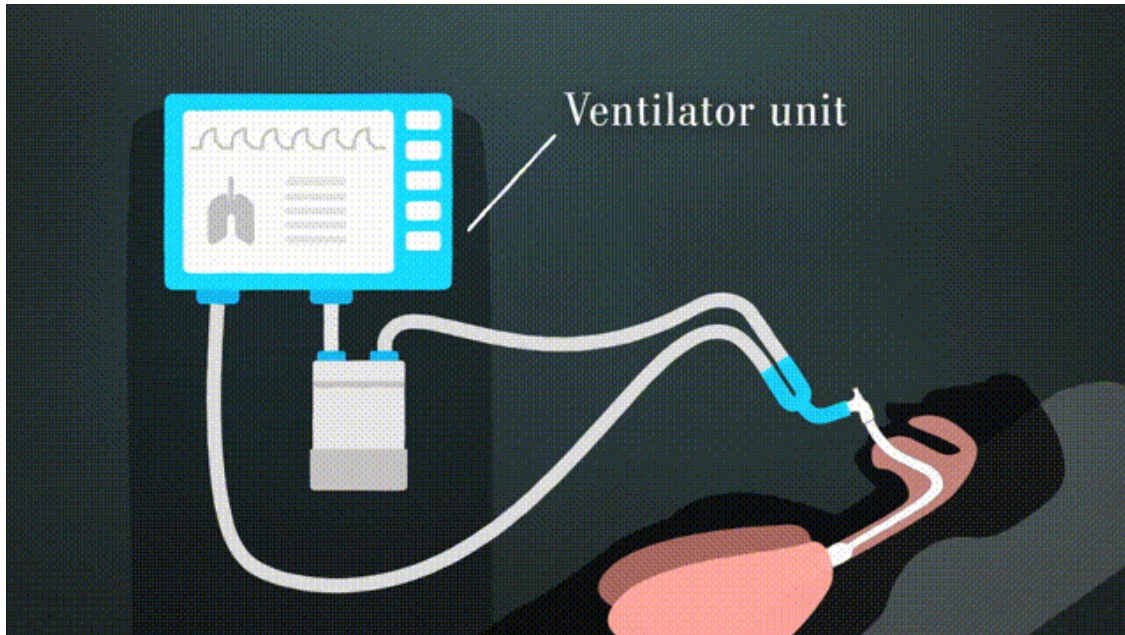






Prevent ventilator-induced lung injury

avoiding ventilator dyssynchrony

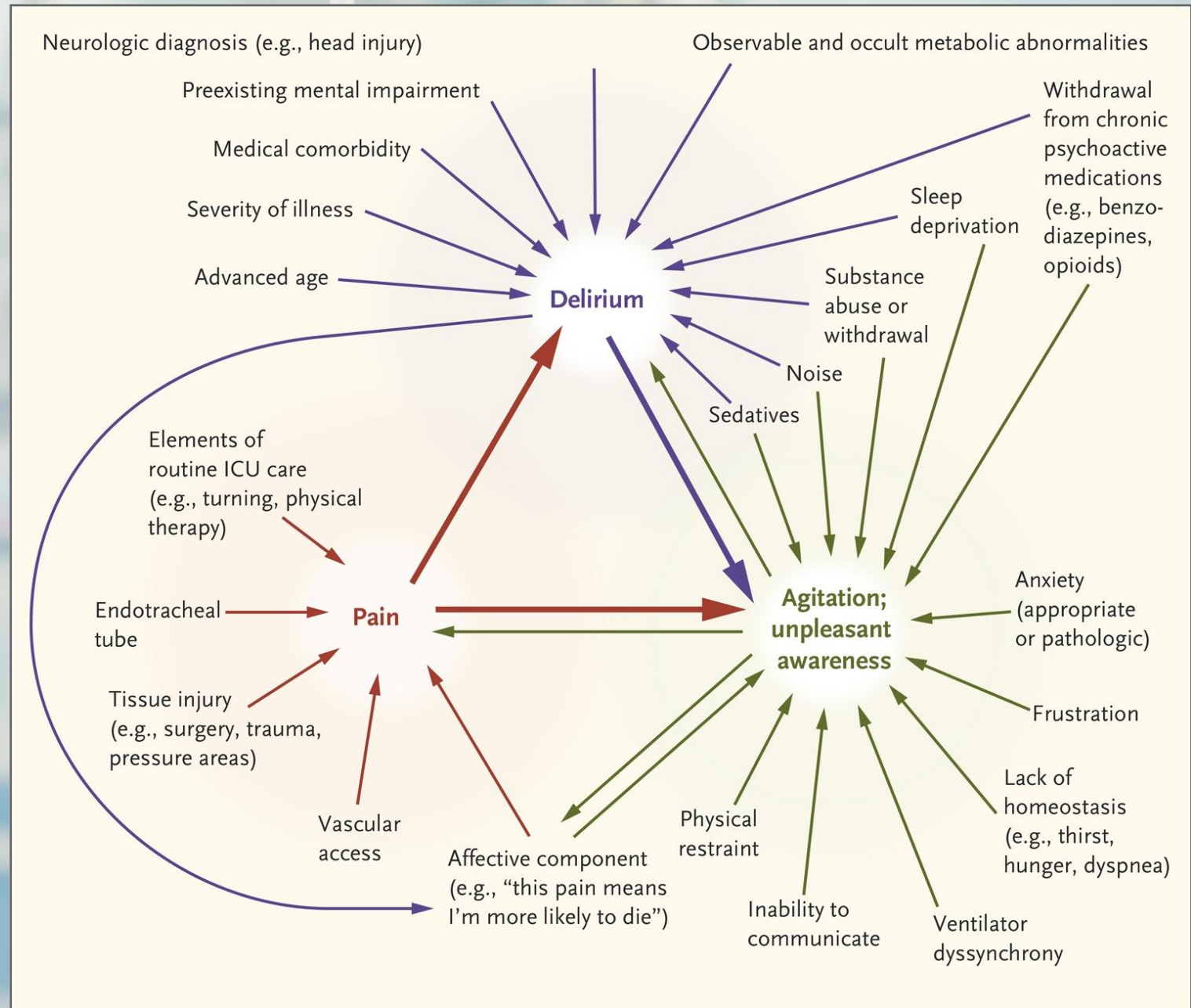


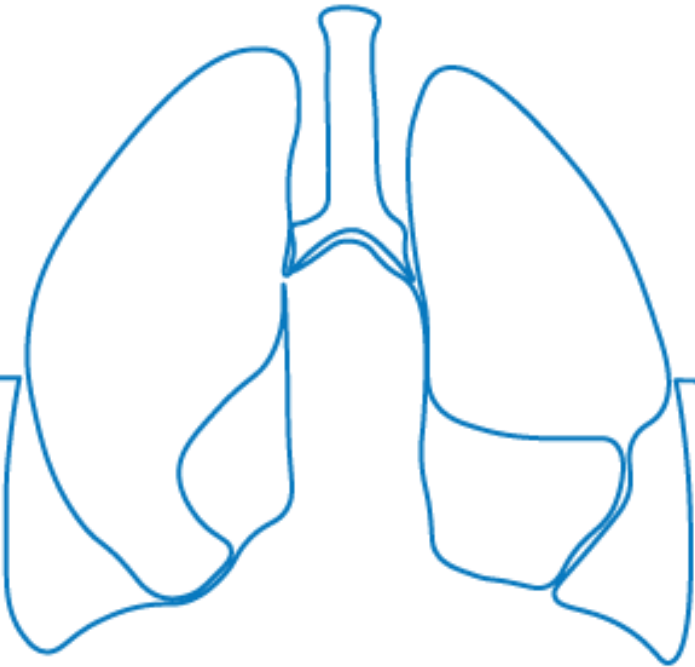
1. Strategy of lung protective ventilation
limiting tidal volumes(V_T) 4-8 mL/kg
Plateau pressures(P_{pla}) < 30 cmH₂O
High positive end-expiratory pressure (PEEP) >12 cmH₂O
Reducing respiratory rates (RR)
2. Sedative agents

ICU triad

Agitation,
Pain,
Delirium

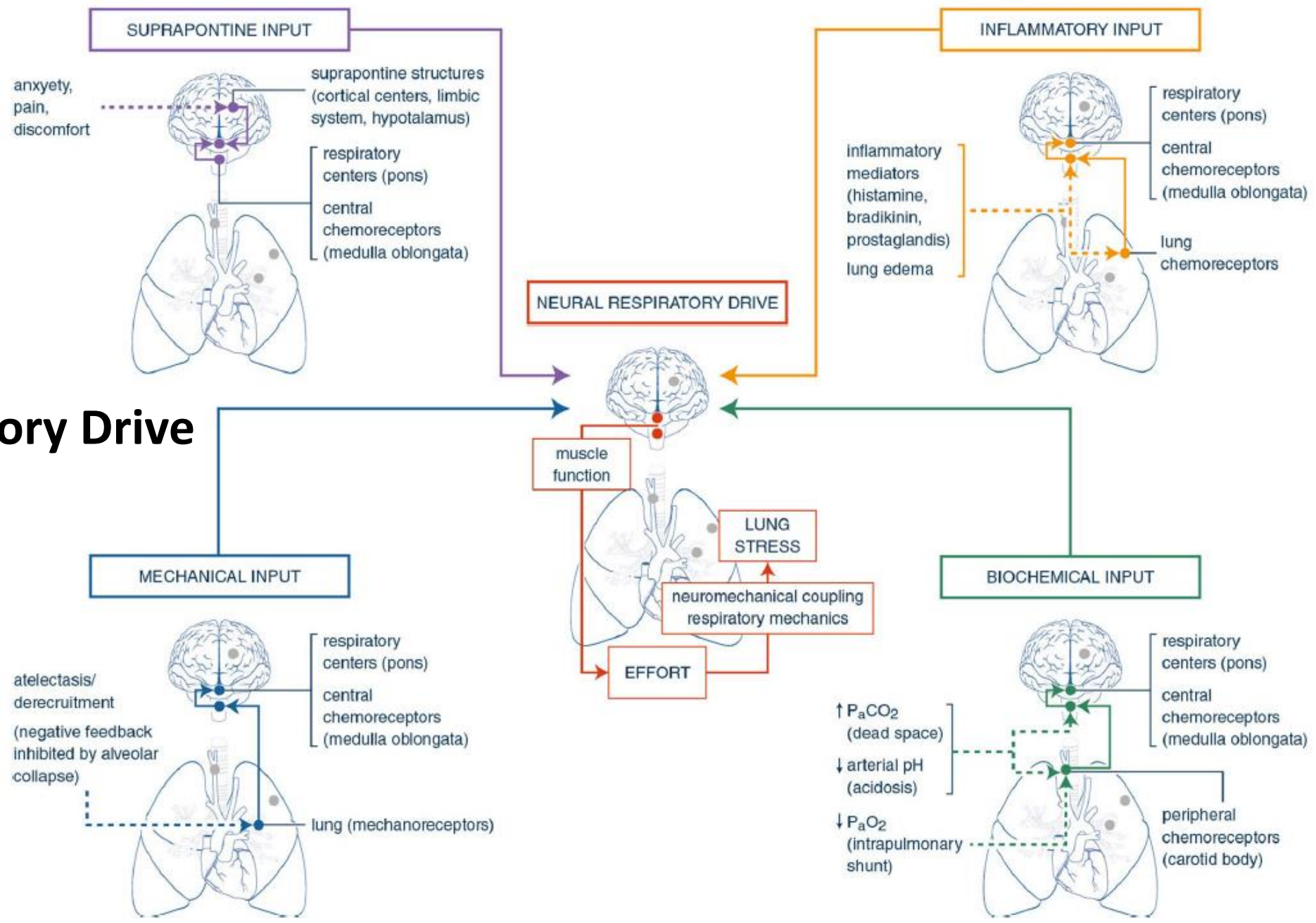
N Engl J Med 2014;
370:444-454





More Sedation in Ventilated COVID-19 Patients

More Respiratory Drive



↑ Respiratory Drive

Determinant	Common etiologies	Mechanisms	Potential interventions (as appropriate)
Hypercapnia	↑ Dead space, ↑ lung and chest wall elastance, ↑ CO ₂ production	Stimulation of central and peripheral chemoreceptors [3, 5, 14, 15]	Ventilatory support; fever and pain control; sedation; ECCO ₂ R [95]
Hypoxemia	↑ Intrapulmonary shunt, V/Q mismatch, ↑ VO ₂ /DO ₂	Stimulation of peripheral chemoreceptors [4, 16]	FiO ₂ [78, 79], PEEP [26, 27]; mechanical ventilation cardiovascular support (fluids, inotropes, vasopressors, red cell transfusion); ECMO
Metabolic acidosis	Shock, acute kidney injury	Stimulation of central and peripheral chemoreceptors [16]	Cardiovascular support; bicarbonate; RRT
Inflammation	ARDS, P-SILI, sepsis	Increased sensitivity of peripheral chemoreceptors to hypoxemia; stimulation of lung chemoreceptors (C-fibers) [19–21]; direct stimulation of respiratory centres by cytokines [24]	Aetiologic treatment; lung- and diaphragm-protective mechanical ventilatory support
Lung atelectasis	Pulmonary edema, inflammatory cells, re-absorption atelectasis	↓ Inhibitory activity from lung slow adapting mechanoreceptors [20]	PEEP [26, 27] and respiratory support; prone positioning; physiotherapy
Agitation	Anxiety, pain, respiratory distress	↑ Descending input [28]	Respiratory support; sedation or anxiolysis; non-pharmacologic (and potentially pharmacologic) treatments of delirium [93, 94]
Poor patient-ventilator interaction	↑ Lung and chest wall elastance leading to flow starvation and increased inspiratory load; intrinsic PEEP causing delayed triggering	↑ Descending input due to discomfort; ↑ inspiratory load due to mismatch between mechanical inflation and neural inspiratory time [30]; stimulation of central and peripheral chemoreceptors in the case of hypercapnia	Adjust ventilation settings, change ventilation modes [80–82], titrate sedation, consider neuromuscular blockade [58]

Study	Study Medication	# Patients	Time in Goal Sedation	# ARDS	Delirium Prevalence	Time to Extubation	ICU LOS	Bradycardia	Hypotension
Carson et al. (2006)	Propofol vs lorazepam	132	Targeted Ramsey Score 2-3 No Significant Difference	57 (43%) PNA or ARDS	N/A	5.8 vs 8.4 days (p=0.04)	Survivors: 8.6 vs 12.7 (P=0.05)	N/A	N/A
MENDS (2007)	Dex vs. lorazepam	107	n/a	39 (36%) Sepsis or ARDS	79% vs 82% (p=0.65)	N/A	7.5 v 9 days (p=0.92)	17% v 4% (P=0.03)	25 v 20% (P=0.51)
SEDCOM (2009)	Dex vs. midaz	366	Goal RASS -2 to 1 77.3% vs 75.1% (p=0.18)	N/A	54% vs 76.6% (p<0.01)	3.7 vs 5.6 days (p=0.01)	5.9 vs 7.6 days (p=0.24)	42.4 v 18.9% (P<0.001)	56.1 vs 55.1% (P=1.00)
MIDEX (2012)	Dex vs midaz	500	Excluded deep sedation 60.7 vs. 56.6% (p=0.15)	N/A	7.7 vs 10% (p=0.43)	4.2 vs 6.1 days (p=0.01)	8.8 vs 10.1 days (p=0.27)	14.2 v 5.2% (P<0.001)	20.7 vs 11.6% (P=0.007)
PRODEX (2012)	Dex vs propofol	498	Excluded deep sedation 64.6% vs 64.7% (p=0.97)	N/A	4.9% vs 9.7% (p=0.056)	2.9 vs 3.9 days (p=0.04)	6.8 vs 7.7 days (p=0.54)	13 vs 10.1% (P=0.328)	13.0 vs 13.4 % (P=1)
SPICE III (2019)	Dex vs usual care (prop or midaz or combo)	3904	Goal -2 to 1 but deep sedation allowed prn 56.6% vs. 51.8% (p not reported)	1576 (40%) "Respiratory Disorder"	40.7% vs 42.5% (p=0.26)	N/A	6 vs 6.3 days (p not reported)	5.1 v 0.5% (P<0.0001)	2.7 vs 0.5% (P<0.0001)

<https://advances.massgeneral.org/research-and-innovation/article.aspx?id=1355>

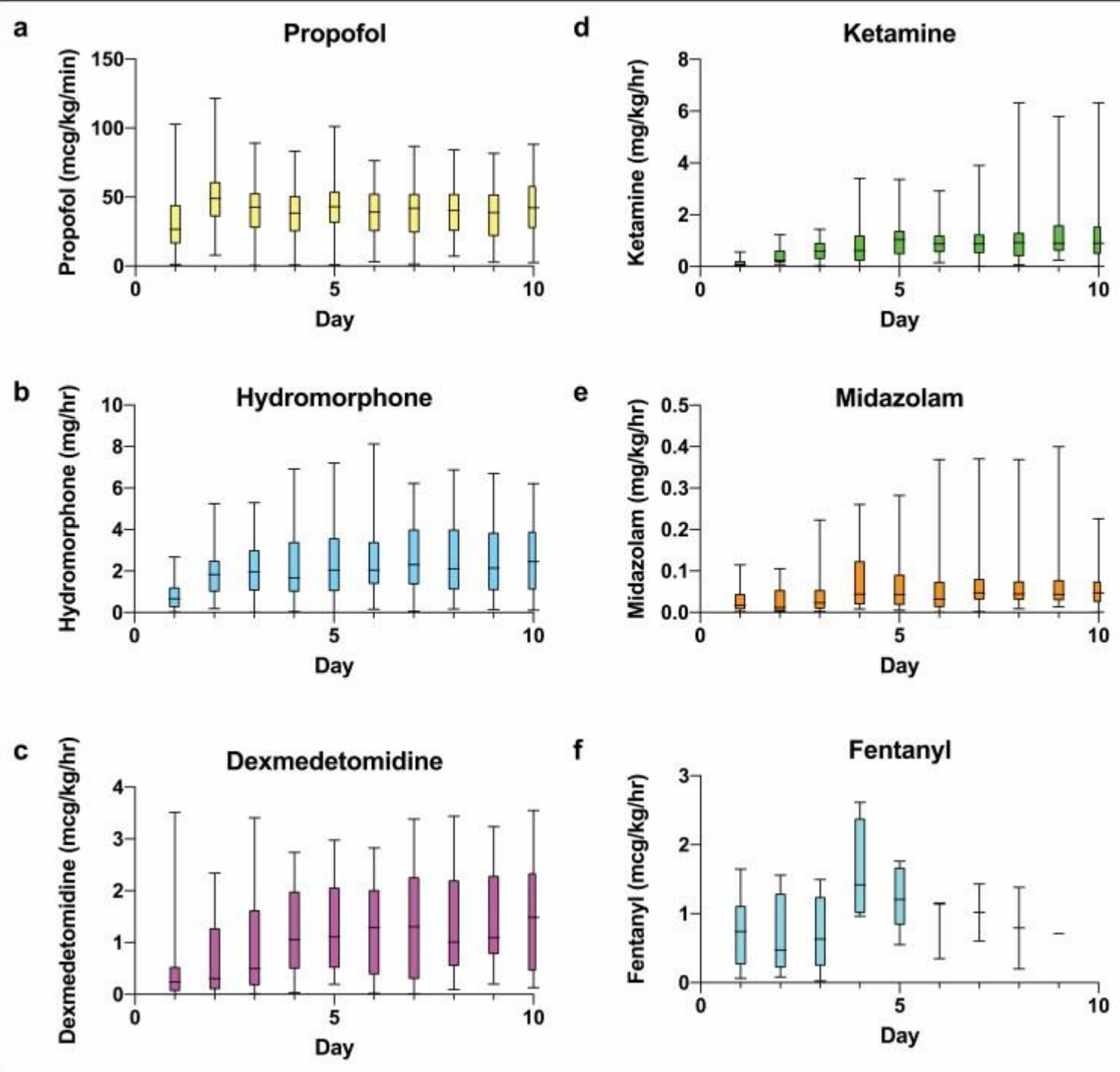


Table 2. Sedative and paralytic agents administered to intubated COVID19 patients over time.*

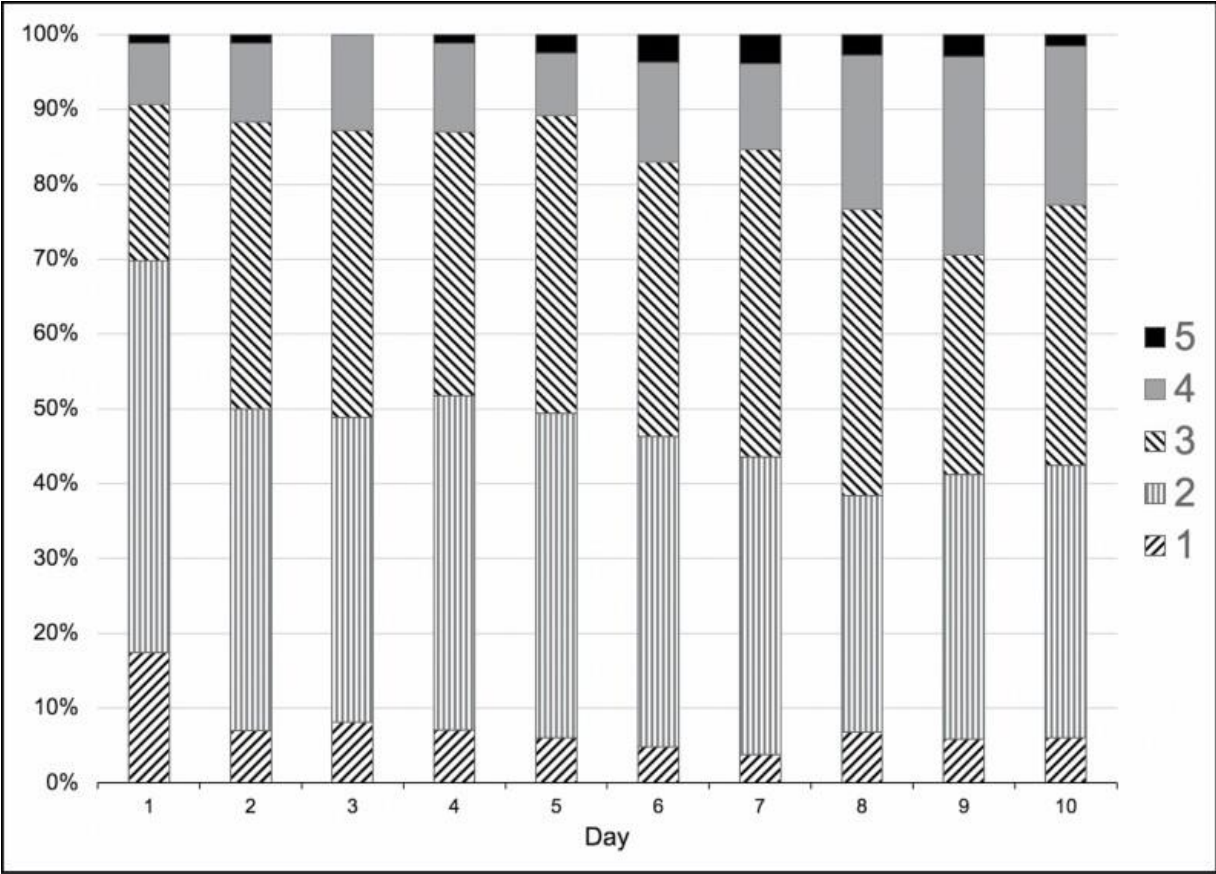
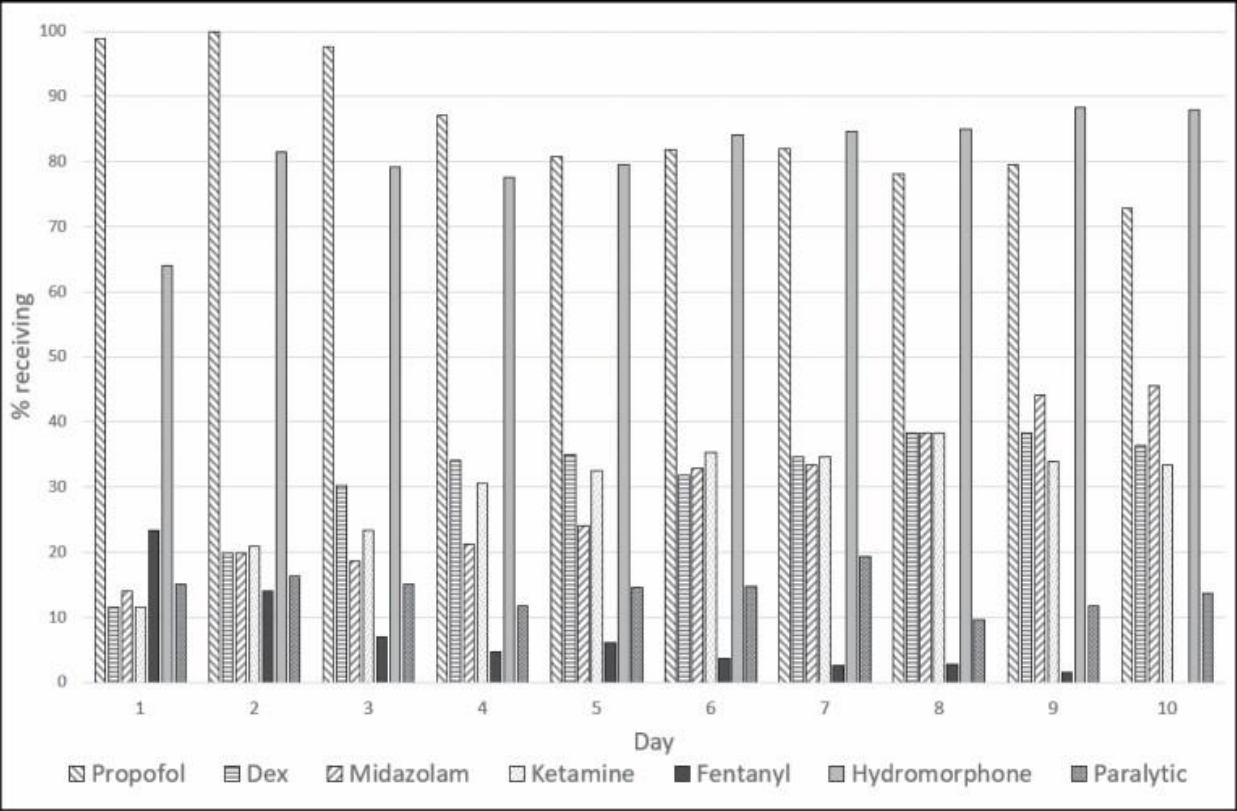
	Propofol (mcg/kg/min)	Dexmedetomidine (mcg/kg/hr)	Midazolam (mg/kg/hr)	Ketamine (mg/kg/hr)	Fentanyl (mcg/kg/hr)	Hydromorphone (mg/hr)	Cisatracurium (mcg/kg/min)	Rocuronium (mcg/kg/min)
Recommended Range**	5-50	0.2-0.7	0.02-0.1	0.05-0.4	0.7-10	0.5-3.0	0-10	0-10
Day 1	26.74 (16.36-44.18)	0.24 (0.07-0.39)	0.02 (0.01-0.03)	0.07 (0.02-0.18)	0.74 (0.31-1.10)	0.67 (0.25-1.17)	0.38 (0.08-1.00)	4.49 (3.65-5.32)
Day 2	48.94 (36.31-60.72)	0.31 (0.11-0.89)	0.01 (0.00-0.05)	0.24 (0.16-0.59)	0.47 (0.25-1.03)	1.83 (1.00-2.49)	1.06 (0.50-2.05)	4.25 (4.23-4.27)
Day 3	42.70 (27.70-52.52)	0.50 (0.19-1.44)	0.03 (0.01-0.05)	0.60 (0.29-0.88)	0.63 (0.38-1.05)	1.96 (1.07-3.00)	0.53 (0.17-1.88)	16.84 (16.84-16.84)
Day 4	38.38 (25.48-50.44)	1.06 (0.69-1.92)	0.04 (0.02-0.10)	0.62 (0.25-1.17)	1.42 (1.11-1.91)	1.68 (1.01-3.28)	1.68 (0.25-2.72)	10.88 (5.77-16.00)
Day 5	42.97 (31.68-53.84)	1.11 (0.52-1.91)	0.04 (0.02-0.08)	1.04 (0.49-1.29)	1.21 (1.13-1.57)	2.04 (1.06-3.52)	1.84 (1.06-3.02)	7.75 (3.30-16.22)
Day 6	39.19 (25.43-52.07)	1.29 (0.42-1.97)	0.04 (0.02-0.07)	0.87 (0.58-1.20)	1.14 (0.74-1.15)	2.04 (1.42-3.39)	2.50 (0.87-3.82)	14.79 (5.02-18.15)
Day 7	41.93 (24.46-52.13)	1.31 (0.35-2.15)	0.05 (0.03-0.08)	0.88 (0.55-1.24)	1.02 (0.81-1.23)	2.30 (1.36-4.00)	1.39 (0.54-2.21)	8.71 (3.86-10.72)
Day 8	40.36 (25.43-52.05)	1.01 (0.55-2.17)	0.05 (0.03-0.08)	0.92 (0.45-1.25)	0.79 (0.50-1.09)	2.11 (1.12-4.00)	2.08 (1.67-2.50)	9.21 (6.11-9.55)
Day 9	38.64 (22.12-51.64)	1.10 (0.82-2.15)	0.05 (0.03-0.08)	0.90 (0.67-1.47)	0.71 (0.71-0.71)	2.15 (1.11-3.84)	1.55 (0.59-2.50)	6.03 (2.71-15.23)
Day 10	42.25 (28.24-57.03)	1.48 (0.64-2.29)	0.05 (0.03-0.07)	0.90 (0.58-1.48)	NA	2.45 (1.19-3.88)	1.26 (0.01-2.50)	4.78 (4.01-6.65)

*Data presented as median (IQR).

**As per the 2013 Society of Critical Care Medicine (SCCM) clinical practice guidelines, excepting paralytics which were per our institutional guidelines.

^aRed shading indicates values that are above published recommended dose ranges.

Percentage of intubated patients with COVID-19 receiving a given sedative, analgesic, or paralytic agent by day of intubation.

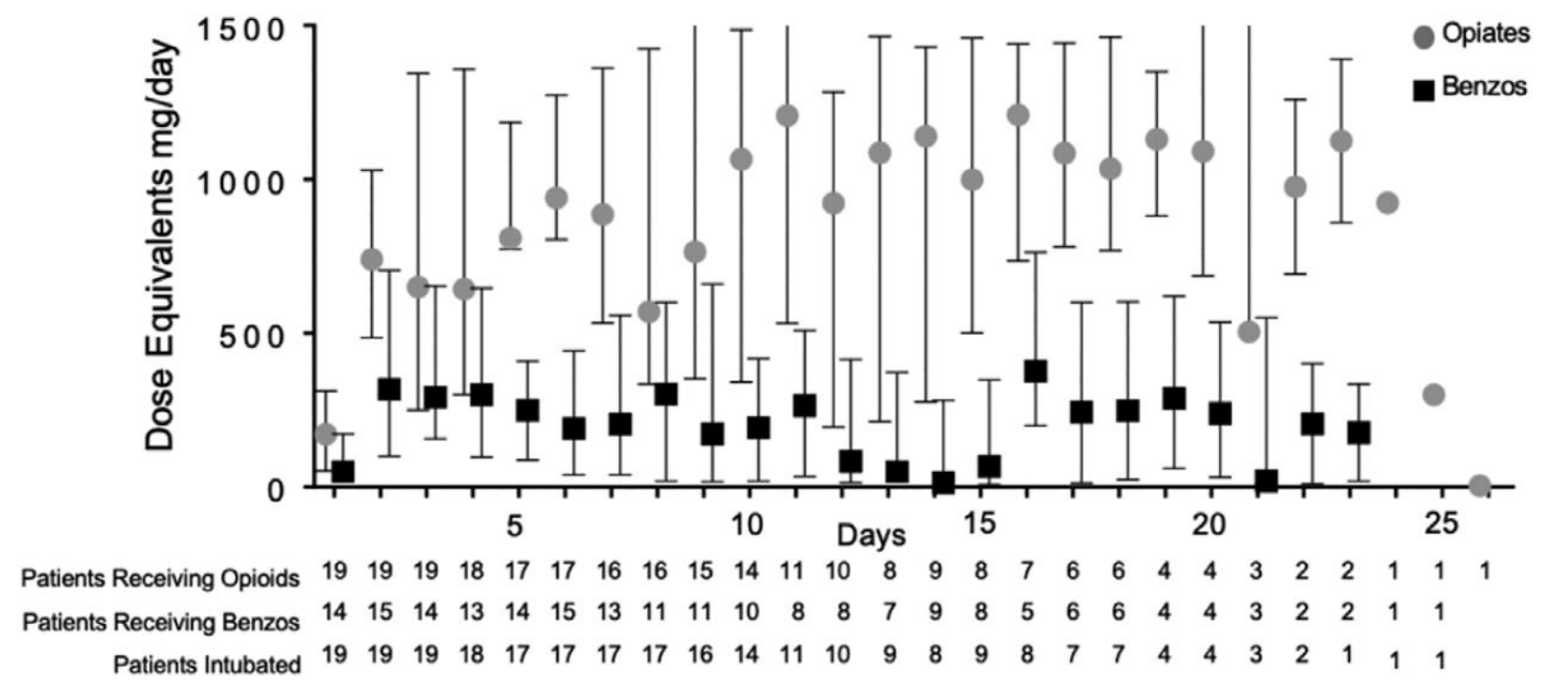


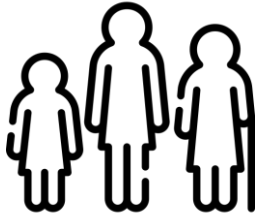
19 patient	intuited + IV (A+S) +/- NMBs(day 2 to 7)	intuited + IV (A+S) + NMBs	intuited + IV (A+S) - NMBs
oral morphine equivalents IQR	775 mg (IQR 648.4–899.7 mg)	937.2 mg (IQR, 667.7–1683 mg)	623.8 mg (IQR, 176.3–726.9 mg)
oral midazolam equivalents IQR	270.9 mg (IQR, 201.3–304.4 mg)	224.7 mg (IQR, 56.56–610 mg)	135 mg (IQR, 40.63–203.8 mg),

interquartile range [IQR]
 Anagelsics(A); Sedaton(S);
 neuromuscular blockade(NMBs)

OSCILLATE trial
morphine
289 mg (IQR, 125.8–480 mg)
midazolam
199 mg (IQR, 100–382 mg)

average APACHE-2 score
19.6 vs 29 (OSCILLATE)



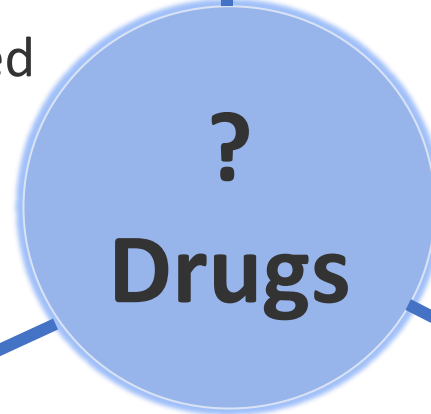


Elderly :

↓ pharmacokinetics & pharmacodynamics with reduced clearance;
↑ increased sensitivity to drugs, prolonged ventilation, delirium, , death.

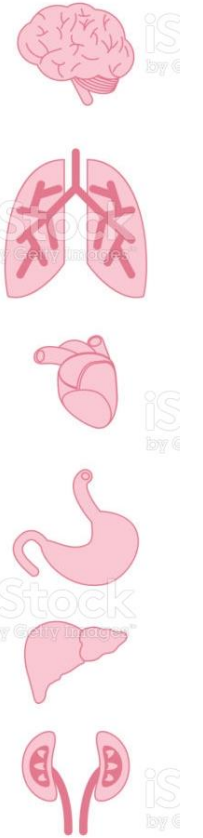
Younger :

higher doses of drugs.
more tolerant to opioids and benzodiazepines.



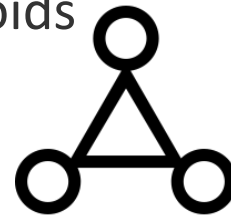
Organ dysfunction:

Acute, or acute on chronic organ dysfunction results in pharmacokinetic and pharmacodynamic changes



Dependence:

These Patients who chronically use opioids and/or psychoactive medications may require higher doses of opioids and/or sedatives.



Agent	Vecuronium	Rocuronium	Cisatracurium	Succinylcholine
Type (structure)	Non-depolarizing	Non-depolarizing	Non-depolarizing	Depolarizing
Type (duration)	Intermediate	Intermediate	Intermediate	Ultrashort
Onset time (min)	3 to 4	1 to 2	4 to 6	1
Elimination half-life (min)				
Normal organ function	50 to 60	60 to 100	23 to 30	<1
Renal impairment	Mild increase	100 to 300	Mild increase	<1
Hepatic impairment	Significant increase	120 to 400	23 to 30	<1
Maintenance dose (mg/kg)	0.01	0.10	0.01	N/A
Infusion dose (mcg/kg/min)	1 to 2	5 to 12	1 to 3	
Elimination route/metabolism	Renal 10 to 50%; hepatic 30 to 50%	Renal 30%; hepatic 70%	Hoffman 30%; ester hydrolysis 60% No active metabolites	Butyrylcholinesterase (plasma cholinesterase, pseudocholinesterase) No active metabolites
Side effects Contraindications	Vagal blockade with large doses	Minimal	None; histamine release at high doses	Myalgia; bradycardia
prolonged ICU administration	X	V, elimination half-life prolonged in ICU patient;	V	X

Properties and Dosing for Analgesic and Sedative Medications in Patients with COVID-19

Opioids	Equivalent Dose	Bolus Dose	CI Dose	Onset (min)	Metabolism	Active Metabolite	Elimination Half-life (h)	ADRs/ Considerations
Fentanyl	0.1	0.35–0.5 mcg/kg Q0.5–1 hr	0.7–10 mcg/kg/hr	1–2	Hepatic	No	2–4 ^b	Accumulation with hepatic impairment and obesity
Hydromorphone	1.5	0.2–0.6 mg Q1–2 hrs	0.25–6 mg/hr	5–15	Hepatic	No	2–3 ^b	Accumulation with hepatic/renal impairment
Morphine	10	2–4 mg Q1–2 hrs	0.5–15 mg/hr	5–10	Hepatic; active metabolite (renal)	Yes	3–4 ^b	Accumulation with hepatic/renal impairment; histamine release
Remifentanyl	~0.1	1.5 mcg/kg ^a	0.5–15 mcg/kg/hr	1–3	Hydrolysis by plasma esterases	No	3–10 min	Ultra short half-life, rebound pain; use IBW if ABW > 130% IBW
Sufentanyl	0.01	0.05 mcg/kg ^a	0.05 mcg/kg/hr	1–3	Hepatic	No	2.7 min	Ultra short half-life, rebound pain; use IBW if ABW > 120% IBW
Alfentanyl	0.75	5–7.5 mcg/kg ^a	0.1–0.2 mcg/kg/min	≤5	Hepatic	No	1.5–1.85 min	Ultra short half-life, rebound pain; use IBW
Methadone	N/A	2.5–10 mg Q6–12 hrs	N/A	10–20	Hepatic	No	15–60 ^b	QTc prolongation, unpredictable PK

Properties and Dosing for Analgesic and Sedative Medications in Patients with COVID-19

Benzodiazepines	Equivalent Dose	Bolus Dose	CI Dose	Onset (min)	Metabolism	Active Metabolite	Elimination Half-life (h)	ADRs/Considerations
Midazolam	2	0.01–0.05 mg/kg	0.02–0.1 mg/kg/hr	2–5	Hepatic	Yes	3–11 ^b	Respiratory depression, CNS depression, hypotension
Lorazepam	1	0.02–0.06 mg/kg Q2–6 hrs	0.01–0.1 mg/kg/hr	15–20	Hepatic	No	8–15 ^b	Respiratory depression, CNS depression, hypotension, propylene glycol toxicity
Diazepam	5	5–10 mg, 0.03–0.1 mg/kg Q0.5–6 hrs	N/A	2–5	Hepatic	Yes	20–120 ^b	Respiratory depression, CNS depression, hypotension, propylene glycol toxicity
Other Sedatives	Mechanism	Bolus Dose	CI Dose	Onset (min)	Metabolism	Active Metabolite	Elimination Half-life (h)	ADRs/Considerations
Propofol	GABA agonist, weak NMDA antagonist	N/A	5–80 mcg/kg/min	1–2	Hepatic	No	3–12 ^b	Hypotension, respiratory depression, hypertriglyceridemia, acute pancreatitis, propofol-related infusion syndrome
Dexmedetomidine	Alpha-2	1 mcg/kg	0.2–1.5 mcg/kg/hr	5–10	Hepatic	No	1.8–3.1	Bradycardia, hypotension
Ketamine	NMDA antagonist	0.5–1 mg/kg	1–5 mg/kg/hr	5–15	Hepatic	Yes	2–3	Excess secretions, emergence phenomenon, sympathetic surge, hypertension
Phenobarbital	GABA agonist	5–10 mg/kg load, 1–2 mg/kg/day in 2–4 divided doses, 65–130 mg	N/A	5	Hepatic	No	80 ^b	Hypotension, propylene glycol toxicity, drug interactions (CYP3A4 inducer)

ABW = actual body weight; ADR = adverse drug reaction; CI = continuous infusion; CNS = central nervous system; GABA = gamma aminobutyric acid; IBW = ideal body weight; IV = intravenous; NMDA = N-methyl-D-aspartate; PK = pharmacokinetics; Q = every (e.g., Q1h: every 1 hr).

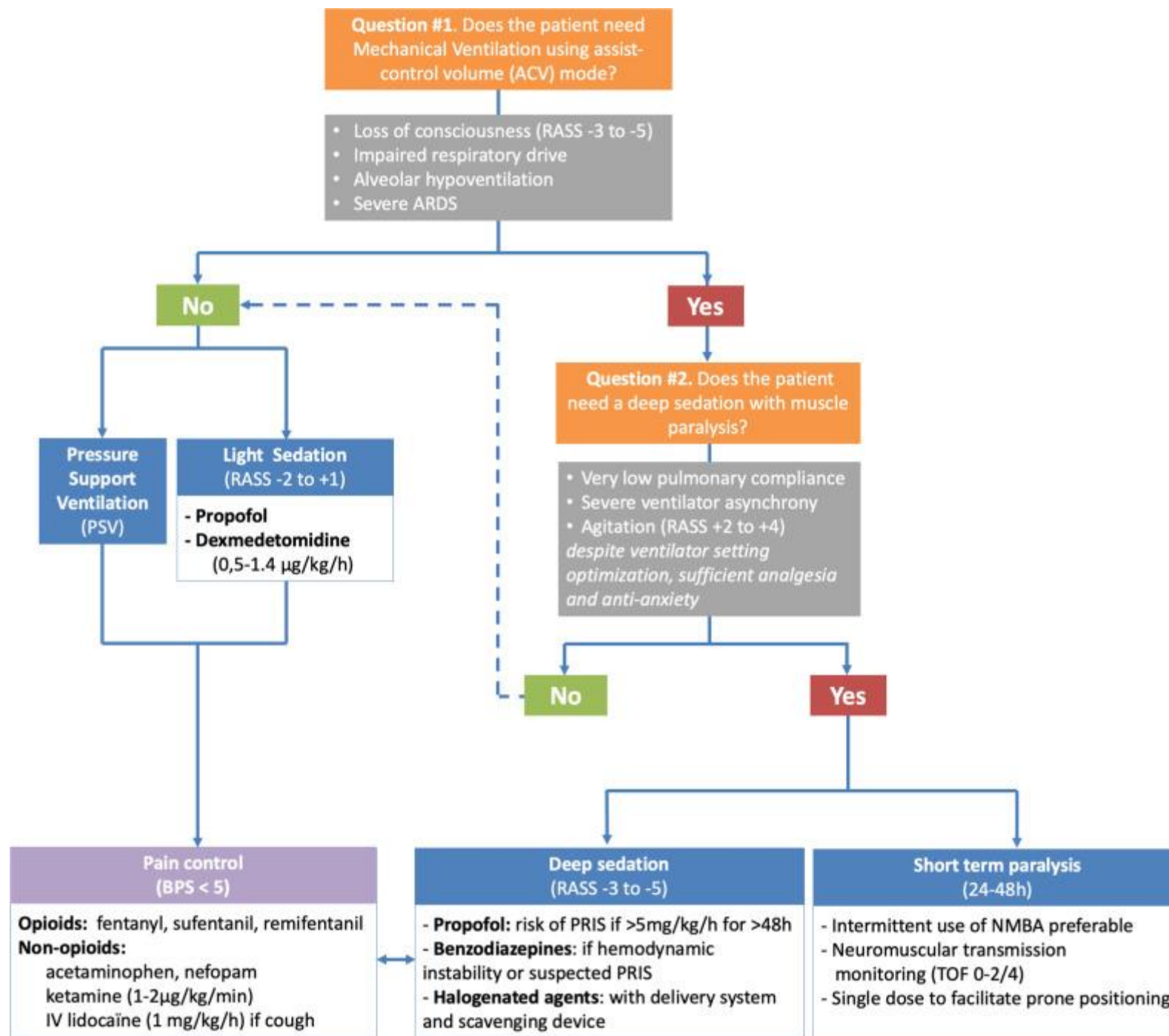
^aNot recommended as bolus alone due to ultra-short half-life

^bContext-sensitive half-life.

Sedatives	Current use	Potential benefits in COVID-19	Potential adverse effects	Any COVID-19 study	Findings related to COVID-19	Recommendation
Etomidate	Induction agent	<ul style="list-style-type: none"> - Hemodynamic stability - Minimal respiratory depression - Reduced risk of histamine release 	<ul style="list-style-type: none"> - Adrenocortical suppression - Hypercarbia - Cardiovascular instability in elderly patients with HTN 	No	N/A	May be used for induction in young patients
Ketamine	<ul style="list-style-type: none"> - Induction agent - Maintenance at low doses - Analgesia in ICU 	<ul style="list-style-type: none"> - Reduces inflammatory markers such as IL-6 - Minimal respiratory depression 	<ul style="list-style-type: none"> - Hallucinations 	Yes	<ul style="list-style-type: none"> - Potential for immune modulation - Neuropsychiatric benefits 	Primary choice for induction of sedation of COVID patients, particularly those that are hemodynamically unstable
Propofol	<ul style="list-style-type: none"> - Induction agent - Maintenance at low doses 	<ul style="list-style-type: none"> - Rapid onset, rapid recovery - Anti-inflammatory/immunomodulatory effects 	<ul style="list-style-type: none"> - Diminished cardiac output, hypotension - Propofol infusion syndrome 	Yes	<ul style="list-style-type: none"> - Myotoxicity - Propofol infusion syndrome 	Should not be used for prolonged deep sedation
Dexmedetomidine	Light sedation in mechanically ventilated patients	<ul style="list-style-type: none"> - Minimal risk of delirium - Hemodynamic stability - Reduced time requiring ventilation - Reduced peri-intubation agitation (lower risk of aerosolizing particles) 	<ul style="list-style-type: none"> - Bradycardia and hypotension with initial bolus - Withdrawal when used in high doses >24 h 	Yes	<ul style="list-style-type: none"> - Combination of Dexmedetomidine and midazolam is effective dual therapy for long term sedation with limited side effects 	Primary choice for long-term sedation when used in conjunction with benzodiazepines
Benzodiazepines	Continuous sedation in the setting of anxiety and agitation	<ul style="list-style-type: none"> - Treatment of acute agitation - Short-term breakthrough sedation 	<ul style="list-style-type: none"> - Hypotension - Reduced respiratory drive - Longer ventilator times - delirium 	Yes		Should not be used as monotherapy for long term sedation due to increased risk of aspiration causing refractory hypoxemia and longer ventilation times
Inhalational Volatile Sedatives	<ul style="list-style-type: none"> - Pediatric patients - Ambulatory surgeries 	<ul style="list-style-type: none"> - Reduced need for hemodynamic support - Reduced need for opioids - Shorter ventilation times 	<ul style="list-style-type: none"> - Malignant hyperthermia 	No	N/A	Use for prolonged sedation is experimental and not FDA approved

Richmond Agitation-Sedation Scale (RASS)

Score	Term	Description
+4	Combative	Overtly combative or violent, immediate danger to staff
+3	Very agitated	Pulls on or removes tubes or catheters, aggressive behavior toward staff
+2	Agitated	Frequent nonpurposeful movement or patient-ventilator dyssynchrony
+1	Restless	Anxious or apprehensive but movements not aggressive or vigorous
0	Alert and calm	
-1	Drowsy	Not fully alert, sustained (>10 seconds) awakening, eye contact to voice
-2	Light sedation	Briefly (<10 seconds) awakens with eye contact to voice
-3	Moderate sedation	Any movement (but no eye contact) to voice
-4	Deep sedation	No response to voice, any movement to physical stimulation
-5	Unarousable	No response to voice or physical stimulation



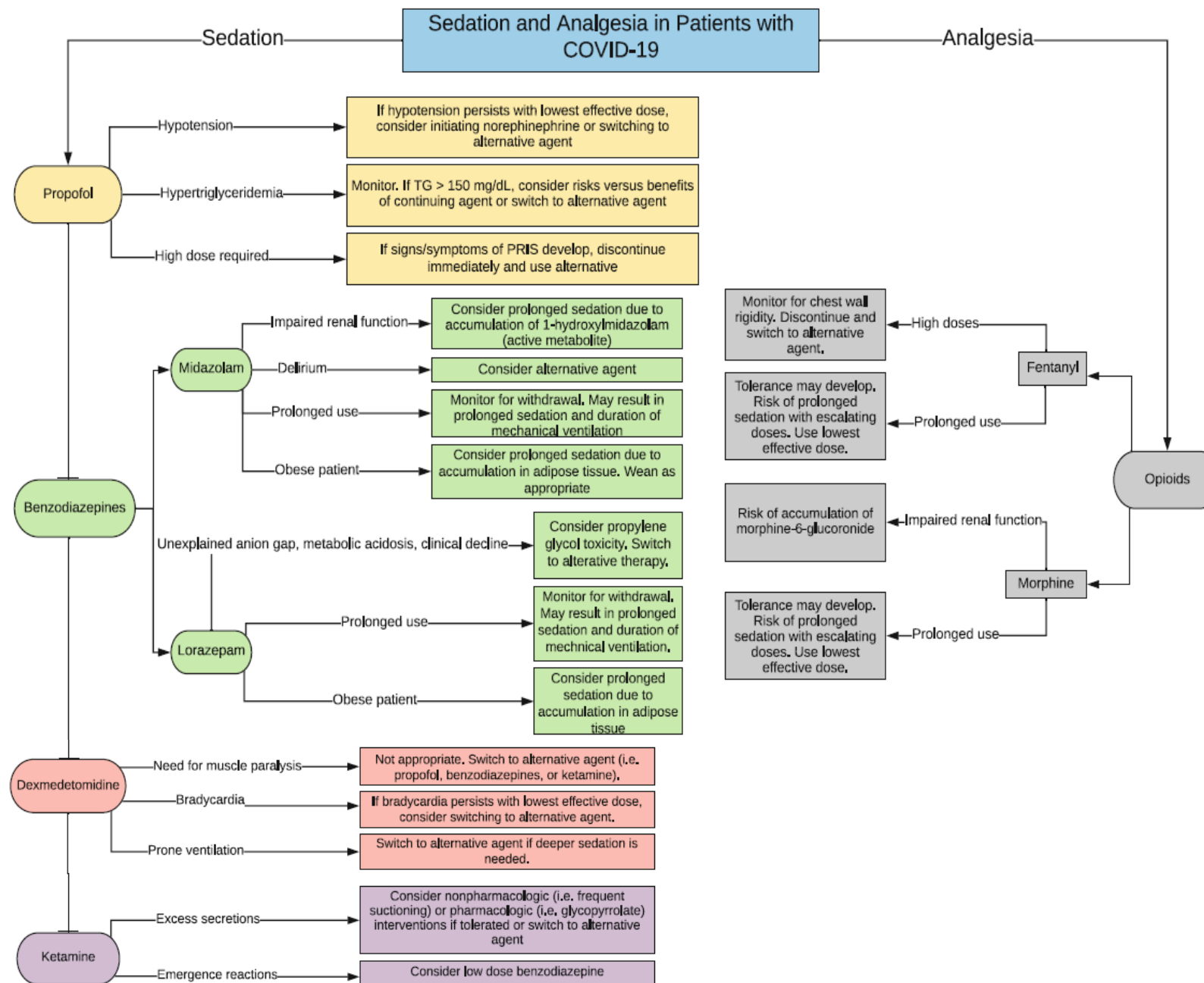
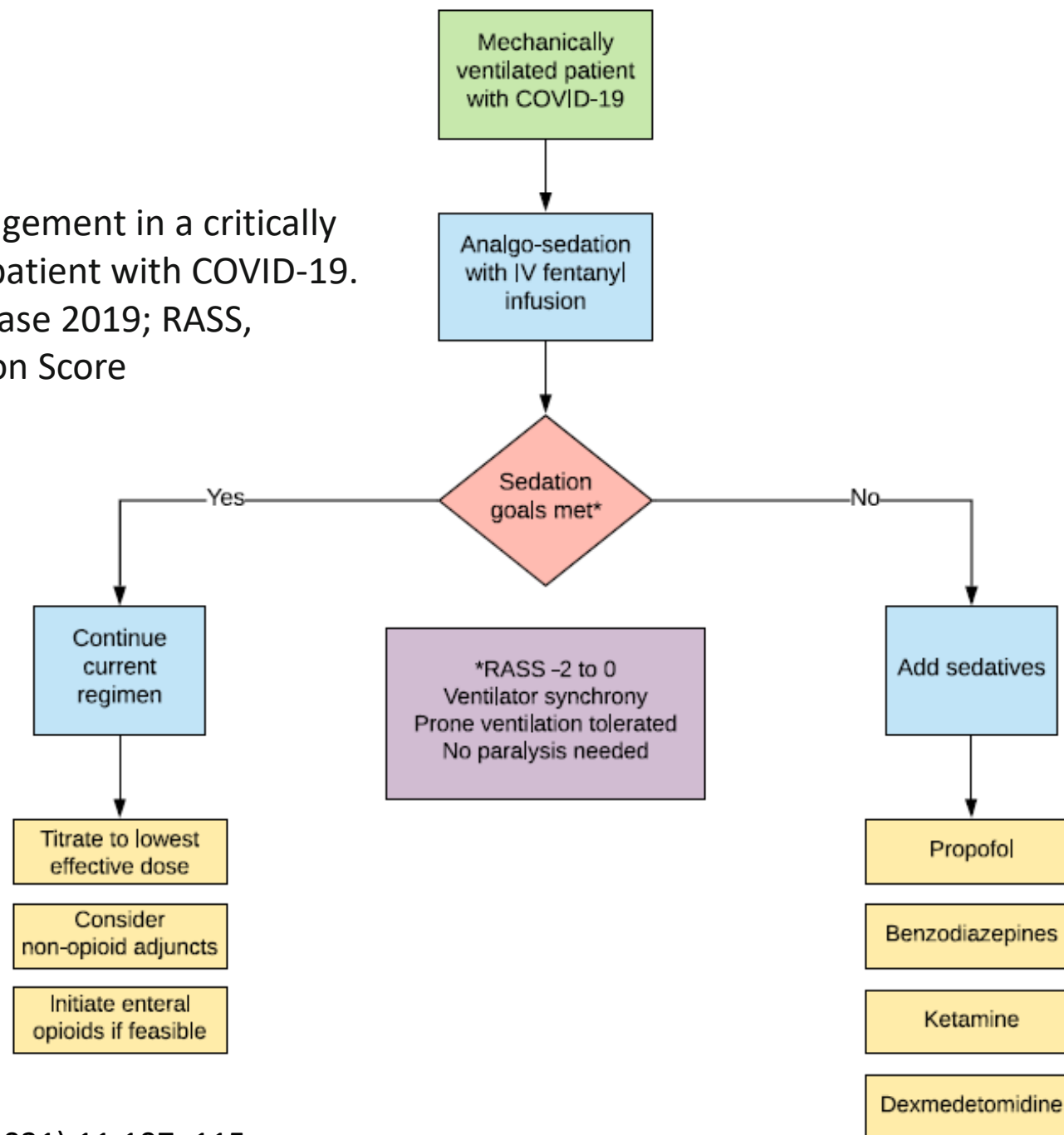


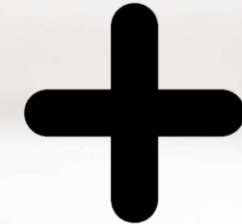
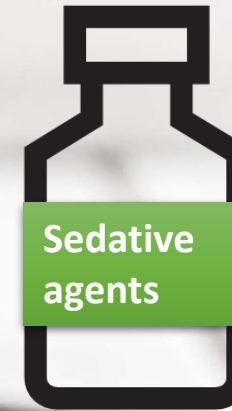
Fig. 1 Medication options for analgesia and sedation in critically ill patients with COVID-19. COVID-19; coronavirus disease 2019; PRIS, propofol infusion syndrome; TG, triglyceride

Overview of sedation management in a critically ill mechanically ventilated patient with COVID-19. COVID-19, coronavirus disease 2019; RASS, Richmond Agitation Sedation Score



Sedation goal

1 Opioid : Fentanyl,
Morphine, Tramadol



Lorazepam,
midazolam, **2**
propofol, Ketamine



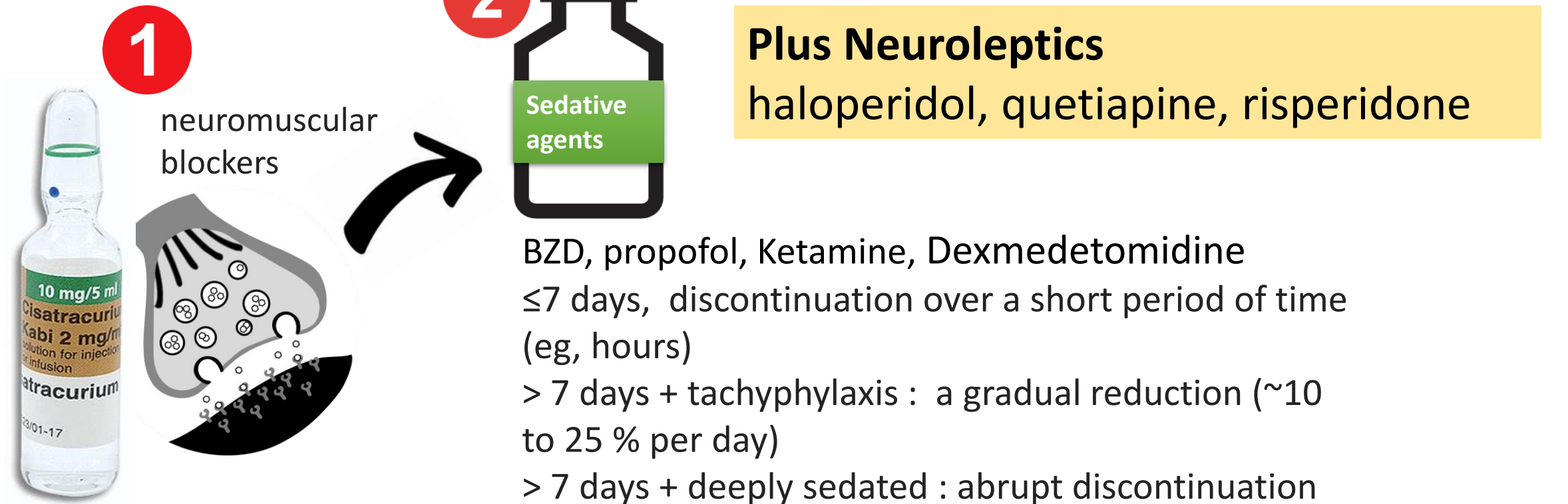
3 neuromuscular blockers
Cisatracurium



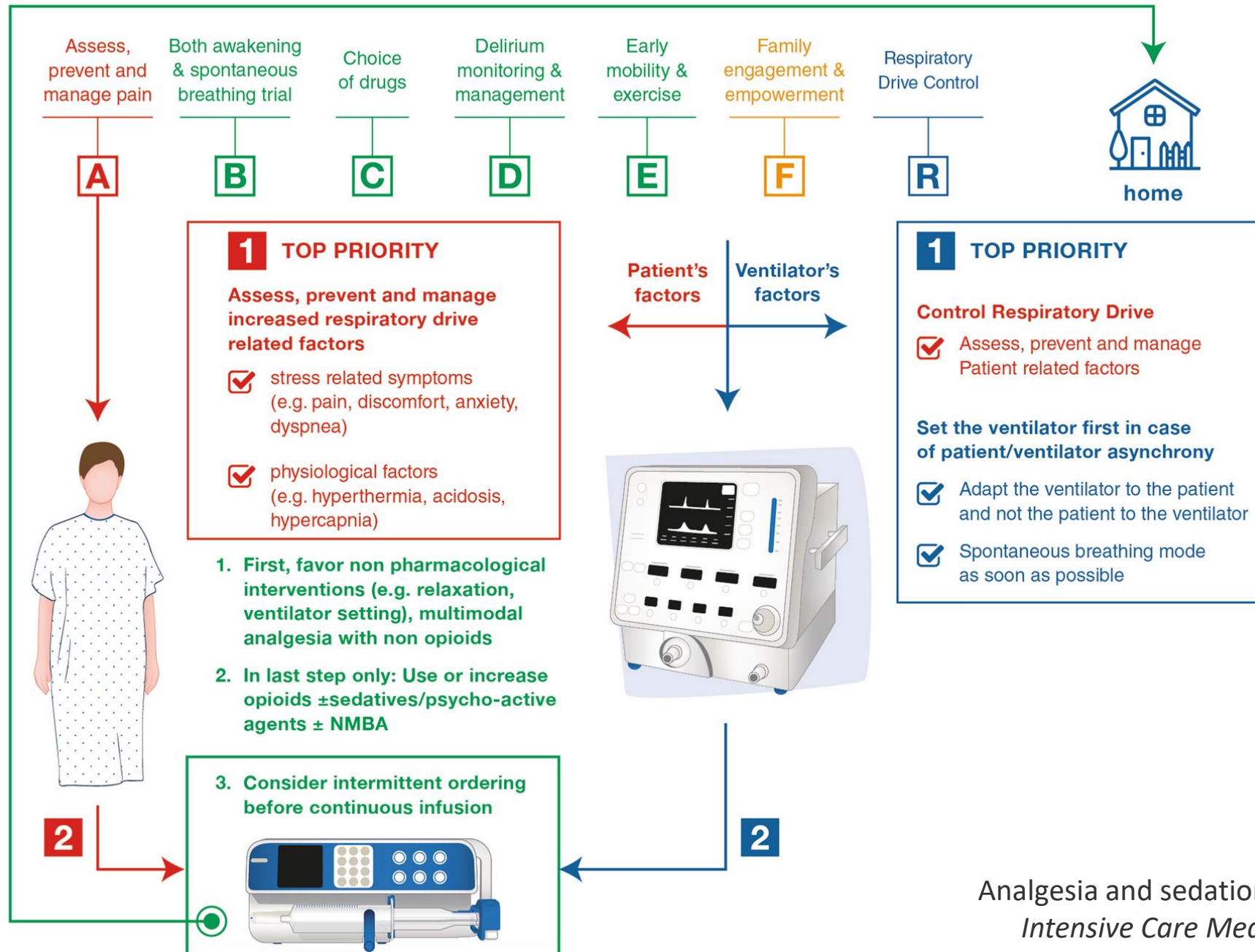
be awake and comfortable with
minimal to no distress

Withdrawal of the sequence and rate of discontinuing the sedative-analgesic agents

individualized consideration



ICU liberation strategy for ARDS



Analgesia and sedation in patients with ARDS.
Intensive Care Med **46**, 2342–2356 (2020).

結論

1. 首先，足夠的止痛
 - Fentanyl
2. 給予鎮靜安眠
 - propofol or midazolam
3. 以適當的量表評估鎮靜程度
 - Richmond Agitation-Sedation Scale (RASS)
4. 最後神經肌肉阻斷劑
 - cisatracurium
5. 常常思考病人給予止痛鎮靜等藥物後的最低劑量
 - 儘早脫離呼吸器，降低ICU滯留、避免delirium.

Reference

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COVID 19 重症團隊



- The COVID-19 pandemic has resulted in the widespread use of deep sedation in the ICU, and there is some data that sedation practices have departed from pre-COVID-19 era recommendations
- Prior to COVID-19, robust evidence demonstrated the benefit of avoiding benzodiazepines, minimizing sedation and using protocolized vent weaning practices
- The burden on critical care services has led to downstream effects on sedation strategies and medication choices. The use of higher total doses of all sedative agents, including benzodiazepines, has been described in critically ill COVID-19 patients
- Targeting less overall sedation is associated with improved outcomes in critically ill mechanically ventilated patients, including mortality and duration of mechanical ventilation. These same principles should be applied to sedation management in COVID-19

Decreased ICU days and avoiding delirium in critically ill patients

