CSHP Webinar
ICU 101 for Pharmacists
Part 2

“Just the facts, ma’am”

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Learning Objectives

• To continue to introduce hospital pharmacists to ICU practices
• To give pharmacists a better understanding of the role of different fluids, inotropes and vasopressors in ICU patients
• To review the diagnosis and treatment of pneumonia in critically ill patients
• To review the prevention and treatment of delirium in the ICU
• To introduce some mechanical ventilation lingo
• To review the regimens/evidence for steroids in prevention of post-extubation stridor
• To discuss some of the considerations in ICU pharmacy practice related to COVID-19 infections
ICU 101 for Pharmacists

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
• Pneumonia in the ICU
• Delirium
• Mechanical Ventilation lingo (brief!)
• Prevention of post-extubation stridor
HEMODYNAMIC SUPPORT IN THE CRITICALLY ILL
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”
INTRAVENOUS FLUIDS
Intravenous Fluids

• D5W
• 2/3 – 1/3
  – 3.3% dextrose, 0.3% NS
• ½ NS (0.45% NaCl)
• Ringer’s Lactate
• NS (normal saline, 0.9% NaCl)
Total Body Water

- Total body water = 60\% total body weight
- Total Body Water:
  - 2/3 intracellular (IC)
  - 1/3 extracellular (EC)
    - 1/4 intravascular (IV)
    - 3/4 interstitial
Intravenous Fluids

• D5W (5% dextrose in water)
  – distributes into total body water
  – prolonged use associated with hyponatremia

• Normal Saline (0.9% sodium chloride, “crystalloid”)
  – distributes into extracellular space
  – prolonged use associated with hypernatremia and hyperchloremic metabolic acidosis

• “Colloid” (albumin, starch)
  – distributes into intravascular space
  – Artificial plasma expanders/starch (Pentaspan, Voluven) no longer used due to ↑ need for RRT
Intravenous Fluids

• D5W

• 2/3 – 1/3
  – 3.3% dextrose, 0.3% NS

• ½ NS (0.45% NaCl)

• Ringer’s Lactate

• NS (normal saline, 0.9% NaCl)

• Collioid

• Choice of IV Fluid for resuscitation?
  – NS, RL, colloid

• Choice of IV Fluid for maintenance?
  – 2/3-1/3, ½ NS
Fluid Controversies in the ICU

- Colloid versus Crystalloid
- Crystalloid
  - Normal Saline versus Ringer’s Lactate
Oncotic and Hydrostatic Pressures
Fluid Resuscitation

Crystalloid
- Normal saline, Ringer’s lactate
- Shorter duration of action (30-60 min)
- Only 1/3 stays in vascular space
- Risks:
  - NS: hypernatremia, hyperchloremic metabolic acidosis
  - Large volumes may contribute to pulmonary and peripheral edema

Colloid
- Blood products (RBC, FFP), Albumin, “starches”
- Less volume required as ↑ oncotic pressure, longer duration of action
- Risks:
  - albumin (blood product)
  - Allergic reactions
  - Pulmonary and peripheral edema
  - Renal dysfunction, coagulopathies
  - Cost!
Evidence on Fluid resuscitation

- 3 multicentre RCTs: 6% HES (tetrastarch) vs normal saline in sepsis
  - No diff in mortality
  - ↑ need for RRT (dialysis)
- Meta-analysis (65 trials) of colloid vs crystalloid for resuscitation
  - no diff in mortality

- Pragmatic, cluster-randomized, multiple crossover trial in 5 ICU’s
  - n =15, 802
- Primary endpoint: Major adverse kidney event at 30 days (death, need for renal replacement therapy or persistent renal dysfunction):
  - Crystalloids 14.3% vs Saline 15.4%; RR 0.9 (95% CI 0.84-0.99, p=.04)


- single-center, pragmatic, multiple-crossover trial
  - n = 13, 347
- Primary endpoint: hospital free days
  - Median 25 days (p=0.41)
- Secondary endpoint: Major adverse kidney event:
  - Crystalloids 4.7 vs Saline 5.6%; RR 0.82 (95% CI 0.70 – 0.85, p=0.01)
INOTROPES AND VASOPRESSORS
Cardiovascular Physiology

\[ \text{BP} = \text{CO} \times \text{SVR} \]

\[ \downarrow \]

\[ \text{HR} \times \text{SV} \]

- **Determinants of Cardiac Output:**
  - Heart Rate
  - Stroke Volume
    - Preload
    - Contractility
    - Afterload

**Abbreviations:**
- BP - Blood Pressure
- CO - Cardiac Output
- SVR - Systemic Vascular Resistance
- HR - Heart Rate
- SV - Stroke Volume
Determinants of Cardiac Output

• **Preload**
  – The volume of blood in the left ventricle at the end of diastole
  – associated with venous return

• **Contractility**
  – Inherent contractile function of cardiac muscle
  – ↑ with β-1 stimulation
  – ↓ with heart disease, negative inotropes (β-blockers, Calcium Channel Blockers, anti-arrhythmic drugs)

• **Afterload**
  – resistance to outflow
  – the force which the myocardium must work against in order to eject its contents
  – “systemic vascular resistance” (also sBP)
Relationship between Preload and Cardiac Output

![Graph showing the relationship between preload and cardiac output, with an indication of pulmonary edema at high cardiac output levels.](image)
Determinants of Cardiac Output

• **Preload**
  – The volume of blood in the left ventricle at the end of diastole
  – associated with venous return

• **Contractility**
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• **Afterload**
  – resistance to outflow
  – the force which the myocardium must work against in order to eject it’s contents
  – “systemic vascular resistance” (also sBP)
Relationship between afterload and cardiac output
Approach to Hypotension

BP = (HR x SV) x SVR

• ↑ Stroke volume
  – (reflex tachycardia)
  – ↑ preload
    • IV fluid / blood products if indicated
  – ↑ contractility
    • inotropes
      – catecholamines (β-1 agonists, sympathomimetics)
      – Phosphodiesterase inhibitors (milrinone)

• ↑ Systemic Vascular Resistance (SVR)
  – ↑ afterload
    • vasopressors
      – α-1 agonists
      – vasopressin
Approach to Hypotension - etiology

- **Hypovolemic Shock**
  - IV fluids (crystalloid)
  - Blood products if indicated

- **Cardiogenic shock**
  - ↑ contractility
    - inotropes
      - catecholamines (β-1 agonists, sympathomimetics)
      - Phosphodiesterase inhibitors (milrinone)
    - Caution: vasoconstrictors impair contractility

- **Septic shock (vasodilatory shock)**
  - ↑ afterload
    - vasopressors
      - α-1 agonists
      - vasopressin
# 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>Tachycardia, 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>
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</tr>
</tbody>
</table>

**HD** high dose  
**LD** low dose
Inotropes

1. Administer catecholamines
   - β-1 agonists, sympathomimetics
2. Inhibit the breakdown of cAMP - phosphodiesterase inhibitors (PDEI)
   - milrinone
3. Inhibit Na-K-ATPase (weak)
   - digoxin

• USES
  - Cardiogenic shock, hypotension in patients with LV dysfunction
• ADVERSE EFFECTS
  - Tachycardia, arrhythmias
  - ↑ demand on heart: coronary ischemia, arrhythmias
Sympathetic Nervous System

- Release of catecholamines
- Stimulation of \( \beta-1 \) receptors in heart
  - ↑ cAMP
  - Calcium Influx
  - Myocardial Contraction
Catecholamines/ Sympathomimetics

- $\beta-1$ agonists
- IV only, fast onset, short duration
  - titratable
- Central line preferred if agent also has $\alpha-1$ agonist activity
## DOPAMINE

<table>
<thead>
<tr>
<th>Receptors</th>
<th>alpha, beta and dopamine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose</strong></td>
<td></td>
</tr>
<tr>
<td>“renal dose”</td>
<td>(0.5-2 mcg/kg/min)</td>
</tr>
<tr>
<td>inotropic dose</td>
<td>(2-10 mcg/kg/min)</td>
</tr>
<tr>
<td>vasopressor dose</td>
<td>(&gt;10 mcg/kg/min)</td>
</tr>
<tr>
<td><strong>Uses</strong></td>
<td></td>
</tr>
<tr>
<td>- used in “crashing” pts when etiology of hypotension unclear</td>
<td></td>
</tr>
<tr>
<td>- hypotension due to heart failure or reduced vascular tone</td>
<td></td>
</tr>
<tr>
<td>- No longer used to maintain renal perfusion</td>
<td></td>
</tr>
<tr>
<td><strong>Adverse Effects</strong></td>
<td></td>
</tr>
<tr>
<td>- tachycardia, arrhythmias</td>
<td></td>
</tr>
<tr>
<td>- high doses: peripheral vasoconstriction, worsening of heart failure</td>
<td></td>
</tr>
</tbody>
</table>
# Dobutamine

<table>
<thead>
<tr>
<th><strong>Receptors</strong></th>
<th>beta-1 receptors (pure inotrope)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose</strong></td>
<td>5- 20 mcg/kg/min</td>
</tr>
<tr>
<td><strong>Uses</strong></td>
<td>- heart failure</td>
</tr>
<tr>
<td></td>
<td>- post MI if BP stable</td>
</tr>
<tr>
<td></td>
<td>- increase in MVO$_2$ due to inotropic properties is</td>
</tr>
<tr>
<td></td>
<td>balanced by vasodilation</td>
</tr>
<tr>
<td><strong>Adverse Effects</strong></td>
<td>- hypotension at high doses (beta-2 stimulation)</td>
</tr>
<tr>
<td></td>
<td>- Tachycardia (through $\beta$-1 stimulation and reflex tachycardia)</td>
</tr>
<tr>
<td><strong>EPINEPHRINE</strong></td>
<td></td>
</tr>
<tr>
<td>-----------------</td>
<td></td>
</tr>
<tr>
<td><strong>Receptors</strong></td>
<td>alpha, beta-1 and beta-2 receptors (similar to dopamine)</td>
</tr>
<tr>
<td><strong>Dose</strong></td>
<td>- vasodilator, bronchodilator (&lt;2 mcg/min, 0.03 mcg/kg/min)</td>
</tr>
<tr>
<td></td>
<td>- inotrope (2-20 mcg/min)</td>
</tr>
<tr>
<td></td>
<td>- vasopressor (&gt; 20 mcg/min)</td>
</tr>
<tr>
<td><strong>Uses</strong></td>
<td>- inotrope in heart failure, cardiogenic shock</td>
</tr>
<tr>
<td></td>
<td>- preloaded syringes used in cardiac arrest, anaphylaxis</td>
</tr>
<tr>
<td><strong>Adverse Effects</strong></td>
<td>↑ lactate (likely peripheral production not anaerobic metabolism)</td>
</tr>
</tbody>
</table>
Sympathetic Nervous System

Release of catecholamines

Stimulation of $\beta$-1 receptors in heart

$\uparrow$ cAMP

Calcium Influx

Myocardial Contraction

PDE
<table>
<thead>
<tr>
<th><strong>MILRINONE</strong></th>
</tr>
</thead>
</table>
| **Mechanism** | - ↑ cAMP (secondary to inhibition of PDE)  
- inotropic and vasodilatory effects (similar to dobutamine) |
| **Dose**       | 0.125 – 0.5 mcg/kg/min |
| **Uses**       | - refractory cardiogenic shock (especially if tolerance to β-1 agonists)  
- pulmonary hypertension |
| **Adverse Effects/Disadvantages** | - Slower onset of action  
- longer duration of adverse effects (especially if renal dysfunction)  
- thrombocytopenia, increased LFT’s (with long term use) |
VASOPRESSORS
Cardiovascular Pharmacology

\[ BP = CO \times SVR \]

\[ HR \times SV \]

BP - Blood Pressure
CO - Cardiac Output
SVR - Systemic Vascular Resistance
HR - Heart Rate
SV - Stroke Volume
• act through stimulation of alpha receptors in periphery
  – high dose dopamine
  – high dose epinephrine
  – norepinephrine (Levophed®)
  – phenylephrine (NeoSyneprine®)

• vasopressin
VASOPRESSORS

• USES:
  – used for hypotension refractory to fluids, inotropes
  – used in pts with decreased vascular tone (sepsis, anaphylaxis, spinal shock)
  – Used to counteract the hypotensive effects of sedation

• ADVERSE EFFECTS:
  – ↓ cardiac output in pts with heart failure
  – ↑ demand on heart
    • Coronary ischemia, arrhythmias
  – peripheral vasoconstriction
  – Tissue damage if extravasation (central line preferred)
Relationship between afterload and cardiac output

Cardiac output

SVR
<table>
<thead>
<tr>
<th>Receptors</th>
<th>Alpha, beta</th>
</tr>
</thead>
</table>
| Dose              | inotropics dose: < 2 mcg/min (0.03 mcg/kg/min)  
|                   | vasopressor dose: > 2 mcg/min                  |
| Uses              | - Vasodilatory shock                           
|                   | - Counteract the hypotensive effects of other drugs (e.g. propofol) |
| Adverse Effects   | excess vasoconstriction, decreased tissue perfusion, ischemia, gangrene |
Vasopressor Trials in Sepsis

- Norepinephrine vs Epinephrine (CAT Study, ICM 2008)
  - [https://doi.org/10.1007/s00134-008-1219-0](https://doi.org/10.1007/s00134-008-1219-0)
  - n=298 with shock randomized to NE vs E to keep MAP $\geq$ 70 mm Hg
  - No difference in time to achieve MAP goals, 28-day or 90-day mortality
    - Transient ↑ HR and lactate in epi group
- Norepinephrine + Dobutamine vs Epinephrine (CATS Study, Lancet 2007)
  - [https://doi.org/10.1016/s0140-6736(07)61344-0](https://doi.org/10.1016/s0140-6736(07)61344-0)
  - n=330 with septic shock randomized to E vs NE + DBA to keep MAP $\geq$ 70 mm Hg
  - No difference in 28-day mortality
- Norepinephrine vs Dopamine (Meta-analysis PLoS One 2015)
  - [https://doi.org/10.1371/journal.pone.0129305](https://doi.org/10.1371/journal.pone.0129305)
  - 11 RCT (n=1710) comparing NE to DA
  - NE lower mortality (RR 0.89, 95% CI 0.81-0.98)
  - NE lower arrhythmias (RR 0.48, 95% CI 0.4-0.58)
<table>
<thead>
<tr>
<th><strong>PHENYLEPHRINE</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Receptors</strong></td>
</tr>
</tbody>
</table>
| **Dose**          | Infusion: 40-250 **mcg/min** (0.5 – 3 mcg/kg/min)  
Boluses: 100 – 200 mcg q10 min |
| **Uses**          | Refractory shock (often as boluses) |
| **Adverse Effects** | - May cause less tachycardia than drugs with combined $\alpha/\beta$ activity  
- Tissue damage if extravasation (central line preferred) |
## VASOPRESSIN

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>vasopressor activity and antidiuretic hormone (ADH) activity</th>
</tr>
</thead>
</table>
| Dose      | - 0.6 - 3 **units/h** (0.01 – 0.05 units/min)  
- Replacement dose/infusion vs titratable |
| Uses      | - Decreased levels in sepsis (in contrast to pts with cardiogenic shock)  
- May reduce norepinephrine requirements (VASST trial) |
| Adverse Effects | **CVS:** ↑ BP, ↓ HR, ↓ CO, arrhythmias, angina  
**GI:** N, V, D, abdo cramps  
**other:** hypersensitivity, water retention (↓ Na), peripheral ischemia, tissue damage if extravasation (central line preferred) |
Vasopressin

• VASST Trial (NEJM 2008)
  – n=778 with septic shock on NE randomized to ↑ NE vs + VSP
  – No difference 28-day mortality
    • ↓ mortality with vasopressin in less severe shock (NE 5-14 mcg/min)

• VANISH Trial (JAMA 2016)
  – https://jamanetwork.com/journals/jama/fullarticle/2540403
  – n= 409 with septic shock; 2x2 – NE vs VSP ± HC
  – No difference in kidney-failure free days, mortality
    • ↓ renal replacement therapy in vasopressin arm
Lack of response to pressors
“Is there a maximum dose of ...?”

- Reassess volume status
- “tachyphylaxis”/tolerance due to down regulation of receptors
  - Add or change to drug which does not mediate effect through receptor (e.g., milrinone, vasopressin)
- Reassess goals of therapy
Oral agents

• Midodrine
  – Alpha agonist
    • 5 – 20 mg po tid/qid

• Ephedrine
  – Alpha and beta agonist
    • 8 – 16 mg po tid/qid

• May help wean off pressors (< 3-5 mcg/min NE)
• Used in patients with chronic hypotension (e.g. spinal cord injuries, hemodialysis)
Navigating Medical Emergencies

https://navme.royalcollege.ca/EN/index.shtml

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 (&gt; 10 mcg/kg/min)</th>
<th>β-1 (2-10 mcg/kg/min)</th>
<th>β-2 (&lt; 2 mcg/kg/min)</th>
<th>Dopamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dopamine</td>
<td>+++</td>
<td>+++</td>
<td>+++</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>
Vasopressors/Inotropes – Bottom Line

• Vasodilatory Shock (e.g. sepsis)
  – Norepinephrine ± vasopressin
    • Add epinephrine if low cardiac output
    • Alternatives: phenylephrine, HD dopamine

• Cardiogenic Shock
  – Dobutamine, milrinone if BP stable
  – Epinephrine, dopamine if ↓ BP
PNEUMONIA IN THE ICU
ICU Pneumonia

<table>
<thead>
<tr>
<th>Common Pathogens</th>
<th>CAP</th>
<th>HAP/ Early VAP (&lt; 72 H)</th>
<th>Late VAP * (&gt; 72H)</th>
</tr>
</thead>
</table>
| Gram (+): *Staph, strept*  
Gram (-): *H. flu, Moraxella*  
Atypicals: *mycoplasma, Legionella* | Gram (+): *Staph, strept*  
Gram (-): *H. flu, Moraxella, E. Coli* | Gram (+): *Staph*  
Gram (-): *Enterobacter, Serratia, Pseudomonas* |

Antibiotic Options

- Ceftriaxone + azithromycin
- Respiratory quinolone (e.g. levofloxacin)
- Ceftriaxone
- Respiratory quinolone (e.g. levofloxacin)
- Pip-tazo
- Cefazolin + Cipro
- Meropenem (if ESβL or MDR)

* Consider local microbiology and antibiograms
VAP Prevention

Colonization of Mouth with Pathogens:
Use Chlorhexidine Mouthwash

Aerosolization of Pathogens:
Use Closed Suction System

NO LONGER USED

Micro-Aspiration of Stomach Contents:
Elevate Head of Bed 45°

Ventilator Circuit Management:
Change per patient or if soiled

Aspiration of Secretions Above Cuff of ETT:
Use ETT with Sub-glottic Secretion Drainage

Airway Humidification:
HME or heated Humidifier.
Change HME every 5-7 days.

Late Ventilator-associated Pneumonia (VAP) – diagnostic challenges

• ↑ temperature
  – Pneumonia vs other infection (e.g. lines)
  – Non-infectious fever

• ↑ WBC
  – Infection vs inflammation
  – Role of other markers (e.g. CRP, procalcitonin)

• ↑ respiratory secretions
  – Respiratory vs tracheobronchitis vs oral

• Worsening oxygenation
  – Infection vs fluid vs other (e.g. ARDS)

• Infiltrate on CXR
  – Pneumonia vs pulmonary edema vs other

• Positive respiratory culture
  – Infection vs colonization
Clinical Pulmonary Infection Score (CPIS)  
(not validated for diagnosis of pneumonia)

**CLINICAL PULMONARY INFECTION SCORE CALCULATION**

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
</table>
| Temperature (°C) | > or equal to 36.5 and < or equal to 38.4 = 0 point  
> or equal to 38.5 and < or equal to 38.9 = 1 point  
> or equal to 39 and < or equal to 36 = 2 points |
| Blood leukocytes, mm³ | > or equal to 4,000 and < or equal to 11,000 = 0 point  
< 4,000 or > 11,000 = 1 point + band forms > equal to 50% = add 1 point |
| Tracheal secretions | Absence of tracheal secretions = 0 point  
Presence of nonpurulent tracheal secretions = 1 point  
Presence of purulent tracheal secretions = 2 points |
| Oxygenation: $P_{A02}/F_{O2}$ mm Hg | > 240 or ARDS (ARDS defined as $P_{A02}/F_{O2} < 200$, pulmonary arterial wedge pressure  
< or equal to 18 mm Hg and acute bilateral infiltrates) = 0 point  
< or equal to 240 and no ARDS = 2 points |
| Pulmonary radiography | No infiltrate = 0 point  
Diffuse (or patchy) infiltrate = 1 point  
Localized infiltrate = 2 points |
| Progression of pulmonary infiltrate | No radiographic progression = 0 point  
Radiographic progression (after CHF and ARDS excluded) = 2 points |
| Culture of tracheal aspirate | Pathogenic bacteria cultured in rare or light quantity or no growth = 0 point  
Pathogenic bacteria cultured in moderate or heavy quantity = 1 point  
Same pathogenic bacteria seen on Gram stain, add 1 point |

CPIS > 6: VAP  
CPIS ≤ 6: short course Abx  
(tracheobronchitis?)

VAP – Treatment
2008 Canadian VAP Guidelines
2016 IDSA/ATS Guidelines

• Early Empiric Therapy when VAP suspected
  – Choice of Abx based on local microbiology patterns and antibiograms
  – Canadian: appropriate spectrum “Monotherapy” vs double GNB
    • VAP Trial (NEJM 2006; 355;2619-30)
      – n=740 VAP (>4 days), randomized to mero + cipro vs mero alone
      – No difference mortality or clinical response rate
  – IDSA/ATS: double antiPseud + MRSA coverage if:
    • Risk factors (e.g. Abx in previous 90 days), > 10% resistance

• De-escalation once C&S back

• Antibiotic discontinuation strategy
  – eg if alternate diagnosis established

• Duration of therapy: 7- 8 days
Antibiotic Resistant Micro-organisms – gram negatives

• Extended spectrum beta-lactamases (ESβL)
  – Constitutive
  – *E. coli, Klebsiella*
  – Rx: ertapenem, quinolones (if sensitive), sulfa, aminoglycosides, ceftolazone-tazobactam

• Inducible beta-lactamases
  – Inducible (ampC gene); resistance may develop to most β-lactams during tx
  – “SPICE-HAM”: *Serratia, Pseudomonas/Providencia, indole (+) Proteus, Citrobacter, Enterobacter, Hafnia, Acinetobacter, Morganella*
  – Rx: carbapenems, quinolones (if sensitive), sulfa, aminoglycosides, ceftolazone-tazobactam, ceftobiprole

• Multi-drug resistant (MDR)
  – *Pseudomonas, Acinetobacter*
  – Rx based on C&S: tigecycline, aminoglycosides, colistin
  – Consider systemic tx + nebulized/intra-tracheal tobramycin or colistin
Duration of Antibiotics for Pneumonia
Chastre J et al. JAMA 2003; 290:2588-98

• n=408 randomized to 8 vs 15 days of Abx for VAP
• No difference in mortality or recurrent infections
  – ↑ antibiotic-free days, ↓ resistant pathogens
  – No difference in duration of MV, organ failure, ICU LOS
• Subgroup with non-fermenting GNB (e.g. *Pseud*)
  – No difference unfavourable outcomes
  – ↑ recurrence rates
Late VAP – Bottom Line

• Empiric antibiotics based on local microbiology and antibiograms
  – *S. aureus, Pseudomonas*
  – Rx: pip-tazo, cefazolin + cipro, meropenem
  – Broader Abx if recent Abx
    • Need to give Abx time to work!

• De-escalate Abx based on C&S
• Reassess Abx if alternate diagnosis
• Duration of therapy: one week
VAP - references

- 2016 IDSA/ATS VAP Guidelines: https://doi.org/10.1093/cid/ciw353
- 2008 Canadian VAP Guidelines: https://doi.org/10.1016/j.jcrc.2007.11.014
- Short Course Antibiotics (CPIS): https://doi.org/10.1164/ajrccm.162.2.9909095
- VAP Trial: https://doi.org/10.1056/NEJMoa052904
- 8 vs 15 days of VAP treatment: https://doi.org/10.1001/jama.290.19.2588
- Chlorhexidine meta-analysis: https://doi.org/10.1001/jamainternmed.2014.359
ICU DELIRIUM
Delirium: under recognized?

• Acute confusional state
  – Fluctuating mental status, inattention or disorganized thinking/altered LOC
  – “ICU psychosis”
  – Can be “hypoactive”
    • Withdrawal, flat affect, apathy, lethargy, ↓ responsiveness

• 50-75% of mechanically ventilated patients
  - ↑ duration of MV, LOS, mortality
  - long-term cognitive deficits?
Causes of Agitation/Delirium in the ICU

- Encephalopathies (sepsis, hepatic, uremia)
- Infection
- CNS tumours
- CNS Trauma
- Acid/base or electrolyte disorders
- Hypoxia

- Endocrine disorders (hypoglycemia, hyperthyroidism)
- Vitamin deficiencies
- Psychiatric illness
- “ICU psychosis”
  - sleep deprivation, loss of sleep/wake cycle
- DRUGS
  - intoxication/withdrawal

Pain, hunger, thirst, bowel/bladder, discomfort
Drug-induced Causes of Agitation/Delirium

- Sympathomimetics
- Antiarrhythmics
  - lidocaine
- Antibiotics, antivirals
- Corticosteroids
- Narcotics, benzodiazepines

- Antihypertensives
- Anticholinergics
  - TCA’s, 1st generation antihistamines
- Anticonvulsants
- Immunosuppressives
- NSAIDS
Delirium

• Assessment/Monitoring
  – Intensive Care Delirium Screening Checklist
  – Confusion Assessment Method for the ICU (CAM-ICU)

• Management
  – Risk factor modification
    • See CHASM
    • Early Mobilization
  – Optimize analgesia/sedation
    • NOTE: Sedation may predispose to delirium!
Confusion Assessment Method for the ICU (CAM-ICU) Flowsheet

1. Acute Change or Fluctuating Course of Mental Status:
   - Is there an acute change from mental status baseline? **OR**
   - Has the patient’s mental status fluctuated during the past 24 hours?

   **NO** ➔ CAM-ICU negative
   **YES** ➔ Inattention

2. Inattention:
   - “Squeeze my hand when I say the letter ‘A’.”
     Read the following sequence of letters: S A V E A H A A R T
     **ERRORS**: No squeeze with ‘A’ & Squeeze on letter other than ‘A’
   - If unable to complete Letters → Pictures

   ➔ > 2 Errors ➔ CAM-ICU negative
   ➔ 0 - 2 Errors ➔ CAM-ICU negative

3. Altered Level of Consciousness
   - Current RASS level

   ➔ RASS = zero ➔ CAM-ICU positive
   ➔ RASS > 0 ➔ CAM-ICU negative

4. Disorganized Thinking:
   1. Will a stone float on water?
   2. Are there fish in the sea?
   3. Does one pound weigh more than two?
   4. Can you use a hammer to pound a nail?

   **Command**: “Hold up this many fingers” (Hold up 2 fingers)
   “Now do the same thing with the other hand” (Do not demonstrate)
   **OR** “Add one more finger” (If patient unable to move both arms)

   ➔ > 1 Error ➔ CAM-ICU negative
   ➔ 0 - 1 Error ➔ CAM-ICU negative

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<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
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<tr>
<td>+4</td>
<td>Combative, violent, immediate danger to staff</td>
</tr>
<tr>
<td>+3</td>
<td>Very Agitated, pulls or removes tube(s) or catheter(s); aggressive</td>
</tr>
<tr>
<td>+2</td>
<td>Agitated, frequent non-purposeful movement, fights ventilator</td>
</tr>
<tr>
<td>+1</td>
<td>Restless, anxious, apprehensive but movements not aggressive or vigorous</td>
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<tr>
<td>0</td>
<td>Alert &amp; calm</td>
</tr>
<tr>
<td>-1</td>
<td>Drowsy, not fully alert, but has sustained awakening to voice (eye opening &amp; contact ≥ 10 sec)</td>
</tr>
<tr>
<td>-2</td>
<td>Light sedation, briefly awakens to voice (eye opening &amp; contact &lt; 10 sec)</td>
</tr>
<tr>
<td>-3</td>
<td>Moderate sedation, movement or eye-opening to voice (but no eye contact)</td>
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<tr>
<td>-4</td>
<td>Deep sedation, no response to voice, but movement or eye opening to physical stimulation</td>
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<tr>
<td>-5</td>
<td>Unarousable, no response to voice or physical stimulation</td>
</tr>
</tbody>
</table>

Source: Pain Manag Nurs © 2009 W.B. Saunders
Delirium

- **Assessment/Monitoring**
  - Intensive Care Delirium Screening Checklist
  - Confusion Assessment Method for the ICU (CAM-ICU)

- **Management**
  - Risk factor modification
    - See CHASM
    - Early Mobilization
  - Optimize analgesia/sedation
    - NOTE: Sedation may predispose to delirium!
CHASM: Interventions for prevention and management of delirium

- **Cognition**
  - Glasses/ hearing aids/ clocks/ calendars
- **Hydration**
- **Agitation**
  - r/o cause
  - Safe environment
- **Sleep-wake**
  - Ear plugs, eye shields
- **Mobility**

Delirium

2018 SCCM Guidelines for the prevention and management of Pain, Agitation/Sedation, Delirium, Immobility and Sleep Disruption in Adult Patients in the ICU

- Analgesic-first sedation strategy (see Part 1)
- Target light levels of sedation (see Part 1) – SAS 3
  - Propofol or dexmedetomidine preferred vs benzodiazepine
    - Conditional recommendation; low quality of evidence
      - (Note: ARDS – deep sedation required – SAS 1-2)

- Prevention – prophylactic drug therapy not recommended
Delirium

2018 SCCM Guidelines for the prevention and management of Pain, Agitation/Sedation, Delirium, Immobility and Sleep Disruption in Adult Patients in the ICU

• Treatment
  – Only tx if distressful symptoms
    • No difference in duration of delirium, MV, ICU LOS or mortality
  – Traditional neuroleptics (haloperidol IV/po)
    • EPS side effects, QT prolongation with high dose
    • Sedation, anticholinergic SE with low potency traditional neuroleptics (e.g. chlorpromazine, methotrimeprazine)
  – Atypical neuroleptics (risperidone, olanzapine, quetiapine – po only)
    • ↓ EPS
  – Dexmedetomidine if agitation/delirium precluding extubation
    • Conditional recommendation; low quality of evidence

April 14, 2020
Drugs for Agitation/Delirium

• Neuroleptics
  – Haloperidol
    • 5-20 mg NG/IV q4-6h standing + prn
    • Infusions 5 – 15 mg/h
  – Quetiapine
    • 25-100 mg NG a8-4h standing + prn
  – Daily ECG’s

• Clonidine
  – 0.1 – 0.5 mg NG q8h (HR, BP monitoring)

• Propranolol (Traumatic Brain Injury)
  – 20 – 120 mg NG q8h (HR, BP monitoring)

• Others
  – Nabilone if hx of THC
  – Benzo only if hx of EtOH/BZD

April 14, 2020
Sleep Promotion

2018 SCCM Guidelines for the prevention and management of Pain, Agitation/Sedation, Delirium, Immobility and Sleep Disruption in Adult Patients in the ICU

• Nonpharmacologic
  – Noise and light reduction
  – Assist-control ventilation

• Pharmacologic
  – SCCM no recommendation: melatonin, dexmedetomidine
  – SCCM recommends against use of propofol for sleep
  – SCCM insufficient evidence: TCA, atypical antipsychotic, BZD, BZD-receptor agonists
Delirium – Bottom Line

• Look/screen for it!
• Try and prevent it!
  • CHASM
  • Early Mobilization
• Treat with neuroleptics if symptoms distressful/harmful
  – Haloperidol vs atypical (quetiapine)
• Promote Sleep
  – ideally with nonpharmacologic strategies
Delirium References

• CHASM:  
  https://doi.org/10.1056/NEJM199903043400901

• 2018 SCCM guidelines on Pain, agitation and delirium:  
  https://doi.org/10.1097/CCM.00000000000003299
MECHANICAL VENTILATION LINGO
Mechanical Ventilation (MV) lingo

• Full support
  – Assist Control (pressure or volume control)
    • ACPC, ACVC
  – Set respiratory rate, set pressure/volume

• Weaning mode
  – Pressure Support (PS)
    • Pt initiates breath (rate and volume dictated by patient)
    • Preset pressure assistance during each spontaneous breath

• Positive end expiratory pressure (PEEP)
  – Pressure in lungs during exhalation
  – Prevents alveoli collapse at the end of expiration

• Spontaneous Breathing Trial (SBT)
  – To see if ready for extubation (“liberation from MV”)
  – T-piece, PSV 6/5, “ZEEP” (zero PEEP/PS)
O$_2$ saturation (SpO$_2$) vs PaO$_2$

- "desat"ing
  - Saturation monitor on finger
  - Correlation to PaO$_2$
  - Target sat > 88-90%

www.airwayjedi.com
## Flow Sheet

### Ventilation

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- **FiO2**
- **SpO2 `Sat`**
- **Pressure Support**
- **“PSV 11/12”**
- **PEEP**

April 14, 2020
PREVENTION OF POST-EXTUBATION STRIDOR
Post Extubation Stridor

• Post-extubation stridor (laryngeal edema) results in high re-intubation rates
  – Incidence: 6-37%
  – Risk Factors: MV > 36 hours, females, short stature, large endotracheal tubes, trauma

• “Cuff leak” test
  – Deflate cuff/occlude airway and listen for air movement on inspiration/expiration
  – Can also measure volume
  – Controversial whether predicts successful extubation

www.researchgate.net
Treatment of Post-extubation Stridor

- Nebulized epinephrine (not for COVID-19 pts)
- Heliox (helium/oxygen)
  - He lower density than O₂
  - Useful when upper airway edema
- Corticosteroids
  - Better if given pre-extubation
- Re-intubation (preferred for COVID-19 pts)
Steroids for the prevention of post-extubation stridor

• Methylprednisolone (NEJM 2007)
  – https://doi.org/10.1016/s0140-6736(07)60526-1
  – RCT, n=698, MV > 36h (median 6d)
  – MP 20mg IV q4h x 12h pre-extubation
  – MP significantly ↓ post-extubation edema and re-intubations

• Dexamethasone (Critical Care 2007)
  – https://doi.org/10.1186/cc5957
  – RCT, n=80, MV > 48h with low cuff-leak volumes
  – Dex 5mg q6h x 24h pre-extubation
  – Dex significantly ↓ post-extubation stridor; no diff in re-intubation rates
Steroids for the prevention of post-extubation stridor – Bottom Line

• Regimens:
  – Methylprednisolone 20 mg IV q4h started 12h pre-extubation
  – Dexamethasone 4 mg IV q6h started 24h pre-extubation

• Controversies:
  – Routine use vs high risk individuals only
COVID-19 CONSIDERATIONS IN PHARMACY
COVID-19 Considerations in the ICU
ISMP Bulletin March 26/April 3, 2020

• Reassessing ICU practices while balancing:
  – Patient Safety, Staff Safety, Drug Supply, PPE supply, Staff shortages

• Bundling of meds (changing admin times)/care/meals
  – D/C unnecessary Rx
  – Changing to SR if appropriate (not ICU)

• Infusions vs intermittent
  – More or less monitoring?
  – Less drug with intermittent

• Minimizing waste (extending expiry?)/contamination of drugs

• Drug Shortages
  – Be creative!
  – Lorazepam/diazepam instead of midazolam
  – Morphine instead of fentanyl/hydromorphone

April 14, 2020
Questions?