NYULH Tisch Campus COVID-19
Analgesia, Sedation, & Neuromuscular Blockade Guidance

General strategy for managing COVID-19 intubated patients in light of critical drug shortages

a **Low level analgesia** for patient comfort
b **Deep sedation** to facilitate ventilator synchrony
c Paralytics if ventilator synchrony cannot be obtained despite deep sedation
d All analgesic, sedative and paralytics will default to ideal body weight in Epic

Analgesia

a. Consider scheduled acetaminophen 1000 mg PO TID (with understanding that it may mask fever)
   i Use lower doses in low body weight patients
b. Selection of opioid agent
   i If patient is on norepinephrine >0.1 mcg/kg/min or IV opioid therapy is *required*:
      1. Fentanyl is the preferred agent
      2. When fentanyl is unavailable due to shortage the following options are available:
         a. Hydromorphone (preferred, based on availability)
         b. Morphine
         c. Remifentanil

IV Opioid	Dosing & Titration	Comments
Hydromorphone	**Intermittent**: 1-2 mg q4-6 hr PRN **Drip initial**: 0.5-1 mg/hr **Drip titration**: in increments of 0.25-0.5 mg/hr Every 30 minutes **Max**: 3 mg/hr	-Histamine-mediated adverse effects (ie., hypotension)
Morphine	**Intermittent**: 4-6 mg q4-6 hr PRN **Drip initial**: 1-2 mg/hr **Drip titration**: in increments of 1-2 mg/hr every 30 minutes **Max**: 20 mg/hr	-Active metabolites accumulate in renal failure -Histamine-mediated adverse effects (ie., hypotension), greater than hydromorphone and fentanyl
Remifentanil	**Intermittent**: not recommended due to short half-life **Drip initial**: 0.05 mcg/kg/min **Drip titration**: in increments of 0.025 mcg/kg/min every 5-10 minutes **Max**: 0.9 mcg/kg/min	-Metabolized rapidly via blood and tissue esterases

   ii If patient is on norepinephrine <0.1 mcg/kg/min and has enteral access
      1. Maintain goal pain and RASS scores with scheduled ***enteral*** opioids + intermittent IV opioids PRN
      2. Consider scheduled oxycodone starting at 5-10 mg PO q6 hrs or hydromorphone 4-8 mg PO q6 hrs

   iii If patient is not on vasopressor support
      1. Consider addition of fentanyl patch at 50% rate of IV fentanyl infusion
         a. Contact clinical pharmacy for assistance in conversion if on alternative opioid
         b. Fever/hyperthermia may increase drug absorption
         c. Must overlap for 8-12 hours with IV therapy to allow for onset
         d. Max dose allowed: 150 mcg/hr patch
         *e. *Remove patch at least 12 hours prior to anticipated extubation; may supplement with IV opioid boluses if needed**

   iv. ALL patients
      1. Prevention of opioid-induced constipation with standard bowel regimen +
         a. Naloxone 2 mg enteral QID OR
         b. Methylnaltrexone subcutaneous every 48 hours
            i. <62 kg: 8 mg
            ii. >62 kg: 12 mg

Sedation

a. Selection of sedative agents

- **If patient is on norepinephrine >0.1 mcg/kg/min or IV sedation is *required*:**
  1. Bolus IV sedatives agents to goal RASS. If patient is not at goal with bolus therapy alone, consider initiation of the following options:
     a. Options, when available: ketamine, benzodiazepines, barbiturates (phenobarbital), or propofol
        i. Please be mindful of propofol dose and duration to minimize risk of Propofol-Related Infusion Syndrome (PRIS) (see below)
     b. Dexmedetomidine is a light sedative and therefore may be insufficient in acute ARDS

Sedative	Dosing & Titration	Comments
Ketamine	**Drip initial**: 0.3-0.5 mg/kg/hr **Drip titration**: in increments of 0.1-0.2 mg/kg/hr every 60 minutes **Max**: 3 mg/kg/hr	- Monitor for the following: BP >140/90 or >20mmHg from baseline HR >20-30% from baseline Increased respiratory secretions Vision changes, fear/panic/hallucinations
Midazolam	**Intermittent**: 2-4 mg q2-4 hr PRN **Drip initial**: 2-4 mg/hr **Drip titration**: bolus 1-2 mg and increase in increments of 1-2 mg/hr every 30 minutes **Max:** 15 mg/hr	- Active metabolite accumulates in renal failure leading to delayed emergence from sedation
Lorazepam	**Intermittent**: 1-2 mg q4-6 hr PRN **Drip initial**: 0.5-1 mg/hr **Drip titration**: bolus 0.5-1 mg and increase in increments of 0.5-1 mg/hr every 30 minutes **Max**: 8 mg/hr (short-term)	- Monitor for propylene glycol toxicity with doses > 50 mg/24 hr (anion gap and osmolar gap metabolic acidosis >10)
Propofol	**Drip initial**:10 mcg/kg/min **Drip titration**: in increments of 5-10 mcg/kg/min every 5-10 minutes **Max:** 75 mcg/kg/min	- Monitor for triglycerides > 400 mg/dL (co-exists with COVID-related secondary HLH) - Monitor for PRIS with high doses (anion gap metabolic acidosis, rhabdomyolysis, arrhythmias, renal failure)

- **If patient is on norepinephrine <0.1 mcg/kg/min and has enteral access**
  1. Schedule 1 enteral GABAminergic agent + 1 enteral antipsychotic agent (or valproic acid) + 1 sleep agent
     a. GABAminergic agents:
        i. Chlordiazepoxide 25-100 mg TID-QID
        ii. Lorazepam 2-4 mg QID
        iii. Phenobarbital 32.4-97.2 mg TID (goal level: 5–40 mg/L; STRONG cytochrome P450 enzyme inducer, be vigilant of drug interactions)
        iv. Gabapentin 300-600 mg TID
     b. Antipsychotic agents:
        i. Haloperidol 0.5-2 mg TID
        ii. Quetiapine 25-50 BID-TID
        iii. Risperidone 0.5-1 mg BID
        iv. If concerned for elevated QTc, may use IV Valproate 10 mg/kg bolus, followed by 15-20 mg/kg/day in 3-4 divided doses (ensure levels are not >100 mg/L). Contraindicated if receiving carbapenem therapy.
     c. Sleep agent:
        i. Melatonin 5-10 mg HS

- **If patient is hypertensive or normotensive**
  1. Consider addition of clonidine patch at dose of 0.1 mg/24 hrs or 0.2 mg/24 hrs
     a. May help facilitate weaning of high-dose dexmedetomidine
     b. Must overlap with IV therapy for at least 2 days to allow for patch onset
     c. Fever/hyperthermia may increase drug absorption

Neuromuscular Blockade

a. Only is required in the presence of ventilator dyssynchrony and ***deep sedation RASS (-4 or -5)***

i. Dyssynchrony is a mismatch between the patients' respiratory demands and the ventilator.

1. May be evidenced by "bucking" the vent, frequent high pressure alarms, or overbreathing the vent despite deep sedation

ii. Paralysis is most appropriate in patients with PaO2/FiO2 ratio < 150

iii. Intermittent dosing is preferred over continuous infusion

b. Selection of agent

i. Cisatracurium is the preferred agent (unaffected by hepatic or renal dysfunction)

ii. When cisatracurium is unavailable due to shortage the following options are available:

1. Rocuronium: preferred, especially in renal dysfunction
2. Vecuronium: use caution in patients with significant hepatic or renal dysfunction due to prolonged effect

Paralytic	Dosing & Titration to Patient-Ventilator Synchrony
Rocuronium	**Intermittent**: 0.5 - 1 mg/kg **Drip initial**: Bolus 0.3 mg/kg + start infusion at 5 mcg/kg/min **Drip titration**: Bolus 0.1 mg/kg + increase in increments of 2 mcg/kg/min every 30-60 minutes
Vecuronium	**Intermittent**: 0.1 - 0.2 mg/kg **Drip initial**: Bolus 0.1 mg/kg + start infusion at 0.5 mcg/kg/min **Drip titration**: Bolus 0.05 mg/kg + increase in increments of 0.3 mcg/kg/min every 30-60 minutes
Cisatracurium	**Drip initial**: Bolus 0.2 mg/kg + start infusion at 1 mcg/kg/min **Drip titration**: Bolus 0.1 mg/kg + increase in increments of 0.5 mcg/kg/min every 30-60 minutes

c. Monitoring

i. Bispectral Index Monitors (BIS) to monitor depth of sedation are **required when available**

1. Extreme caution should be used when titrating down sedative medications to avoid an awake and paralyzed state
    a. Sedative-specific considerations:
        i. **Dexmedetomidine** provides insufficient sedation and amnesia in patients who are paralyzed and is not to be used as monotherapy
        ii. **Ketamine** may confound BIS interpretation, as it increases BIS numerically by increasing theta wave activity
    b. *If BIS available*:
        i. Target BIS goal: 40-60
    c. *If no BIS available*:
        i. Ensure adequate sedation and analgesia are achieved **prior to** neuromuscular blockade as evidenced by RASS of -4 or -5

ii. Train-of-four (TOF) to monitor depth of paralysis is **not required**

1. Paralytic doses may be increased for ventilator dyssynchrony and/or patient movement
2. *Paralytic doses should be re-evaluated and attempted to be reduced several times per day to avoid severe myopathy and polymyoneuropathy.*

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