Penn Medicine
Hospital of the
University of Pennsylvania

Pain, Agitation, Delirium and Neuromuscular Blockade During COVID-19

April 8, 2020

Disclaimers

- No protocols on sedation during COVID-19 have been published
  - Observational or interventional
- Many institutions are putting forth guidelines distributed via email
- Many clinicians have a strong opinion on the topic
- **The CC pharmacy team has led the recommendations today. Thank you.**

Common Issues

- ABCDEF
  - Concerns for self-extubation in an isolation environment (SAT as a risk factor)
  - Delirium VERY pronounced (drugs, environment)
  - Mobility interventions have been reduced (staff exposure, PPE, restrictions)
  - Family is absent

- Drug shortages
- Ventilator asynchrony in patients requiring higher PEEP

Interventions for PAD During COVID-19 from CCC

- Global
  - Be prepared for shortages.
  - Oral therapies (opiates, sedatives) are reasonable to consider
    - Avoid when on vasopressors and NOT fully volume resuscitated

Interventions for PAD During COVID-19: Analgesia

- Intermittent analgesia is reasonable to consider
  - Morphine may be a good choice to enact this strategy (NONSEDA, Strom et al)

- In wakeful patients (RASS 0 to -1 /-2), consider oral analgesics prior to continuous infusion.

- Continuous infusions
  - Fentanyl > hydromorphone > morphine
    - Morphine infusions in major prior clinical trials (Kress et al; Carson et al)
  - Begin simultaneous oral analgesic therapy when MV expected >24hrs
    - Standing acetaminophen (avoiding given *risks shortage*; may mask fever)
    - Oxycodone 10-20 mg q6h standing, hydromorphone 4-6 mg Q6h standing
    - Methadone 5 mg Gtube Q8h OR Methadone 2.5 mg IV Q8H** (see QTc information)

Interventions for PAD During COVID-19: QTc measurments

- Qtc prolongation is a risk with our drugs of choice
  - Hydroxychloroquine, chloroquine, azithromycin, lopinavir/ritonavir
  - Neuroleptics, methadone, amiodarone

- Review the guideline from EP
  - Formal baseline
  - Follow-up telemetry QTc within 1-2 hours after dosing
  - Ranges (adjust measurement for BBB when appropriate, QT minus QRS duration and add 100 ms)
    - < 470 ms: low risk
    - 470-490 ms: moderate (if increases, withhold and continue monitoring until < 500msec)
    - > 490 ms: high
      - If QTC > 550 ms or if ventricular arrhythmias are observed after the QTc prolongs to > 500 ms after initiating treatment, stop drug immediately and consider contacting EP

Drug Shortage: Alternatives to Fentanyl

TABLE 3. Pharmacology of Opiate Analgesics (1, 128, 440, 472)

Opiates	Equi-Analgesic Dose (mg) IV	Equi-Analgesic Dose (mg) PO	Onset (IV)	Elimination Half-Life	Context-Sensitive Half-Life	Metabolic Pathway
Fentanyl	0.1	N/A	1–2 min	2–4 hr	200 min (6 hr infusion); 300 min (12 hr infusion)[a]	N-dealkylation CYP3A4/5 substrate
Hydromorphone	1.5	7.5	5–15 min	2–3 hr	N/A	Glucuronidation
Morphine	10	30	5–10 min	3–4 hr	N/A	Glucuronidation
Methadone	N/A[c]	N/A[c]	1–3 d	15–60 hr	N/A	N-demethylation CYP3A4/5, 2D6, 2B6, 1A2 substrate
Remifentanil	N/A	N/A	1–3 min	3–10 min	3–4 min	Hydrolysis by plasma esterases

Opiates	Active Metabolites	Intermittent Dosing	IV Infusion Rates	Side Effects and Other Information
Fentanyl	None	0.35–0.5 µg/kg IV q0.5–1 hr	0.7–10 µg/kg/hr	Less hypotension than with morphine. Accumulation with hepatic impairment.
Hydromorphone	None	0.2–0.6 mg IV q1–2 hr[b]	0.5–3 mg/hr	Therapeutic option in patients tolerant to morphine/fentanyl. Accumulation with hepatic/renal impairment.
Morphine	6- and 3-glucuronide metabolite	2–4 mg IV q1–2 hr[b]	2–30 mg/hr	Accumulation with hepatic/renal impairment. Histamine release.
Methadone	N-demethylated derivative	IV/PO: 10–40 mg q6–12 hr IV: 2.5–10 mg q8–12 hr	Not recommended	May be used to slow the development of tolerance where there is an escalation of opioid dosing requirements. Unpredictable pharmacokinetics; unpredictable pharmacodynamics in opiate naïve patients. Monitor QTc.[d]
Remifentanil	None	N/A	Loading dose: 1.5 µg/kg IV Maintenance dose: 0.5–15 µg/kg/hr IV	No accumulation in hepatic/renal failure. Use IBW if body weight >130% IBW.

Interventions for PAD During COVID-19: Sedatives

- Reports that clinicians encouraged to select deeper RASS goals to avoid self-extubation
  - May be false sense of protection, may actually worsen late phase recovery
  - De-escalation seems better than SAT
  - *If it occurs, full PPE donning prior to all rescue (clinician safety 1st)*
- Sedation may reduce otherwise mega-opiate infusion doses
  - Particularly helpful to use low(er) dose propofol

Interventions for PAD During COVID-19: Sedatives

- Propofol remains sedative of choice for early management
  - Check daily TGs when > 300-400mg/dL
  - *Consider a liberalized TG threshold to 800mg/dL 5% rate of pancreatitis when > 1000mg/dL
- Dexmedetomidine is sedative of choice for delirious patients with resolving lung injury
  - Limited by bradycardia and described risk of later course cardiomyopathy/myocarditis

- Intermittent (non-propofol) sedatives better than continuous
  - *Consider adjunctive phenobarb (130mg load IVP, then use oral route)
- *In cases of sustained sedative infusion, begin intermittent enteral sedatives
  - Lorazepam 1-2mg, clonazepam 1-2mg, oxazepam 10-30mg
- Other adjunctive therapies
  - Neuroleptics (caution Qtc), valproic acid (drug interactions), gabapentin (?efficacy)

Interventions for PAD During COVID-19: Sedation Escalation

- If a patient has a RASS of -4/-5 but demonstrate ventilator asynchrony:
  - If double stacking, consider flow and inspiratory time adjustments
  - Reports of isolated hypoxia and, occasionally, concomitant hypotension
    - Suspected abdominal de-recruitment, possible diaphragmatic steal
  - Additional use of sedation with a low RASS: less likely to help synchrony, more likely to lead to excessive sedation and waste of drug
    - *Trial single dose of NMBA to assess situation

Interventions for PAD During COVID-19: NMBA

Recommendations:

35. For mechanically ventilated adults with COVID-19 and **moderate to severe ARDS**:

35.1. We **suggest** using, as needed, intermittent boluses of neuromuscular blocking agents (NMBA), over continuous NMBA infusion, to facilitate protective lung ventilation (weak recommendation, low quality evidence).

35.2. In the event of persistent ventilator dyssynchrony, 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 (weak recommendation, low quality evidence).

- Several professional societies recommend NMBAs in moderate to severe ARDS
  - Pooled estimates from 3 RCTs (431 patients) showing a reduction in 90-day mortality with an NMBA infusion as compared with no NMBA infusion
- ROSE trial: 1,006 patients moderate or severe ARDS to receive either an infusion of NMBA for 48 hours or intermittent NMBA boluses prn.
  - The continuous infusion of cisatracurium did not improve any patient important outcomes.
- Due to differences in design between the ROSE trial and the earlier trials, we did not perform a meta-analysis for mortality outcome, although the pooled estimate for barotrauma favored continuous NMBA infusion (RR 0.55, 95% CI 0.35 to 0.85).
- The panel suggests that a continuous NMBA infusion should be reserved for patients who have an indication for ongoing paralysis in which intermittent dosing may not suffice, such as patients with persistent ventilator dyssynchrony, and patients needing ongoing deep sedation prone ventilation, or persistently high plateau pressures. The effect of NMBAs on long-term outcomes is unclear.

Interventions for PAD During COVID-19: Sedation Minimization

- Prior to interrupting/minimizing sedation, assess airway resistance
  - In addition to usual checks every 6 hours*
  - Higher risk for airway concretions with absence of humidity/heated humidity
  - May contribute to asynchrony

- Earliest manifestation of asynchrony may be hypoxia, hypotension
  - Possibly from abdominal de-recruitment, diaphragmatic steal
  - During interruption, trial higher PEEP (~5cm H2O) to counteract hypoxia and allow for some sedative washout
    - Discuss the implications of this on concerns over proning and timing
  - If cycling out of control, use of single dose NMBA

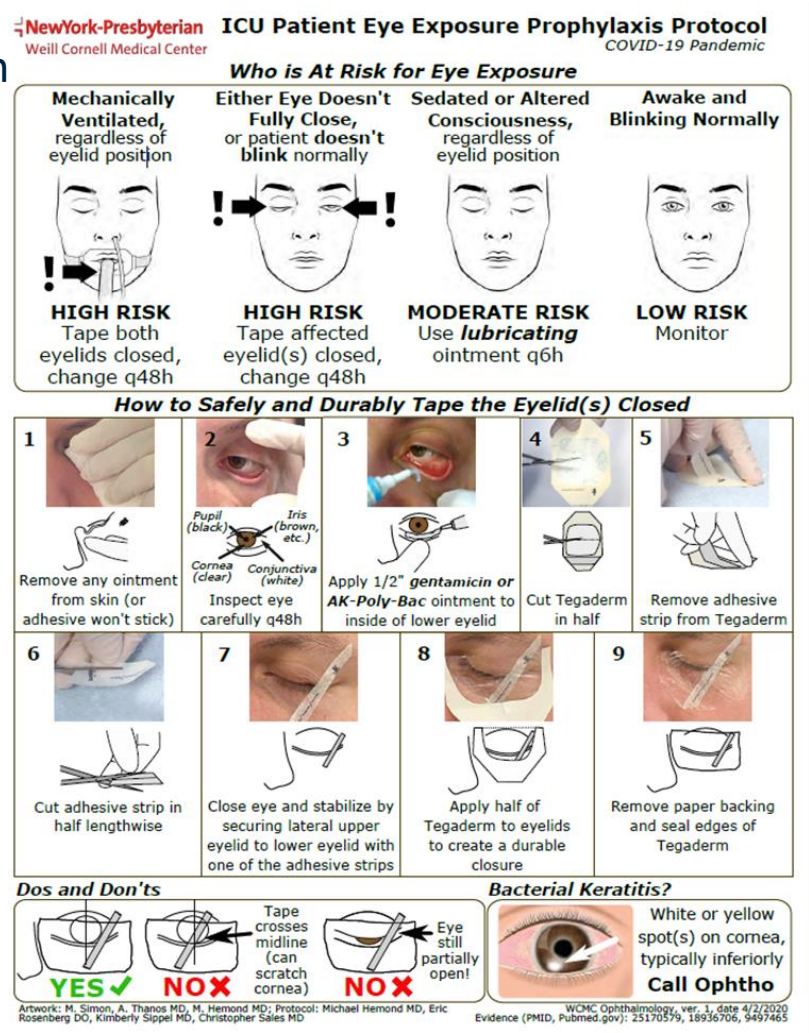
Intermittent NMBA

- Intermittent dosing:
  - Vecuronium (preferred): prolonged with both liver and renal dysfunction
  - Alternative: Rocuronium: prolonged by liver dysfunction
  - Dosing (both): 0.1 – 0.2 mg/kg every 4-6 hours

- Dose and frequency will vary based on organ dysfunction
  - Organ dysfunction may reduce dose and frequency needs
  - Use ventilator synchrony and/or TOF (goal 1-2/4) to guide

Keeping an Eye on the Details

- American Academy of Ophthalmology: mild conjunctivitis (early) associated with COVID 19 as well as mild peri-orbital erythema (late).
  - Neither of these require ocular treatment
  - Simple topical lubrication is can be used for comfort IF needed.
- Prevent exposure keratopathy and abrasions during MV
- First tier: Lacrilube to both eyes QID
  - Artificial Tear Ointment: Lacrilube, Refresh PM, artificial tear ointment (with no med)
- Second tier:
  - Ophthalmic ointment with antibiotic: E-mycin, PSO, etc. (using vehicle)
- Do NOT use anything containing a steroid (eg. maxitrol, tobradex)



DRAFT: Pending Infection Control Review

PENN MEDICINE COVID -19

Infection Control and Patient Management Guidance- Therapy Services

Version 7; Last Modified: 4/2/2020

STATUS	LOCATION	PROVIDER PROCESS	ISOLATION PRECAUTIONS	PERSONAL PROTECTIVE EQUIPMENT (PPE)	THERAPY INTERVENTION GUIDANCE/DIRECTIVE
Patient Under Investigation (PUI) Evaluating if patient requires COVID-19 testing and test location based on clinical presentation	Inpatient	• Provide patient a surgical mask • Provider: evaluate patient ○ Stable → further evaluation; consider COVID-19 test send out ○ Assessed to be unstable→ consult designated ID approver for in-house COVID-19 test approval	DROPLET + CONTACT	Healthcare Workers (HCW): Surgical mask, eye protection, gloves, reusable gowns	**Routine PT/OT/SLP interventions are not considered aerosolized procedures even if patient at risk of coughing during session and session > 10 minutes at close proximity.** **Exceptions: treating patients s/p tracheostomy, N95 mask may be indicated** **Occupational/Physical Therapy**:. º Therapist will discuss with primary team purpose of therapy consult. If essential/critical therapy needs have been identified (e.g. patients requiring therapy evaluation for safe discharges to home/post acute rehab setting, DME needs, significant impairment from baseline function), therapist will complete consult and develop plan of care if patient able to actively participate. º Maintain all isolation precautions during all sessions per patient isolation status. . º Consider gathering patient information via nursing and/or phone interview with patient. **Speech Language Pathology** º Therapist will discuss with primary team purpose of therapy consult. If essential/critical therapy needs have been identified, continue with care. º Maintain all isolation precautions during all sessions per patient isolation status.
Decision to Test R/O COVID 19 Testing patient to rule out COVID-19	Inpatient (Routine care)	• Place "Special Respiratory Precautions" sign • Enter "COVID-19 Rule Out" flag in Penn Chart • Alert Material Management & EVS of test sent, potential COVID-19 (inpatient only) • Alert Clinical Director of test sent (inpatient only)	DROPLET + CONTACT	Healthcare Workers (HCW): Surgical mask, eye protection, gloves, reusable gowns	
	Inpatient (Performing aerosolized procedures)	• Place "Special Respiratory Precautions" sign • Enter "COVID-19 Rule Out" flag in Penn Chart • Alert Materials Management & EVS of test sent, potential COVID-19 (inpatient only)	CONTACT + AIRBORNE	Healthcare Workers (HCW): PAPR or N95 respirator, eye protection + gloves, reusable or disposable gowns	
COVID-19 Positive Test results positive	Inpatient Acute Care Unit or ICU	• Enter "COVID-19 Confirmed" flag in Penn Chart • Alert EVS of COVID-19 room → Obtain biohazard trash cans • Alert Materials Management that PAPR, N95 & face shields needed • Alert Clinical Director that test is positive	Default: DROPLET + CONTACT Upgrade: Contact + Airborne-Based on need for aerosolized procedures following consult with primary team, nursing, Infection Control	A surgical mask, eye protection + gloves and gown can be used for routine care ***HCW: PAPR or N95 respirator, eye protection, gloves, and isolation gowns for care that includes risk of aerosolized procedures.	

FOLLOW YOUR ENTITY-SPECIFIC GUIDANCE FOR THE APPROPRIATE PPE SUPPLIES, PPE DONNING AND DOFFING SEQUENCE, AND ISOLATION SIGNAGE

Other Comments

- More liberal use of restraints
- Journals

- Things for which I seek help
  - Ketamine
  - Valproic acid safety and dosing

- We will try to use data to guide future recommendations