ICU 101 for Pharmacists

"Just the facts, ma’am"

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Overview

• ICU basics
• “ICU lingo”

Drugs

– Sedation
– Neuromuscular Blockers (NMB)
– Vasopressors/Inotropes
– Antibiotics
– Steroids
  • Septic shock
  • ARDS
  • Pre-extubation
– Drug dosing in CRRT

Diseases

– Sepsis
  • Pressors, steroids
– Acute Respiratory Distress Syndrome (ARDS)
  • Sedation, NMB, steroids
– Delirium
ICU 101

Part 1

• Welcome to the ICU
• Lines and Tubes
• Drugs in the ICU
• Stress Ulcer Prophylaxis
• Analgesia and Sedation
• Sepsis
• ARDS
  – Neuromuscular blockers
• Drug dosing in CRRT

Part 2

• Fluids
• Inotropes and Vasopressors
• Mechanical Ventilation lingo (brief!)
• Prevention of post-extubation stridor
• Delirium
• Antibiotics
Welcome to the ICU!

April 9, 2020
The Flow Sheet

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value1</th>
<th>Value2</th>
<th>Value3</th>
<th>Value4</th>
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<tbody>
<tr>
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<tr>
<td>NIBP mean</td>
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<td>NIBP Location</td>
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<td>Temp Source</td>
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<tr>
<td>Cooling Blanket On</td>
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<tr>
<td>Warming Blanket On</td>
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<td>FentaNYL</td>
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<td>midazolam</td>
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<td>propofol</td>
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<td>norepinephrine</td>
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<td>1</td>
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<tr>
<td>Humulin R</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Notes:
- Axillary
THE BASICS
ICU Basics – Lines and Tubes

• Lines:
  – Arterial lines (“Art line”, radial, femoral)
    • BP Monitoring
      – Mean arterial pressure (MAP) = dBP + 0.3 (sBP-dBP)
      – Target MAP > 60-65 mm Hg
        » Consider organ perfusion (CNS, u/o, pt’s baseline BP, co-morbidities – TBI, SCI, CVA)
    • Arterial blood gases (ABG’s), bloodwork
  – Central lines (“IJ’s”, “subclavian”)
    • Fluids, IV meds, TPN
    • Single vs multiple lumen
  – Other Vascular Catheters (“Vasc Cath”)
    • dialysis

TBI = traumatic brain injury, SCI = spinal cord injury, CVA = stroke
ICU Basics – Lines and Tubes

- Endotracheal (ET) tube
- Enteral feeding tubes
  - Nasogastric (NG), nasojejunal (NJ)
  - Enteral feeds and PO meds
  - Blocked feeding tubes:
    • Pancrealipase + sodium bicarb tab
    • NOT Coca Cola!!
- Foley catheters
- Other
  - Chest tubes
  - Drains (Jackson Pratt, “JP”)
# Drugs in the ICU

<table>
<thead>
<tr>
<th>ICU-specific</th>
<th>Non ICU specific</th>
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<tbody>
<tr>
<td>Stress Ulcer Prophylaxis</td>
<td>Analgesia</td>
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<tr>
<td>Sedation</td>
<td>DVT prophylaxis</td>
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<tr>
<td>Vasopressors/Inotropes</td>
<td>Bowel Routines</td>
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<tr>
<td></td>
<td>Antibiotics</td>
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<tr>
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<td>Antihypertensives</td>
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<tr>
<td></td>
<td>Antiarrhythmics</td>
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<tr>
<td></td>
<td>Insulin</td>
</tr>
</tbody>
</table>

SHORT TERM GOALS VS LONG TERM OUTCOMES!!
Drugs In the ICU – routes of administration

• Intravenous
  – Infusions, intermittent
  – Reliable
  – Prefer rapid onset, short duration
    • Titratable
• Enteral – see next slide
• Inhalation
  – NO nebulization for COVID-19 pts!
  – MDI canisters can be given through the ventilator
    • e.g. salbutamol, ipratropium, fluticasone, Advair® inhaler (not Diskus)
    • Double dose to account for loss in tubing (e.g. salbutamol 8 puffs q4h)

• Other
  – Topical
  – PR
Drugs In the ICU – enteral administration

- Crush most Rx and put down enteral feeding tubes
  - EC:
    - Switch to non-EC (eg ASA 80 mg instead of EC ASA 81 mg)
  - SR:
    - If possible, switch to IR and change dose/dosing interval
      - Change Diltiazem ER 180 mg daily to Diltiazem 60 mg NG q8h
    - If not, crush and change dose/dosing interval
      - Change Bupropion SR 300 mg daily to Bupropion SR 100 mg NG TID
    - Avoid capsules with SR beads (e.g. M-Eslon, Hydromorph Contin)
      - Beads get stuck at bottom of syringe; unreliable dose
      - Use IR instead (solutions or tabs)

- Consider interactions with feeds (e.g. phenytoin)
- NG tubes larger bore than NJ tubes
- May need higher doses to account for ↓ absorption
Other drug-related issues

• Insulin
  – Continuous enteral feeding → IV insulin infusions
  – Less BG monitoring with SC?

• IV compatibility
  – Check Micromedex® for Y-site compatibility
  – Heparin, insulin – lots of incompatibilities
  – Lack of info:
    • Take 1cc from each bag and mix together
    • Observe x 5 min for physical incompatibility

• Pre-admission meds
  – Restart critical Rx (e.g. chronic steroids)
STRESS ULCER PROPHYLAXIS
Stress Ulcer Prophylaxis (SUP)

• Stress ulcers:
  – Multiple, superficial gastric erosions
  – Result from poor gut perfusion (impaired GI defense)

• At Sunnybrook:
  – ranitidine IV/PO on CrCU admission order sets
  – Discontinue when tolerating enteral feeds
  – PPI only if indicated (lansoprazole FASTAB)

• ICU’s are moving away from SUP due to evidence that does not change outcomes (see below and SUP references)

• Evidence:
  – H2RA vs sucralfate (RCT 1998)
    • ↓ in clinically important bleeding with ranitidine (1.7 vs 3.8%)
  – PPI vs placebo (RCT 2018)
    • no significant difference in 90-day mortality
  – PPI vs H2RA (cluster randomized trial 2020)
    • no significant difference in 90-day all-cause mortality
Stress Ulcer Prophylaxis – Bottom Line

- H2RA
- PPI
- Nothing (if enteral feeding)
Stress Ulcer Prophylaxis references

  - prospective, multi-centre randomized, double-blind trial in 1200 ICU patients
  - significant ↓ in clinically important bleeding with ranitidine vs sucralfate (1.7 vs 3.8%, 95% CI 0.21-0.92)
  - nonsignificant ↑ in pneumonia with ranitidine (19.1 vs 16.2%, 95% CI 0.92 – 1.51)
  - no difference in ICU mortality (22.3 vs 23.5%, 95% CI 0.84 - 1.26)

  - prospective, multi-centre randomized, double-blind trial in 3298 ICU patients
  - no significant difference in 90-day mortality (31.1 % with pantoprazole compared to 30.4% with placebo)
  - significant ↓ in clinically important GI bleeding (2.5 vs 4.2%, 95% CI 0.4 – 0.86)
  - no difference in infectious complications (VAP, CDAC: 16.8 vs 16.9%, 95% CI 0.84- 1.16)

- The PEPTIC Investigators. Effect of Stress Ulcer Prophylaxis With Proton Pump Inhibitors vs Histamine-2 Receptor Blockers on In-Hospital Mortality Among ICU Patients Receiving Invasive Mechanical Ventilation. JAMA 2020 [https://jamanetwork.com/journals/jama/article-abstract/2759412](https://jamanetwork.com/journals/jama/article-abstract/2759412)
  - Cluster randomized crossover trial in 50 ICU’s (n=26, 982)
  - No significant difference in 90-day all-cause mortality (18.3% PPI vs 17.5% H2RA, RR 1.05 95% CI 1.00 – 1.10, p=0.054)
  - Clinically important GI bleeding in 1.3% on PPI vs 1.8% on H2RA (p=0.009)
  - No difference in CDAC, hospital or ICU LOS
ICU Sedation

Benefits of Sedation

• Promote patient comfort/amnesia
  – Tolerate mechanical ventilation
• Decrease physiologic consequences of critical illness/ minimize oxygen consumption
• Decrease patient harm

Risks of Sedation

• Prolonged mechanical ventilation
  – Increased ICU complications
  – Increased ICU LOS
Analgesia and Sedation

  - Maintain light levels of sedation
  - Use of a validated sedation scale (SAS, RASS)
  - **analgesia-first sedation preferred**
  - The choice of sedative should be driven by the indication and goals of sedation in each patient, the pharmacology of the sedative in a particular patient, and the costs
  - Non-benzodiazepine sedation (propofol, dexmedetomidine) may be preferred over benzodiazepines
Analgesia in the ICU

- **Opioids**
  - Infusions vs intermittent + prn
  - Usually avoid morphine due to accumulation of metabolites (esp in renal dysfunction)
  - Fentanyl “Context sensitive half-life” = Basic Pharmacokinetic Principles
    - Distribution half-life vs elimination half-life
      - Single doses – fast on/fast off (distribution)
      - Infusions – longer duration (elimination)
  - Adverse effects: respiratory depression, sedation, hypotension if volume depleted, constipation (need bowel routines with stimulant laxatives)

- **Non-opioids**
  - Acetaminophen (po,pr, ?IV)
  - NSAIDS (generally avoid due to ↓ renal perfusion, antiplatelet effects)
  - Gabapentin, pregablin for non-neuropathic pain
# Opioid Analgesics

<table>
<thead>
<tr>
<th></th>
<th>Morphine</th>
<th>Fentanyl</th>
<th>Hydromorphone</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Onset</strong></td>
<td>&lt; 5 min</td>
<td>&lt; 1 min</td>
<td>&lt; 5 min</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td>3 – 4 h</td>
<td>0.25 h with single doses</td>
<td>2 – 3 h</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 – 3 h with multiple</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>doses/infusions</td>
<td></td>
</tr>
<tr>
<td><strong>Kinetics</strong></td>
<td>accumulation of</td>
<td>lipophillic: fast</td>
<td>preferred in ARF</td>
</tr>
<tr>
<td></td>
<td>metaabolism in</td>
<td>onset, offset</td>
<td>due to less accumulation</td>
</tr>
<tr>
<td></td>
<td>renal failure</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Side effects</strong></td>
<td>↓ BP if volume</td>
<td>least histamine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>depleted</td>
<td>release</td>
<td></td>
</tr>
<tr>
<td><strong>Dose</strong></td>
<td>1- 2 mg</td>
<td>50 – 100 mcg</td>
<td>0.2 – 0.4 mg</td>
</tr>
</tbody>
</table>

*NOTE: textbook conversion 10mg morphine = 100 mcg fentanyl*
Pain Scales

Visual analogue scale

CPOT

Critical Care Pain Observation Tool

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Description</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Facial expression</td>
<td>No muscular tension observed</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Presence of frowning, brow lowering, orbit tightening, and levator contraction</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>All of the above facial movements plus eyelid tightly closed</td>
<td>2</td>
</tr>
<tr>
<td>Body movements</td>
<td>Does not move at all (does not necessarily mean absence of pain)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Slow, cautious movements, touching or rubbing the pain site, seeking attention through movements</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Pulling tube, attempting to sit up, moving limbs/ thrashing, not following commands, striking at staff, trying to climb out of bed</td>
<td>2</td>
</tr>
<tr>
<td>Muscle tension</td>
<td>No resistance to passive movements</td>
<td>0</td>
</tr>
<tr>
<td>Evaluation by passive flexion and extension of upper extremities</td>
<td>Resistance to passive movements</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Strong resistance to passive movements, inability to complete them</td>
<td>2</td>
</tr>
<tr>
<td>Compliance with the ventilator (intubated patients)</td>
<td>Alarms not activated, easy ventilation</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Alarms stop spontaneously</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Asynchrony; blocking ventilation, alarms frequently activated</td>
<td>2</td>
</tr>
<tr>
<td>OR</td>
<td>Tolerating ventilator or movement</td>
<td>0</td>
</tr>
<tr>
<td>Vocalization (extubated patients)</td>
<td>Talking in normal tone or no sound</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Sighing, moaning</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Crying out, sobbing</td>
<td></td>
</tr>
</tbody>
</table>
Analgesia and Sedation

  - Maintain light levels of sedation
  - Use of a validated sedation scale (SAS, RASS)
  - Analgesia-first sedation preferred
  - The choice of sedative should be driven by the indication and goals of sedation in each patient, the pharmacology of the sedative in a particular patient, and the costs
  - Non-benzodiazepine sedation (propofol, dexmedetomidine) may be preferred over benzodiazepines


## Sedation-Agitation Scale: SAS

<table>
<thead>
<tr>
<th>Score</th>
<th>Term</th>
<th>Descriptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>Dangerous Agitation</td>
<td>Pulling at ET tube, trying to remove catheters, climbing over bedrail, striking at staff, thrashing side-to-side</td>
</tr>
<tr>
<td>6</td>
<td>Very Agitated</td>
<td>Requiring restraint and frequent verbal reminding of limits, biting ETT</td>
</tr>
<tr>
<td>5</td>
<td>Agitated</td>
<td>Anxious or physically agitated, calms to verbal instructions</td>
</tr>
<tr>
<td>4</td>
<td>Calm and Cooperative</td>
<td>Calm, easily arousable, follows commands</td>
</tr>
<tr>
<td>3</td>
<td>Sedated</td>
<td>Difficult to arouse but awakens to verbal stimuli or gentle shaking, follows simple commands but drifts off again</td>
</tr>
<tr>
<td>2</td>
<td>Very Sedated</td>
<td>Arouses to physical stimuli but does not communicate or follow commands, may move spontaneously</td>
</tr>
<tr>
<td>1</td>
<td>Unarousable</td>
<td>Minimal or no response to noxious stimuli, does not communicate or follow commands</td>
</tr>
</tbody>
</table>
Analgesia and Sedation

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## Sedation in the ICU

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>24h cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opioids</td>
<td>Analgesia</td>
<td>Respiratory Depression</td>
<td>$1-20</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>?Amnestic properties</td>
<td>? ↑ delirium, accumulation, ↑ PTSD</td>
<td>$10-20</td>
</tr>
<tr>
<td>Propofol</td>
<td>Rapid reversal, ?NMDA antagonism</td>
<td>Hypotension, cost, PRIS (rare)</td>
<td>$200-400</td>
</tr>
<tr>
<td>Ketamine</td>
<td>↑ BP, HR, bronchodilation</td>
<td>“Emergence reactions”</td>
<td>$75-300</td>
</tr>
<tr>
<td>Neuroleptics</td>
<td>Less sedating, no respiratory depression</td>
<td>EPS (typical), Limited IV availability (atypicals)</td>
<td>&lt; $10</td>
</tr>
<tr>
<td>Propranolol</td>
<td>Less sedating, no respiratory depression</td>
<td>Limited literature (TBI), ↓ BP/HR</td>
<td>&lt;$1</td>
</tr>
<tr>
<td>Clonidine</td>
<td>Less sedating, no respiratory depression</td>
<td>Limited literature, ↓ BP/HR</td>
<td>&lt;$1</td>
</tr>
<tr>
<td>Dexmedetomidine</td>
<td>“conscious sedation”, no respiratory depression</td>
<td>↓ BP/HR, cost</td>
<td>$200-600</td>
</tr>
</tbody>
</table>
Sedation

Light Sedation
Target SAS 3
• prn opioids if pain (po/IV)
• ?prn midazolam or other benzo (po/IV)
  – ?↑ risk of delirium
• Low dose propofol
• prn or standing neuroleptics (po/IV) for agitation
• po clonidine, IV dexmedetomidine

Heavy Sedation (ARDS)
Target SAS 1-2
• Opioid infusions
• Midazolam infusions
• High dose propofol
• High dose ketamine
• General Anaesthetic (inhaled) - UHN
Light Sedation

• prn opioids if pain
  – Hydromorphone 0.2 – 0.4 mg IV q2-4h prn
  – Hydromorphone 0.5 – 1 mg po/NG q2–4h prn
• prn midazolam or other benzo (po/IV)
  - Midazolam 1-2 mg IV q 1-2h prn
  - Lorazepam 0.5 – 1 mg po/NG/SL q8h prn
• Low dose propofol
  – 10-20 mcg/kg/min IV infusion
• prn or standing neuroleptics (po/IV) for agitation
  – Quetiapine 25 – 50 mg po/NG q4h prn
  – Haloperidol 5-10 mg IV q4h prn
• po clonidine, IV dexmedetomidine
  – Clonidine 0.1-0.2 mg po/NG q8h
  – Dexmedetomidine 0.5 – 1.5 mcg/kg/h IV infusion
**DEXMEDETOomidine**

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Central α-2 agonist</th>
</tr>
</thead>
</table>
| Benefits        | - Produces “Conscious Sedation”  
|                 | - No respiratory depression  
|                 | - ?less delirium than benzodiazepines |
| Adverse Events  | - hypotension, bradycardia |
| Metabolism      | Hepatic  
|                 | - Distribution half-life: 6 min  
|                 | - Elimination half-life: 3h |
| Cost/day        | 0.5 – 1.5 mcg/kg/h: $200-600 |
Deep Sedation

• Opioid infusions
  – Hydromorphone 0.1 – 2 mg/h
  – Fentanyl 50-200 mcg/h

• Midazolam infusions
  – 1-5 mg/h

• High dose propofol
  – 40 – 80 mcg/kg/min

• High dose ketamine
  – 1-2 mg/kg/h

• General Anaesthetic (inhaled) – UHN
  – Isoflurane, sevoflurane
<table>
<thead>
<tr>
<th><strong>PROPOFOL</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mechanism</strong></td>
</tr>
<tr>
<td><strong>Benefits</strong></td>
</tr>
<tr>
<td><strong>Adverse Events</strong></td>
</tr>
<tr>
<td><strong>Metabolism</strong></td>
</tr>
<tr>
<td><strong>Cost/day</strong></td>
</tr>
</tbody>
</table>
Propofol Infusion Syndrome (PRIS)

- Case reports in adults with high dose (~80 mcg/kg/min) for > 48h
  - Especially in pts with high sympathetic tone (eg head trauma, sepsis) or receiving catecholamine infusions (eg norepi)
- Brady/tachycardia, myocardial dysfunction, metabolic acidosis, rhabdomyolysis, renal failure
- Monitor:
  - Daily ECG (Brugada), CK
  - Daily triglycerides (R/A if > 5 mmol/L)

Note: green urine ≠ PRIS
### KETAMINE

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>IV dissociative anaesthetic which blocks NMDA receptors</th>
</tr>
</thead>
</table>
| Benefits  | - Analgesia and sedation  
- Less hypotension  
- Bronchodilation  
- Safe to use if ↑ ICP |
| Adverse Events | - Adverse CNS effects which may worsen delirium |
| Metabolism | Hepatic  
- Distribution half-life: 10-15 min  
- Elimination half-life: 2.5 h |
| Cost/day   | 0.5 – 1 mg/kg/h: $80-160 |
Volatile anesthetics (isoflurane, sevoflurane)

- Associated with faster awakening and shorter extubation times
- Advantages
  - Low cost, rapid and easy titration
  - Minimal hemodynamic effects (low dose)
  - Not renally/hepatically cleared
  - Low systemic accumulation
- Disadvantages
  - Feasibility limited by delivery system/scavenging devices
  - Side effects: risk of malignant hyperthermia, accumulation of fluoride
AnaConDa device

• “AnaConDa” (Anesthetic Conserving Device, Sweden)
  – Small miniature vaporizer which can be connected to an ICU ventilator
  – Also use scavenging devices (cannisters of Deltasorb) to reduce environmental emissions
Analgesia and Sedation – Bottom Line

• Analgesic first strategy (titrate to validated scale)
  – Use non-opioids to ↓ opioid use
  – Bowel routine if on opioid

• For most patients, target lighter levels of sedation (e.g. SAS 3)

• For ARDS patients, need deeper sedation (SAS 1-2)
  – Opioids, midazolam, propofol, ketamine
Analgesia and Sedation references

SEPSIS
Sepsis (Old Definition): a disease continuum

Infection/Trauma
SIRS

Sepsis

Severe Sepsis

A clinical inflammatory response arising from a nonspecific insult, including ≥2 of the following:

- Temperature ≥38°C or ≤36°C
- HR ≥90 beats/min
- WBC count ≥12 000/mm³ or ≤4000/mm³, or >10% immature neutrophils
- Respirations ≥20/min

Sunnybrook
HOLLAND BONE AND JOINT PROGRAM
Sepsis: Defining a disease continuum

Infection/Trauma

SIRS

Sepsis

Severe Sepsis

SIRS with a presumed or confirmed infectious process

Note: sepsis ≠ bacteremia
Sepsis: Defining a disease continuum

- Infection/Trauma
- SIRS
- Sepsis
- Severe Sepsis

Sepsis with ≥1 sign of organ failure:
- Cardiovascular (refractory hypotension)
- Renal
- Respiratory
- Hepatic
- Hematologic
- CNS
- Unexplained metabolic acidosis

Shock
Sepsis: Defining a disease continuum

Infection/Trauma
SIRS

Sepsis

Severe Sepsis

Sepsis with ≥1 sign of organ failure
- Cardiovascular
- Renal
- Respiratory
- Hepatic
- Hematologic
- CNS
- Unexplained metabolic acidosis

Septic Shock
Refractory hypotension

The Sepsis Cascade

Endothelium

- TNF, IL-1, 6, 8, 10, 12, 18
- Platelet activating factor
- Prostaglandins
- Reactive oxygen and nitrogen species
- Proteases
- Bradykinin

- NO

- Haemorrhage
- Vasodilation
- Intravascular coagulation
- Protein C
- ↑ Permeability

Jeremy Jaramillo's Blog
Treatment of Sepsis

1. Treatment of Infection
   o Source control when indicated
   o Anti-infectives
     o IV antibiotics within 1h (empiric broad spectrum then narrow with C&S)

2. Hemodyamic Support
   o Fluids
   o Vasopressors (Norepinephrine, Vasopressin)
   o Low dose corticosteroids

3. Treatment of Sepsis Cascade
   o Failed Pharmacologic Strategies: high dose corticosteroids, monoclonal antibodies against endotoxin, anti TNF drugs, IL-1 receptor antagonists, activated Protein C
Hemodynamic Support in Sepsis

• Fluids (more to come in Part 2)
  – **Crystallloid** (Normal Saline vs **Ringer’s Lactate**) vs Colloid (albumin)
  – Surviving Sepsis Campaign: 30 mL/kg crystalloid within 1st 3h
• Vasopressors (more to come in Part 2)
  – Vasoconstrictors: norepinephrine, phenylephrine, vasopressin
  – Surviving Sepsis Campaign:
    • First line - **Norepinephrine**
    • Second line – add vasopressin or epinephrine
• Corticosteroids (hydrocortisone)
  – Hydrocortisone 200 IV mg/day (usually 50 mg IV q6h) if “refractory shock”
## Catecholamines

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Pharmacologic Effects</th>
<th>Hemodynamic Effects</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>α-1 (vessels)</td>
<td>Vasoconstriction (↑ SVR)</td>
<td>↑ BP</td>
<td>Ischemia (peripheral, coronary)</td>
</tr>
<tr>
<td>β-1 (heart)</td>
<td>↑ HR, contractility</td>
<td>↑ Cardiac output</td>
<td>Arrhythmias, coronary ischemia</td>
</tr>
<tr>
<td>β-2 (lungs, vessels)</td>
<td>Vasodilation (↓ SVR)</td>
<td>↓ BP</td>
<td>Reflex tachycardia, arrhythmias</td>
</tr>
</tbody>
</table>

SVR = systemic vascular resistance
# Catecholamines

<table>
<thead>
<tr>
<th></th>
<th>α-1</th>
<th>β-1</th>
<th>β-2</th>
<th>dopamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>dopamine</td>
<td>++++ (HD)</td>
<td>+++</td>
<td></td>
<td>++++ (LD)</td>
</tr>
<tr>
<td>dobutamine</td>
<td>+</td>
<td>+++</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>epinephrine</td>
<td>++++ (HD)</td>
<td>+++</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>isoproterenol</td>
<td></td>
<td>+++</td>
<td>++++</td>
<td></td>
</tr>
<tr>
<td>norepinephrine</td>
<td>+++</td>
<td>++++ (LD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>phenylephrine</td>
<td>+++</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Hemodynamic Support in Sepsis

- **Fluids** (more to come in Part 2)
  - *Crystalloid* (Normal Saline vs *Ringer’s Lactate*) vs *Colloid* (albumin)
  - Surviving Sepsis Campaign: 30 mL/kg crystalloid within 1st 3h

- **Vasopressors** (more to come in Part 2)
  - Vasoconstrictors: norepinephrine, phenylephrine, vasopressin
  - Surviving Sepsis Campaign:
    - First line - *Norepinephrine*
    - Second line – add vasopressin or epinephrine

- **Corticosteroids** (*hydrocortisone*)
  - Hydrocortisone 200 IV mg/day (usually 50 mg IV q6h) if “refractory shock”
“No one should die in an ICU without a trial of steroids”
The history of steroids in the ICU

1976: 1st RCT >70% reduction in mortality from sepsis!

1980/90’s: >100 RCTs of steroids in sepsis; no overall benefit

Meduri 1998: Steroids for ARDS

2006 ARDS Net Trial: no benefit!

Annane 2002: Physiologic doses for relative adrenal insufficiency

2008 CORTICUS/2018 ADRENAL: no benefit!
## Steroids in Sepsis

<table>
<thead>
<tr>
<th>RCTs of LD steroids in sepsis</th>
<th>Study Population</th>
<th>Steroid regimen</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annane JAMA 2002</td>
<td>n=299 SAPS II ~60 60% medical ICU</td>
<td>HC 50mg IV q6h / fludrocortisone 50 mcg NG daily x 7 d</td>
<td><strong>28-day mortality:</strong> 53% vs 63% (p=0.02) in nonresponders</td>
<td>- 77% ACTH “nonresponders”</td>
</tr>
<tr>
<td>CORTICUS NEJM 2008</td>
<td>n=499 SAPS II ~50 30% medical ICU</td>
<td>HC 50 mg IV q6h x 5d then taper over 6d</td>
<td>- No diff 28-day mortality (39 vs 36%, p=0.69) - <strong>HC:</strong> ↓ shock, ↑ infection</td>
<td>- prematurely terminated - 47% nonresponders - No diff ACTH responders/ nonresponders</td>
</tr>
<tr>
<td>ADRENAL NEJM 2018</td>
<td>n=3658 APACHE II ~24 70% medical ICU</td>
<td>HC 200mg/day (IV infusion) x 7 d</td>
<td>- no diff 28-day mortality (22 vs 24%, p=0.13) - <strong>HC:</strong> ↓ shock, MV, ICU LOS; ↑ BG/Na</td>
<td></td>
</tr>
<tr>
<td>APROCCHSS NEJM 2018</td>
<td>n=1241 SAPS II =56 80% medical ICU</td>
<td>HC 50mg IV q6h / fludrocortisone 50 mcg NG daily x 7 d</td>
<td>28-day mortality: 34% vs 39% (p=0.06) - <strong>HC:</strong> ↓ shock; ↑ BG</td>
<td>↓ <strong>90-day mortality:</strong> (43 vs 49%, p=0.03)</td>
</tr>
</tbody>
</table>
Sepsis – Bottom Line

- Antibiotics, source control
- Fluids (crystalloid)
- Vasopressors: Norepinephrine +/- vasopressin
- Hydrocortisone 50 mg IV q6h if refractory shock
Sepsis References

• Surviving Sepsis Campaign 2016:
  https://journals.lww.com/ccmjournal/Fulltext/2017/03000/Surviving_Sepsis_Campaign___International.15.aspx

• ADRENAL Trial (NEJM 2018):

• APROCCHSS Trial (NEJM 2018):
ACUTE RESPIRATORY DISTRESS SYNDROME (ARDS)
Acute Respiratory Distress Syndrome (ARDS)

- Acute lung injury characterized by:
  - Acute onset
  - Diffuse bilateral infiltrates on CXR
  - $\text{PaO}_2/\text{FiO}_2$ of $< 300$ (with PEEP $\geq 5$)
    - $7.32/40/75/24$ (pH/CO$_2$/O$_2$/HCO$_3$), FiO$_2$ 60% (0.6)
      - P/F ratio = $75/0.6 = 125$
  - Rule out cardiogenic pulmonary edema
    - PCWP $< 18$, ECHO, BNP
- Can be secondary to direct insult (eg pneumonia, aspiration) or indirect injury (eg pancreatitis, sepsis, massive transfusion)

PEEP = positive end expiratory pressure, PCWP = pulmonary capillary wedge pressure, BNP = brain natriuretic hormone
Treatment of ARDS

- Supportive Care!
- Treat underlying cause (e.g. sepsis)
- Mechanical Ventilation
  - “Lung Protective Ventilation” (tidal volumes of 6mL/kg)
- Refractory ARDS strategies
  - Neuromuscular Blockade
  - Prone positioning of patients
  - inhaled nitric oxide, (inhaled epoprostenol)

- Failed pharmacologic strategies
  - Steroids (methylprednisolone 2 mg/kg/day)
  - Surfactant, ketoconazole, statins, IV β-2 agonists
Steroids in COVID-19

• The CDC recommends against routine use of corticosteroids in the management of COVID-19 over concerns that corticosteroids may prolong viral replication.

• Surviving Sepsis Campaign COVID-19:
  – recommends AGAINST the routine use corticosteroids in mechanically ventilated adults with COVID-19 with respiratory failure (without ARDS).
  – recommends using systemic corticosteroids in mechanically ventilated adults with COVID-19 and ARDS
    • A report of 26 patients with severe COVID-19 demonstrated a shorter duration of supplemental oxygen when methylprednisolone was used.

• GTA COVID-19 guidelines:
  – **Should not be offered** to COVID-19 patients outside of a clinical trial unless other indications
Steroids in *late* ARDS ("Meduri protocol")

- **1991/1994 Meduri et al (Fibroproliferative stage)**
  - Case series of pts with ARDS
- **1998 JAMA “RCT” (Meduri et al)**
  - n=24!!! on day 7 of ARDS (16 MP 2mg/kg/d vs 8 placebo)
  - 4 of placebo group crossed over to MP
  - Reduced mortality in group that received steroids (ITT analysis)
- **ARDS Net trial (NEJM 2006; 354:1671-84)**
  - RCT, n=180 with ARDS (after day 7)
  - No difference mortality
  - Increased mortality if received steroids and enrolled > 14 days after onset of ARDS
NEUROMUSCULAR BLOCKERS
Neuromuscular Blocking Drugs

- Inhibits Skeletal muscle (“Chemical Paralysis”)
  - Smooth muscle (e.g. cardiac, GI) not affected
  - NEED sedation! (i.e. paralyzed but awake)

- Depolarizing
  - Succinylcholine
  - Causes muscle to contract thereby preventing subsequent contractions
  - Not appropriate for continuous use

- Non-Depolarizing
  - Rocuronium, cis-atracurium
    - (Pancuronium, vecuronium, atracurium – no longer on the Canadian market)
    - Blocks receptor so acetylcholine (Ach) cannot cause muscle contraction
Neuromuscular Blockers

• Monitoring
  – Monitor response with peripheral nerve stimulator
    • Target 1-2 twitches on Train of Four or to clinical response
  – Deep Sedation required!
  – Other routine care: eye care, physiotherapy, monitoring for pressure ulcers, DVT prophylaxis
Neuromuscular Blockers

• SCCM 2016 guidelines (indications):
  – early in the course of acute respiratory distress syndrome (for patients with a $\text{paO}_2/\text{FiO}_2$ less than 150), life-threatening situations associated with profound hypoxemia, respiratory acidosis, or hemodynamic compromise, to manage overt shivering in therapeutic hypothermia

• Surviving Sepsis Campaign COVID-19:
  – For mechanically ventilated adults with COVID-19 and moderate to severe ARDS, the SCCM recommends the use of as needed, intermittent boluses of NMBAs, to facilitate protective lung ventilation.
  – The SCCM recommends using a continuous NMBAs infusion for up to 48 hours in the event of persistent ventilator dyssynchrony, the need for ongoing deep sedation, prone ventilation, or persistently high plateau pressures.
Neuromuscular Blockers in ARDS

• ACURASYS Trial (NEJM 2010)
  – n=340, moderate-severe ARDS (P/F ratio < 150)
  – Cisatracurium 15 mg then 37.5 mg/h x 48h vs placebo, initiated within 48h of ARDS
  – ↓ mortality at 28 days (23.7 vs 33.3%, p=0.05), no diff at 90 days (31.6 vs 40.7%, p=0.08)
    • Benefit in pts with P/F ratio < 120

• ROSE Trial (NEJM 2019)
  – n=1106 (stopped for futility), moderate-severe ARDS (P/F ratio < 150)
  – Cisatracurium 15 mg then 37.5 mg/h x 48h vs placebo, initiated within 48h of ARDS
  – No diff in 90-day mortality (42.5 vs 42.8%, p=0.93)
## Nondepolarizing Neuromuscular Blockers

<table>
<thead>
<tr>
<th></th>
<th>ROCURONIUM</th>
<th>CIS-ATRACURIUM (not available in CrCU)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Loading dose</strong></td>
<td>0.5 mg/kg</td>
<td>0.1 mg/kg</td>
</tr>
<tr>
<td><strong>Maintenance dose (dose to TOF)</strong></td>
<td>0.25 – 1 mg/kg/h</td>
<td>0.06-0.2 mg/kg/h</td>
</tr>
<tr>
<td><strong>Duration of effect</strong></td>
<td>20 – 35 min</td>
<td>45-60 min</td>
</tr>
<tr>
<td><strong>Metabolism</strong></td>
<td>Hepatic</td>
<td>Spont degradation</td>
</tr>
</tbody>
</table>
| **Side effects**        | • some ↑ HR,BP with high doses | • accumulation of metab in renal failure  
                          |                                   | • less histamine release          |
| **Cost**                | $100-200/day        | $200-400/day                           |
ARDS – Bottom Line

• Role of steroids
  – Methylprednisolone 1-2 mg/kg/day IV given once daily or divided bid
  – Unclear role

• Role of neuromuscular blockers
  – Use to facilitate mechanical ventilation (prn dosing)
  – Consider infusion if persistent ventilator dyssynchrony, the need for ongoing deep sedation, prone ventilation, or persistently high plateau pressures.
Neuromuscular Blockers References


• ACURASYS Trial (NEJM 2010):

• ROSE Trial (NEJM 2019):
DRUG DOSING IN CONTINUOUS RENAL REPLACEMENT THERAPIES
# Types of Dialysis

<table>
<thead>
<tr>
<th></th>
<th>Intermittent Hemodialysis (IHD)</th>
<th>Slow Low Efficiency Dialysis (SLED)</th>
<th>Continuous Renal Replacement Therapy (CRRT)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Frequency/Duration</strong></td>
<td>3x/week x 4-6h</td>
<td>3-5x/week x 6-12h</td>
<td>24 x 7</td>
</tr>
</tbody>
</table>
| **Advantages**          | Less anticoagulation (heparin in circuit)  
Better for K+/toxin removal | Better tolerated if ↓ BP  
No anticoagulation | Done by CrCU RN’s  
**Better tolerated if ↓ BP**  
Better volume removal |
| **Disadvantages**       | Done by IHD RN’s  
More hemodynamic instability and electrolyte shifts | Done by IHD RN’s | Citrate anticoagulation; requires CaCl infusion |
Drug Dosing in Dialysis

- Intermittent hemodialysis (IHD)
  - Reduce dose and dose around dialysis
  - e.g. Pip-tazo 4.5 g IV q12h, dosed at 0600/1800h
  - e.g. vanco 500 – 1000 mg IV post each IHD (3x/week)

- Slow low efficiency dialysis (SLED)
  - Reduce dose and dose around dialysis
  - e.g. Pip-tazo 4.5 g IV q12h, dosed at 0600/1800h

- Continuous renal replacement therapy (CRRT)
  - Beta-lactams – usual dose (i.e. pip-tazo 4.5 g IV q6h)
  - Vancomycin – 1250mg IV q24h
Drug Dosing in Dialysis References

http://kdpnet.louisville.edu/renalbook/adult/
General ICU and COVID-19 References

- Navigating Medical Emergencies (Royal College of Physicians and Surgeons with CSHP): [https://navme.royalcollege.ca/EN/index.shtml](https://navme.royalcollege.ca/EN/index.shtml)
- [www.criticalcarelearning.ca](http://www.criticalcarelearning.ca) (Phase 2 – Pharmacy)
- The Society of Critical Care Medicine (SCCM) Surviving Sepsis Campaign COVID-19: [https://journals.lww.com/ccmjournals/Abstract/onlinefirst/Surviving_Sepsis_Campaign__Guidelines_on_the.95707.aspx](https://journals.lww.com/ccmjournals/Abstract/onlinefirst/Surviving_Sepsis_Campaign__Guidelines_on_the.95707.aspx)
- GTA Covid-19 Clinical Practice Guidelines: [https://docs.google.com/document/d/1XUm7drwXQdcmj29BAOd4RcyPgXTwEm9TNvmNjH0g49U/mobilebasic](https://docs.google.com/document/d/1XUm7drwXQdcmj29BAOd4RcyPgXTwEm9TNvmNjH0g49U/mobilebasic)
Introduction

Authors: Benoit Cardinal, Sharon Yamashita
Editors: Marc Perreault, Salmaan Kanji

This chapter includes the clinical drug summaries for medications with inotropic and vasopressor activity.

Inotropes and vasopressors are used for hemodynamic support in patients who do not respond to adequate fluid resuscitation and to treat various shock syndromes, including cardiogenic and septic shock. The different agents have variable receptor affinities (Table 1), resulting in different hemodynamic profiles (Table 2). Although the direct hemodynamic effects can be predicted by the receptor activity, the overall hemodynamic changes observed may be a reflection of both the direct effects of the drug and the indirect effects that occur in response to these direct effects.

All sympathomimetic drugs are administered intravenously and have a rapid onset of activity, with the effects dissipating quickly after discontinuation. The doses of these drugs are usually titrated to hemodynamic targets, such as a mean arterial pressure > 65 mm Hg and/or evidence of adequate organ and tissue perfusion.

The most recent guidelines for the use of inotropes and vasopressors in sepsis were published in the 2016 Surviving Sepsis Campaign.[1]

Table 1: Receptor Activity of Sympathomimetic Drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>α-1</th>
<th>β-1</th>
<th>β-2</th>
<th>Dopamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dopamine</td>
<td>+++ (≥ 10 mcg/kg/min)</td>
<td>+++ (2–10 mcg/kg/min)</td>
<td>+++ (&lt; 2 mcg/kg/min)</td>
<td></td>
</tr>
<tr>
<td>Dobutamine</td>
<td></td>
<td>+++</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Epinephrine</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Phenylephrine</td>
<td>+++</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isoproterenol</td>
<td>+++</td>
<td>+++</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Introduction

Authors: Alexandra Cheung, Jennifer Teng
Reviewers: Joseph Blais
Editor: Sharon Yamashita

This chapter includes the clinical drug summaries for the neuromuscular blockers.

Neuromuscular blocking agents interfere with neuromuscular transmission, either by acting as an agonist (depolarizing) or as a competitive antagonist (nondepolarizing) at the postsynaptic acetylcholine receptor. Depolarizing neuromuscular blockers, such as succinylcholine, cause muscle depolarization, preventing further generation of action potentials. In contrast, nondepolarizing neuromuscular blockers, such as rocuronium and cisatracurium, block acetylcholine from binding to its receptor.

Neuromuscular blocking agents can be used on a short term basis for procedures such as rapid sequence intubation, or can be used on a more prolonged basis to help reduce oxygen consumption and facilitate mechanical ventilation. Prolonged use of neuromuscular blockers may be necessary in patients with severe hypoxemia, elevated intracranial pressure, excessive shivering and severe acute respiratory distress syndrome (ARDS).

Neuromuscular blocking agents cause paralysis of the respiratory muscles and should be administered only by those who are familiar with its actions and complications and who are skilled in the management of artificial respiration. Facilities must be available to provide immediate tracheal intubation and mechanical ventilation while the patient is paralyzed until spontaneous breathing returns. It is important to anticipate intubation difficulties, particularly when used as part of rapid sequence intubation. A neuromuscular monitoring device (e.g., peripheral nerve stimulator) is recommended to measure neuromuscular function in order to monitor drug effect and confirm recovery from neuromuscular blockade prior to extubation.

Neuromuscular blocking agents do not have analgesic or amnestic properties. Sedation should be administered prior to or in conjunction with these agents to avoid distress to the patient.

Patients receiving sustained neuromuscular blockade should also receive general care aimed at reducing complications, such as corneal abrasions, muscle atrophy and pressure ulcers.

References

ICU 101 Part 2

- Fluids
- Inotropes and Vasopressors
- Mechanical Ventilation lingo (brief!)
- Prevention of post-extubation stridor
- Delirium
- Antibiotics
Questions?