Sedation, Analgesia, and Paralytic Strategies in Critically Ill Amid the COVID-19 Pandemic

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Disclosure

- I have no relevant financial relationships to disclose

Objectives

- Review sedative and analgesic agents used to treat critically ill patients with COVID-19
- Review neuromuscular blocking agents and dosing strategies for management of COVID-19 Acute Respiratory Distress Syndrome (ARDS)
- Discuss optimal sedation strategies for critically ill patients with COVID-19 ARDS

Pre-Assessment Question 1

Which of the following adjunct agents can be used to reduce fentanyl requirements in a patient with high sedation tolerance suffering from refractory opioid-induced constipation:

A. Sufentanil
B. Clonidine
C. Ketamine
D. Acetaminophen

Pre-Assessment Question 2

Which of the following agents can be used for management of dexmedetomidine withdrawal:

A. Lorazepam 2-4 mg PO Q6 hrs
B. Clonidine 0.1-0.4 mg PO Q6 hrs
C. Gabapentin 300 mg PO Q6 hrs
D. Phenobarbital 60 mg PO Q6 hrs

Pre-Assessment Question 3

Which of the following is true for paralysis with neuromuscular blocking agents (NMBAs):

A. NMBAs should always be initiated as high-dose continuous infusion
B. It is recommended to target light sedation during NMB paralysis
C. Bowel regimen and eye lubricant should be ordered for all paralyzed patients
D. It is recommended to titrate paralytic to the goal TOF of 3

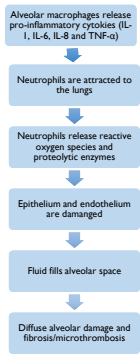
Morbidity And Mortality Due To COVID

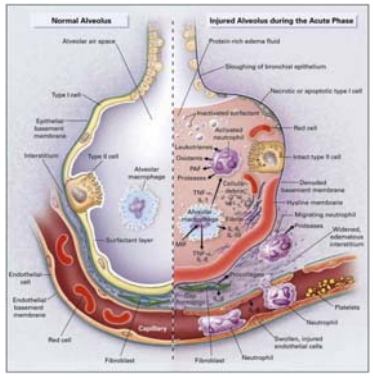
A meta-analysis of 17 studies and 2486 patients:

- ✓ 33% of those hospitalized with COVID-19 develop ARDS
- ✓ 1/4 (26%) require transfer to an ICU and of those 3/4s will require IMV
- ✓ Mortality in hospitalized patients: 16.9% (vs 5.8% for patients with influenza)
- ✓ Mortality in ICU patients: 40%
- ✓ Mortality in ICU patients requiring IMV: 59%

Tzotzos SJ. Crit Care. 2020; 24: 516
Piroth L et al. Lancet Respir Med. 2021;9(3):251-259

Pathophysiology of ARDS





Matthay MA, Zimmerman GA. Am J Respir Cell Mol Biol. 2005;33:319-27
https://www.atsjournals.org/doi/abs/10.1165/rcmb.F305. Image use permitted by author for educational purposes

2018 SCCM PADIS Guidelines

- Suggest using light vs deep sedation (conditional recommendation, low quality of evidence)
- Suggest using propofol or dexmedetomidine over benzodiazepines (BZDs) in mechanically vented patients (conditional recommendation, low quality of evidence)
- BIS monitoring is best suited for sedative titration during deep sedation of neuromuscular blockade

ABCDEF multi-intervention approach					
A	B	C	D	E	F
Assessment, prevention, and management of pain	Both spontaneous awakening trials and spontaneous breathing trials	Choice of sedation and analgesia	Delirium assessment, prevention, and management	Early mobility and exercise	Family engagement and empowerment

Surviving Sepsis Campaign: COVID-19 Update

- Low tidal volume (4-8 ml/kg of IBW) and often high PEEP
- Target plateau pressure of < 30 cm H2O.
- The use of lung recruitment maneuvers (intended to open otherwise closed lung segments, such as 40 cm H_2O inspiratory hold for 40 seconds) is suggested, over not using recruitment maneuvers (weak recommendation, LQE), but using staircase (incremental PEEP) recruitment maneuvers is not recommended (strong recommendation, moderate QE)
- Deep sedation for those with vent dyssynchrony or hypoxemia
- Intermittent boluses of NMBAs over continuous NMBA infusion to facilitate protective lung ventilation
- In the event of persistent ventilator dyssynchrony or the need for ongoing deep sedation, prone ventilation, or persistently high plateau pressures, we suggest using a continuous NMBA infusion for up to 48 hours.

Alhazzani et al. Surviving Sepsis Campaigne: COVID-19 Update. Crit Care Medicine. 2021;49(3):e219-e234

Pain and Sedation Assessment

1. Richmind Agitation and Sedation Scale (RASS)

+4	Combative; overtly violent; immediate danger to staff
+3	Very agitated, pulls or removes tubes/catheters; aggressive
+2	Agitated; frequent non-purposeful movements; fights ventilator
+1	Restless; anxious but not aggressive/vigorous
0	Alert and calm
-1	Drowsy; not fully alert but sustained awakening; eye contact to voice >10 secs
-2	Light sedation; briefly awakens to voice with eye contact <10 secs
-3	Moderate sedation; movement or eye opening to voice but no eye contact
-4	Deep sedation; no response to voice; movement or eye opening to physical stimulation
-5	Unarousable; no response to voice or physical stimulation

2. Ramsay Sedation Scale

Sedation Level	Score
Patient is anxious and agitated or restless, or both	1
Patient is co-operative, oriented, and tranquil	2
Patient responds to commands only	3
Patient exhibits brisk response to light glabellar tap or loud auditory stimulus	4
Patient exhibits a sluggish response to light glabellar tap or loud auditory stimulus	5
Patient exhibits no response	6

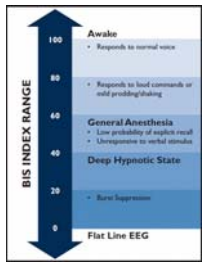
3. Critical-Care Pain Observation Tool (CPOT)

Indicator	Description	Score
Facial expression	Relaxed, neutral	0
	Tence	1
	Grimacing	2
Body movement	Absence	0
	Protection	1
	restlessness	2
Muscle tension	Relaxed	0
	Tense, rigid	1
	Very tense or rigid	2
Compliance with the vent	Tolerating vent	0
	Coughing but tolerating	1
	Fighting the vent	2
or vocalization	Or	
	Talking in normal tone	0
	Sighing and moaning	1
	Crying out, sobbing	2

Gelinas C et al. Am J Crit Care. 2006;15(4):420-427
Sessler CN. Crit Care.2008;12 (Suppl 3):S2

BIS and Train of Four Monitoring

Depth of Sedation (BIS)



Depth of Paralysis (TOF)

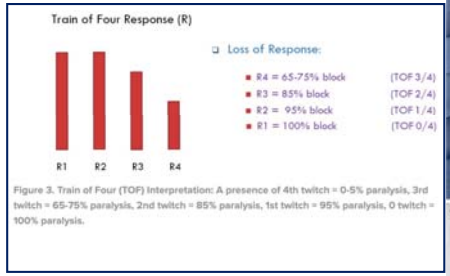


Figure 3. Train of Four (TOF) Interpretation: A presence of 4th twitch = 0-5% paralysis, 3rd twitch = 65-75% paralysis, 2nd twitch = 85% paralysis, 1st twitch = 95% paralysis, 0 twitch = 100% paralysis.

Renew JR. *J Intensive Care.* 2020;8:37;
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7245849/figure/Fig1/
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Schwarz G et al. The Internet J Neuromonit. 2004;4(1)

Sedation Requirements

- Historically standard ventilator strategies employed in ARDS (low tidal volume, high PEEP) were not associated with the need for deeper sedation
- Lighter sedation and daily sedation interruptions (DSI) are associated with shorter time on a vent, less delirium and lower tracheotomy rates (Kress et al, Devlin et al)
- Patients with COVID-19 ARDS require deeper and prolonged sedation due to:
  - Increased respiratory drive in hypoxemic respiratory failure which can be perceived as the need for deep sedation
  - Atelectasis and decreased lung and chest wall compliance requiring higher PEEP
  - Higher sedation tolerance (possibly due to younger age, good baseline health and intense inflammatory response)
  - Need for Extracorporeal Membrane Oxygenation (ECMO)

Mehta S. *Ann Intensive Care*. 2014;4:33
Kress et al. *N Engl J Med* 2000;342:1471–1477
Devlin JW et al. Crit Care Med.46(9):1457-1463
Martin JAJ. N Engl J Med. 2019;380:365–378
Hanidziar D. Anesth Analg. 2020:1

Sedation Now And Then

	John Hopkins patient survey, March 2020		OSCILLATE trial, 2013	
	Not on NMBAs	On NMBAs (53%)	HFOV	Standard vent settings
Study population	24 patients with ARDS diagnosis from COVID-19 PNA		548 patients from 38 centers in 5 countries; Intubated, PaO2:FiO2 <200mmHg and bilateral air-space opacities on CXR 83% vs 68% received NMBA	
Median opioids doses (morphine equivalent), mg	623.8	937.2	289	240
Median midazolam doses, mg	135	224.7	199	141
Median duration on a vent, days	11		11	

Potential Issues

- Prolonged context-sensitive half-life and accumulation (fentanyl and midazolam)
- Hyperalgesia and opioid dependance, gut dysmotility (opioids)
- Hypertriglyceridemia (propofol)
- Tolerance and tachyphylaxis, fever (dexmedetomidine, opioids)
- Fever (dexmedetomidine)
- Drug shortages and availability issues

Analgosedation

Opioids (Analgosedation)

	Bolus and infusion	Onset, min	Metabolism	Elimination t1/2	ADRs/Considerations
Fentanyl	0.35-0.5 mcg/kg q 0.5-1 hr; 0.7-10 mcg/kg/hr	1-2	Hepatic	2-4 hrs	Accumulation in adipose tissue and in hepatic impairment, Large doses associated w/t chest rigidity, serotonin syndrome (0.09%)
Remifentanil	0.5- 15 mcg/kg/hr	1-3	Hydrolysis by plasma esterases	3-10 min	Ultra short t1/2, rebound pain, hypotension, use IBW for ABW>130% IBW
Sufentanil	0.3- 1.5 mcg/kg/hr	1-3	Hepatic	2-3 hrs	Ultra short t1/2, rebound pain, use IBW for ABW>120% IBW
Alfentanil	0.5- 1.5 mcg/kg/min	5	Hepatic	1.5-2 hrs	Use IBW for ABW>120% IBW
Hydromorphone	0.2-0.6 mg q 1-2 hr; 0.5- 3 mg/hr	5-15	Hepatic	2-3 hrs	Accumulation with hepatic/renal impairment
Morphine IV	2- 4 mg q 1-2 hr; 2- 30 mg/hr	5-10	Hepatic, active metabolite renally eliminated	3-4 hrs	Accumulation with hepatic/renal impairment Histamine release
Methadone IV/PO	N/A 2.5-10 mg Q6-12 hrs	30-60	Hepatic	12 -60 hrs	Unpredictable PK, QTc prolongation Serotonin syndrome

Devlin JW et al. Crit Care Med 2018
Adams. CD et al. Pharmacotherapy. 2020;40(12):1180–1191

Oral and Topical Opioids

	Equivalent dose	Onset, min	Metabolism	Duration, hrs	ADRs/Considerations
Morphine PO	30 mg	30	Hepatic	3-6	Avoid use in renal dysfunction
Hydrocodone	30 mg	10-20	Hepatic	4-8	Doses > 160 mg/day of hydrocodone ER (Hysingla® or Zohydro® ER) pose increased risk of QTc prolongation. Use with caution in renal dysfunction; Caution in renal dysfunction
Oxycodone	20 mg	10-15	Hepatic	3-6	Use with caution in renal dysfunction
Tramadol	-	30-60	Hepatic	3-7	Increased risk of serotonin syndrome; Lower seizure threshold; Max daily dose 400 mg Reduce dosing interval to Q12 hrs for CrCl<30 ml/min
Fentanyl patch	[12.5]	12-24 hrs	Hepatic	48-72	Variable absorption in fever, diaphoresis and vasopressor use; takes 12 hrs to full effect

Ammar MA et al. J Intens Care Med. 2021;36(2):157-174
Adams. CD et al. Pharmacotherapy. 2020;40(12):1180–1191

Opioid-Induced Side-Effects

- Respiratory depression
- Chest wall rigidity with high doses of fentanyl (mostly observed in pediatric patient population
- Constipation, ileus
  - Ensure every patient has bowel regimen ordered
  - Consider naloxegol or methylnaltrexone if discontinuation is not an option; rule out SBO prior to use
- CNS depression, confusion, delirium

Other Sedatives

Bing Creative Commoins[free to share and use]: https://www.aliem.com/on-horizon-propofol-for-migraines/propofol/

Propofol

	Details
Mechanism of action	GABA receptor agonist, weak NMDA antagonist
Dosing range	5-50 mcg/kg/min (max 80 mcg/kg/min)
PK	2-compartment model; Onset- seconds, duration 3-10 min*
ADRs	Hypotension, respiratory depression, hypertriglyceridemia, acute pancreatitis, propofol-related infusion syndrome (PRIS)
Monitoring	• BP, cardiac function • Pancreatitis: baseline and Q72 hr TG (draw from opposite arm or pause propofol, flush line and then draw), lipase • Propofol-related Infusion Syndrome (PRIS): generally associated with doses ≥50 mcg/kg/min and duration >48 hrs Monitor pH/LDH/CPK, potassium, EKG
Clinical pearl	When starting TPN, lipids generally should be avoided while the patient is on propofol

**Propofol tends to accumulate with prolonged use and time to awakening can be significantly prolonged*

Ammar MA et al. J Intens Care Med. 2021;36(2):157-174
Mike LA. Pract Gastroenterol. 2010;81:16-24

Hypertriglyceridemia With Propofol

***Devlin et al*: Propofol-Associated Hypertriglyceridemia and Pancreatitis in the Intensive Care Unit**
- Of the 159 patients, 18% developed hypertriglyceridemia (TG≥400 mg/dL) and of those 21% had a serum triglyceride concentration of 1000 mg/dl or greater.

Table 1. Characteristics of Serum Triglyceride Concentrations and Propofol Infusions Administered to 29 Patients with Hypertriglyceridemia

Characteristic	Value
Maximum serum triglyceride concentration (mg/dl)	696 (403–1737)
Propofol rate when hypertriglyceridemia detected (μg/kg/min)	50 (5–110)
Cumulative propofol dose before hypertriglyceridemia detected (mg)	15,032 (3638–235,110)
Time from start of propofol to when hypertriglyceridemia detected (hrs)	54 (14–319)

Data are median (range).

***Kenes et al*: Propofol-Associated Hypertriglyceridemia in COVID-19 vs Non-COVID ARDS**
- of 50 patients, 33% vs only 4.3% experienced TG≥500 mg/dL, p=0.014. Remained statistically significant after adjusting for propofol dose and propensity score matching.

Utilize different agent if TG>500-800 (see your institution protocols)

Devlin JW. Pharmacother.2005;25(10):1348–1352
Kenes MT. Crit Care Expl 2020; 2:e0303

Benzodiazepines

- MOA: Benzodiazepines are CNS GABA-A receptor agonists that produce amnestic, anxiolytic, sedative, and anticonvulsant effects
- Use for sedation has diminished significantly over the last decade due to increased ICU and hospital lengths of stay, MV duration, delirium and cognitive dysfunction
  - Might be a good first line sedative for those going through alcohol/BZD/drug withdrawal
  - Consider intermittent bolus dosing when possible

Adams. CD et al. Pharmacotherapy. 2020;40(12):1180–1191

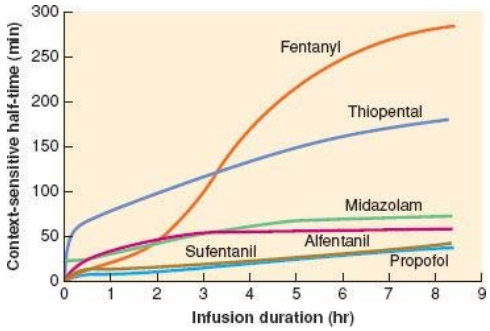
Benzodiazepines

	Dosing	Onset	T 1/2	Considerations
Midazolam (Versed) IV	1-10 mg/hr; 0.02-0.1 mg/kg/hr; 0.5 -4 mg q 15 min -1hr	2-5 min IM/IV	3 hrs	- Accumulation in renal impairment and obesity, - Hypotension
Lorazepam (Ativan) IV	1-10 mg/hr; 0.01-0.1 mg/kg/hr; 0.5-4 mg q 2-6 hrs	5-20 min IM/IV	12 hrs	-Preferred BZD for hepatic impairment; -Propylene glycol toxicity with IV formulation leading to wide anion gap metabolic acidosis - Risk at> 1 mg/kg/day and/or with osmol gap of> 10 mOsm/L
Diazepam (Valium) IV	Intermittent dosing 2-10 mg q 3-6 hrs PRN	3 min IV	20-120 hrs	- Oral doses can be used to wean continuous infusion - Propylene glycol toxicity with IV formulation leading to wide anion gap metabolic acidosis

Ammar MA et al. J Intens Care Med. 2021;36(2):157-174
Adams. CD et al. Pharmacotherapy. 2020;40(12):1180–1191

Context-sensitive Half-life of Sedatives

- The longer the duration of infusion (or "context"), the more drug will deposit into the tissues
- Sedatives with prolonged context-sensitive half-life:
  - Fentanyl
  - Midazolam
  - Thiopental



Spina SP. Pharmacotherapy. 2007;27 (3): 389–98
Hughes M et al. Anesthesiology. 1992;76:334-341

Dexmedetomidine (Precedex)

	Details
Mechanism of action	Centrally-acting alpha-2 receptor agonist
Dosing range	0.1-1.5 mcg/kg/hr
PK	Onset: 5-10 min, duration 60-120 min
ADRs	Hypotension, bradycardia, fever, withdrawal syndrome with prolonged use
Monitoring	BP, HR
Clinical pearl	• Not to be used for deep sedation • Poses very weak analgesic properties, ensure adequate analgesia ordered if pain control is needed • Withdrawal can manifest as tachycardia, hypertension and agitation, AMS • Clonidine can be used to help transition off Precedex drip

Glaess SS et al. *Am J Health Syst Pharm*. 2020
Gagnon DJ. *Pharmacotherapy*. 2015;35(3):251-9
Devlin JW. *Crit Care Med*. 2018

Dexmedetomidine vs Clonidine

	Dexmedetomidine	Clonidine
Dose	0.1-1.5 mcg/kg/hr	0.1-0.4 mg Q6-8 hrs
α2 vs α1 receptor affinity	1,600:1	220:1
Half-life	2 hrs	12 hrs
BP lowering effect	+	+++
Site of action	Centrally-acting	Central and peripheral

- Wang et al and Gagnon et al showed lower opioid and benzodiazepine requirements while on clonidine
- 23% of patients who were started on clonidine to wean off dexmedetomidine, were inadvertently continued on clonidine on discharge

Bouajram RH et al. Crit Care Expl. 2019; 1:e0035
Wang JG et al. Crit Care. 2017;21(1):75
Terry k et al. *SAGE Open Med*. 2015;3:2050312115621767

Clonidine for Dexmedetomidine Withdrawal

Gagnon et al:

- Patients well controlled on dexmedetomidine for 12-24 hrs with SAS scored of 3-4 and hemodynamically stable (HR≥50, MAP≥65 and SBP≥90 without pressor support)
  - Start with 0.2-0.5 mg PO Q6-8 hrs
    - Consider lower initial dosing in patients<100 kg, elderly >70 yo and dexmedetomidine (Precedex) dosing <0.7 mcg/kg/hr
    - Adjust dose or frequency if agitation not controlled
  - With each dose reduce Precedex drip by 25%. Once pt is completely weaned off Precedex, start clonidine taper. For example, for maintenance regimen of 0.3 mg Q6 hrs:
    - 0.3 mg PO every 6 h for 4 doses;
    - then 0.3 mg PO every 8 h for 3 doses;
    - then 0.3 mg PO every 12 h for 2 doses;
    - then 0.3 mg PO per day for 1 dose, then discontinue

Gagnon DJ. *Pharmacotherapy*. 2015;35(3):251-9

Withdrawal Timeline

Study by Bouajram et al:

- Patients enrolled (n=42): dexmedetomidine infusion for >72 hrs + at least 2 signs of withdrawal during a single assessment.
- Signs of withdrawal : tachycardia (HR> 90 bpm), hypertension (SBP> 140 mm Hg or MAP > 90), RASS >+1, positive CAM-ICU, and a WAT-1 score ≥ 3
- Dosing as per Gagnon et al study discussed in the previous slide

Results:

- ✓Median time on dexmedetomidine for all patients was 9.6 days (5.8–12.7 d)
- ✓There was a statistically significant difference in median dexmedetomidine peak rate between patients who experienced withdrawal compared to those who did not (1 µg/kg/hr [0.8–1.2 µg/kg/hr] vs 0.7 µg/kg/hr [0.5–1 µg/kg/hr], respectively; p = 0.02)
- ✓Higher hourly rate >0.8 and cumulative daily doses of >12.9 µg/kg/d were associated with withdrawal
- ✓Most prevalent withdrawal symptoms observed included delirium, hypertension, and agitation (93%, 48%, and 33%, respectively)

Glaess SS et al. *Am J Health Syst Pharm.* 2020
Bouajram RH et al. *Crit Care Expl.* 2019;1:e0035

Ketamine

	Details
Mechanism of action	NMDA antagonist, mu and k-receptor agonist (analgesia)
Dosing range	Analgesia: 0.1-0.5 mg/kg/hr, sedation: 0.5-5 mg/kg/hr
PK	Onset: 5-15 min, duration: 5-30 min, full recovery in 1-2 hrs
ADRs	laryngospasm, excess secretions, emergence phenomenon, delusions/delirium, sympathetic surge, hypertension
Monitoring	HR, BP, O2Sat, ECG
Clinical pearl	Use caution in patients with: • Elevated ICP • Cardiovascular disease (increase in myocardial O2 demand, decompensation, reduced CO in HF) • Patients with psychiatric conditions Provides opioid-sparing effect

Ammar MA et al. J Intens Care Med. 2021;36(2):157-174
Adams. CD et al. Pharmacotherapy. 2020;40(12):1180–1191

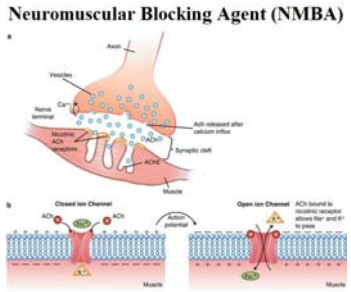
Summary

- Perform daily sedation interruption (DSI) for qualifying patients
- Tachyphylaxis and tolerance possible with prolonged sedation
- Target lighter sedation and shortest duration possible
- Oral clonidine and opioids can be used to taper off IV sedation while preventing withdrawal
- Oral opioids and benzodiazepines can play a role in sedation maintenance during drug shortages (equivalent dose calculation will be necessary)

Neuromuscular Blocking Agents (NMBAs)

Neuromuscular Blocking Agents: Overview

- Mechanism of action:
  - **Depolarizing agent**: Ach receptor agonist that prevents repolarization resulting in phase I and eventually phase 2 blockade
  - **Non-depolarizing agents:** Ach receptor antagonists- competitively bind to Ach binding site preventing ion channel opening and generation of action potential
- ADRs: - respiratory muscle paralysis
  - myopathies with prolonged use
  - increased peripheral vascular resistance
- Monitoring: vital signs, degree of muscle paralysis



Murray MJ et al. *Crit Care Med*. 2016;44:2079-2103
Image: https://www.openpr.com/news/2041796/neuromuscular-blocking-agent-nmba-market-growth-and-status
Open access

Non-depolarizing NMBAs

	Bolus dosing, mg/kg	Infusion dose, mcg/kg/min	Onset, min	Duration, min	Metabolism/ excretion	Side-effects
Aminosteroids						
Rocuronium	0.6-1.2 (round to nearest 50mg)	8-12 Titrate by 1-2 every 15min	1-2	30-60	hepatic	↑HR, ↑ PVR
Vecuronium	0.1-0.2 (round to nearest 10mg)	0.8-1.2 Titrate by 0.2—0.3 every 15min	3-4	35-45	Hepatic, renal	Hemodynamic instability, ↓HR
Pancuronium	0.05- 0.1	1-2	2-3	60-100	Hepatic, renal	↑HR, hypotension, min histamine release
Benzylisoquinoloniums						
Cisatracurium	0.1- 0.2 or 15 mg	1- 4 or Fixed 37.5 mg/hr	2-4	45-60	Hoffman elimination	Bronchospasms Does not affect BP and HR
Atracurium	0.4-0.5 (round to nearest 50 mg)		3-5	20-35	5-10% renal, Hoffman elimination	Histamine release, ↓BP, ↑HR; Toxic metabolite: laudanosine -> seizures

Ammar MA et al. J Intens Care Med. 2021;36(2):157-174

Current Guideline Recommendations

2016 NMBA Guidelines:

- Early initiation of continuous NMBA infusion if PiO2:FiO2<150 (weak, moderate quality of evidence)

COVID-19 update on NMBA:

- Mechanically ventilated patients with moderate to severe ARDS:
  - Suggest PRN boluses of NMBAs over continuous infusion to facilitate protective ventilation (weak, low quality of evidence)
- In the event of vent dyssynchrony when deep sedation and proning don't improve oxygenation
  - Suggest using continuous infusion for up to 48 hrs (weak. Low quality of evidence)

Murray MJ. Crit Care Med. 2016;44(11):2079-2103
Alhazzani W. Intensive Care Med. 2020 May;46(5):854-887

EXAMPLE

When PRN Boluses Didn't Help

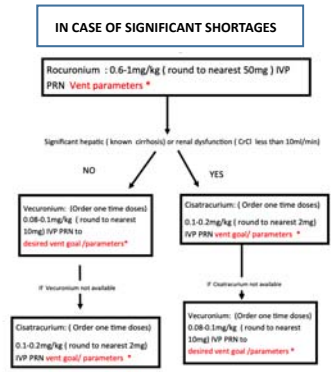
STANDARD OF CARE

Cisatracurium 15 mg IVP followed by 37.5 mcg/kg/min infusion x 48 hours

If cisatracurium is not available

Vecuronium :
0.08— 0.1mg/kg IV Bolus followed by Infusion
Initiate : 0.8mcg/kg/min
Titrate by : 0.2—0.3 mcg/kg/min every 15min

Rocuronium :
0.6- 1mg/kg IVP bolus followed by infusion
Initiate at 8mcg/kg/min
Titrate by: 1-2 mcg/kg/min every 15min



Courtesy of University of Illinois Hospital and OSF

Role of NMBAs in ARDS

	ACURASYS, 2010	ROSE, 2019
Patient population	- 340 patients in 20 ICUs in France with ARDS and P/F< 150 and PEEP≥5 - enrolled within ~16 hrs of diagnosis - 28% of patients in the cisatracurium (CSA) group and 29% in the placebo group were proned	- 1006 in 48 hospitals of USA with ARDS and P/F< 150 and PEEP≥5 - Enrolled within ~7.6 hrs of diagnosis - 16% of patients were proned - Stopped at 2nd interim analysis for futility (no pre-specified stopping rule)
Intervention	- Cisatracurium 15 mg bolus followed by 37.5 mg/hr infusion for 48 hrs	
	Both groups targeted deep sedation	- Control group utilized light sedation to RASS –1 - Cisatracurium 20 mg PRN boluses allowed for both - 17% in control group received NMBA

Papaziani L. et al. N Engl J Med. 2010;363(12):1107-1116
Moss M et al. N Engl J Med. 2019;380(21):1997-2008

Role of NMBAs in ARDS

	ACURASYS, 2010	ROSE, 2019
Primary outcomes	- Hazard ratio for death at 90 days was 0.68 (95% CI, 0.48 to 0.98; P=0.04) for CSA vs placebo, after adjustment for both the baseline PaO2:FIO2 and plateau pressure and the Simplified Acute Physiology II score.	- 90-day mortality: 42.5% in CSA group vs 42.8% in placebo (95% CI, -6.4 to 5.9; P=0.93)
Secondary endpoints	- Crude 90-day mortality was 31.6% (95% CI, 25.2 to 38.8) vs 40.7% (95% CI, 33.5 to 48.4) for CSA vs placebo group (P=0.08) - Mortality at 28 days was 23.7% (95% CI, 18.1 to 30.5) with CSA and 33.3% (95% CI, 26.5 to 40.9) with placebo (P=0.05).	- No difference in the: In-hospital death at 28 days Days free of a vent of day 28 Days not in the ICU at 28 days Days not in the hospital at 28 days - Serious CV adverse events: 14 vs 4, p=0.02

Papaziani L. et al. N Engl J Med. 2010;363(12):1107-1116
Moss M et al. N Engl J Med. 2019;380(21):1997-2008

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Monitoring

- Before starting paralytics:
  - ✓ Baseline TOF (indicating site and voltage)
  - ✓ RASS at -5 or BIS of 40-60
- During paralysis:
  - ✓ Ventilator synchrony, O2 saturations, PaO2:FiO2, ABG as needed
  - ✓ Renal and hepatic function
- Upon discontinuation of paralysis:
  - ✓Monitor TOF and once achieved 3 to 4 twitches, can lighten the sedation

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Drug Interactions with NMBAs

Drugs that reduce the effect of NMBAs	Drugs that potentiate the effect
Phenytoin	Corticosteroids
Carbamazepine	Aminoglycosides, Polymixin B, tetracyclines, vancomycin
Valproic acid	Lithium carbonate
Ranitidine	Dantrolene
Azathioprine	Magnesium
	Calcium channel blockers
	Beta blockers
	Local and inhaled anesthetics

NMBAs potentiate harmful effect of steroids: increase muscle weakness and progression to polyneuropathies and myopathies may occur

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Summary

- Use adjusted BW in obese patients
- Limit NMB to 48 hours or less, consider boluses before starting continuous infusion
- Ensure deep sedation targeting RASS of –4 to –5 is started for all patients prior to initiating NMB; Sedation is not to be titrated or interrupted for the duration of paralysis
- When using NMBA boluses over continuous infusion, dose to vent synchrony and not based on a TOF goal
- Need to balance vent compliance, nursing workload and potential shortages

Murray MJ et al. Crit Care Med. 2016;44(11):2079-2103

General Takeaways

- Sedation management in critically ill COVID-19 presents a great challenge
- Titrate to sedation goals and utilize minimum effective dose
- Use of non-traditional regimens can reduce dose/time of exposure to continuous infusions, accumulation and withdrawal
- Patients needing paralytic should be deeply sedated to RASS of –4 to –5 prior to starting NMBA and sedation should not be titrated until after neuromuscular recovery is achieved

General Takeaways

- Consider the use of intermittent dosing of longer-acting agents to minimize the need for agents with limited availability.
  - ✓ Scheduled high-dose Q6-Q8hr PO lorazepam to minimize the need for propofol or midazolam
  - ✓ Scheduled PO oxycodone or methadone (or fentanyl patch) to minimize the need for intravenous fentanyl or hydromorphone
  - ✓ Intermittent doses of IV rocuronium, vecuronium or pancuronium to minimize the need for cisatracurium.
- Ensure appropriate hand-off upon patient transfer from the ICU and from the hospital so new team is aware of the plan

Patient Case

TP is a 52 yo AA male intubated emergently due to O2 desaturation and now have developed ARDS and AKI. His current vitals are: HR in the 50s and MAP of 58.

What sedative/analgesic would you suggest?

- Propofol
  - Hypotensive effect, may require to start a vasopressor
- Dexmedetomidine
  - Bradycardia, hypotension possible
- Midazolam and morphine
  - Accumulation of active metabolites in AKI, prolonged T1/2

Options: fentanyl, ketamine, lorazepam, hydromorphone

Patient case cont.

TP's O2 sat is not improving and he is dyssynchronous on the vent despite fentanyl 200 mcg/kg/hr, so the team decided to prone and start NMBA. At this point HR is 82 and MAP is 68 not on pressors. What sedative should we add on?

Patient case cont.

Propofol is added to fentanyl with the RASS goal of –5. What should we monitor while on propofol?

A. O2 sat, HR and troponin
B. pH, BG and SCr to assess for PRIS
C. Triglycerides to assess for pancreatitis
D. Osmolar gap, pH and propylene glycol level

Patient case cont.

21 days later the patient's respiratory function is improving (FiO2 at 50%, PEEP at 6), but sedation cannot be weaned (patient developed tachycardia, agitation and tachypnea during DSI). Current sedation:

- Fentanyl at 200 mcg/hr (day 21)
- Propofol 50 mcg/kg/min (day 18)
- Precedex at 0.7 mcg/kg/hr (day 14)

Identify the causes and how to manage:

- Withdrawal --> taper infusions down by 25% daily +/- overlap with a taper of oral agents
- Hyperalgesia/pain--> optimize non-opioid regimen, add on oral opioid taper or fentanyl patch
- Delirium--> optimize sleep-wake cycle, remove stressors, short course of atypical antipsychotics
- Agitation --> oral benzodiazepines, antipsychotics

Patient case cont.

Example: to wean off continuous fentanyl drip after prolonged exposure:

1. Calculate TDD of fentanyl: 200 x 24=4,800 mcg
2. Convert to morphine equivalent (apply 25-50% dose reduction):
   - 25 mcg/hr of fentanyl= 60 mg of PO morphine/day
   - 200 mcg/hr of fentanyl= 480 mg of PO morphine/day
   - 480 mg MME x 0.5=240 mg/day
3. Convert to oxycodone:
   - 30 mg of morphine PO= 20 mg of oxycodone PO
   - 240 mg morphine PO = 160 mg oxycodone PO
4. Start oxycodone 40 mg solution or tab Q6 hrs via G tube, start weaning fentanyl drip by 25% with each subsequent oxycodone dose starting at dose 2
5. On day 3 start oxycodone taper

McPherson ML. Demystifying Opioid Conversion Calculations: A Guide for Effective Dosing, 2nd Edition.2018

Post-Assessment Question 1

Which of the following adjunct agents can be used to reduce fentanyl requirements in a patient with high sedation tolerance suffering from refractory opioid-induced constipation:

A. Sufentanil
B. Clonidine
C. Ketamine
D. Acetaminophen

Post-Assessment Question 2

Which of the following agents can be used for management of dexmedetomidine withdrawal:

A. Lorazepam 2-4 mg PO Q6 hrs
B. Clonidine 0.1-0.4 mg PO Q6 hrs
C. Gabapentin 300 mg PO Q6 hrs
D. Phenobarbital 60 mg PO Q6 hrs

Post-Assessment Question 3

Which of the following is true for paralysis with neuromuscular blocking agents (NMBAs):

A. NMBAs should always be initiated as high-dose continuous infusion
B. It is recommended to target light sedation during NMB paralysis
C. Bowel regimen and eye lubricant should be ordered for paralyzed patients
D. It is recommended to titrate paralytic to the goal TOF of 3

Questions?

Allergy to Opioids: Cross-reactivity

Opioid name	Class	Derivatives
Morphine	Phenanthrenes	Buprenorphine* Codeine Hydrocodone* Oxycodone* Hydromorphone* Naloxone* Naloxegol* Oxymorphone*
Fentanyl	Phenylpiperidines	Meperidine Ramifentanil Sufentanil
Methadone	Diphenylheptanes	Propoxyphene
Tramadol	Phenylpropylamines	Tapentadol
Pentazocine	Benzomorphans	Phenazocine

*Agents lacking 6-OH group of morphine generally have low cross-reactivity even within the class

Fudin J. Pharmacy Times 2018

NMBA Reversal

	Indication	Dosing	Side-effects
Sugammadex	Rocuronium Vecuronium	-TOF 1-2: 4 mg/kg -TOF>2: 2 mg/kg -Immediate rocuronium reversal: 16 mg/kg	Bradycardia, hypotension; accumulation in renal/hepatic impairment; Nausea; Might reduce effect of hormonal contraception;
Neostigmine + glycopyrrolate	Non-depolarizing NMBAs	0.03-0.07 mg/kg, max 5 mg 0.2 mg per 1 mg of neostigmine	Bradyarrhythmias; Dizziness; Increased bronchial secretions; Bronchospasms Nausea, vomiting, diarrhea; Urinary urgency;

No reversal exists for succhinylcholine