Controversies in Patient Management in ICU

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Learning Objectives

Recognize complications of nutritional support therapy

Recommend the optimal therapeutic approach to achieve a glycemic goal in specific clinical settings

Identify the most appropriate therapeutic paradigm to facilitate mechanical ventilation
Nutrition Therapy
Nutrition Support

• Nutrition support in critically ill adults has progress over the years due to innovations in nutrition delivery techniques and practices

• Nutrition Support
  – Preserve lean body mass
  – Maintain immune function
  – Avert metabolic complications
Nutrition Therapy

• Contemporary practice focus on nutrition “therapy”, which involve treatment methodologies to offset metabolic responses to stress and oxidative cellular injury in critically ill patients

• Consensus is that the prefer route of nutrition is via the oral or enteral route due to enhancement in patient outcomes
Timing of Parenteral Nutrition

• Providers are divided on when to initiate parenteral nutrition
  – ASPEN recommends delaying parental nutrition in healthy patients with no apparent protein-caloric deficit by seven days
  – ESPEN recommendations to initiate parenteral nutrition therapy in within 24-48 hours if enteral administration is not tolerated or contraindicated

Is early parenteral therapy the most important meal of an ICU stay?
CALORIES Trial

- Harvey and colleagues performed a multicenter, randomized, control trial involving intensive care unit (ICU) patients who were expected to receive nutritional support for a minimal of 2 days
- Patients were randomly assigned to receive nutrients via parenteral or the enteral route
- Median time to initiation of feeding was comparable in the parenteral and enteral route groups
  - 24 vs. 22 hours

CALORIES Trial
Results

• All-cause mortality at 30 days was the primary outcome
  – 33.1% in the parenteral group and 34.2% in the enteral group did not survive, p=0.57

• Parenteral route group experience lesser rates of hypoglycemia
  – 3.7% vs. 6.2%, p=0.006

• Enteral route group experience more episodes of vomiting
  – 8.4% vs. 16.2%, p<0.001
CALORIES Trial
Results

- Incidence of infectious complications among the parenteral and enteral route group was comparable
  - 0.22 vs. 0.21, p=0.72 respectively

- Amount of calories delivered was similar among the two groups
  - 89 vs 74 kcal/kg, respectively
  - Majority of the patients did not receive the targeted nutrition goal of 25 kcal/kg
Early Parenteral Nutrition in Critically Ill Patients

- Doig and colleagues studied the administration of early parenteral nutrition in patients with contraindications to enteral nutrition
  - Inclusion criteria required the presence of a central venous access
  - Fewer mechanical ventilation
    - 7.26 days vs. 7.73 days, p=0.01
  - Comparable incidence of catheter bloodstream infections in the early parenteral nutrition group vs. standard of care
    - 4.55% vs. 4.69%, p>0.99

Early Parenteral Nutrition in Critically Ill Patients

• Casaer and colleagues implemented a similar comparison
  – Initiation of parenteral nutrition within 48 hours (early-initiation group) versus 8 days (late-initiation group) after ICU admission
  – Central venous access was not an inclusion criteria
  – Greater percentage of patients require mechanical ventilation beyond 2 days in the early-initiation group
    • 40.2% vs. 36.3%, p=0.006
  – Higher incidence of infection
    • 26.2% vs. 22.8%, p=0.008

Inpatient Hyperglycemia Management
Definition

• Diabetes Mellitus (DM): disease characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both
  – Chronic hyperglycemia
    • Associated with long-term damage and dysfunction
    • Failure of various organs
• Acute diabetic or hyperglycemic state
  – Stress hyperglycemia
    • Elevated counter-regulatory hormone
      – Epinephrine, Glucagon, Cortisol
• Hyperglycemia during hospitalization is a predictor of morbidity and mortality

Prevalence

• Hyperglycemia among hospitalized patients
  – National survey of 44 U.S. hospitals
    • University Health System Consortium (UHC)
    • Veteran Health Administration (VHA)
• Single value >200 mg/dL
  – 77% (UHC) and 76% (VHA)
• Persistent hyperglycemia (blood glucose >200 mg/dL for 3 consecutive days)
  – 38% (UHC) and 18% (VHA)
  – 41% (UHC) and 41% (VHA) for patients with sliding scale as sole therapy

Pharmacotherapy

• Traditional oral agents
  – Biguanides
  – Sulfonylureas
  – Meglitinides
  – Thiazolidinediones
  – α-glucosidase inhibitors

• Insulin
  – Rapid acting
  – Short acting
  – Intermediate acting
  – Long acting

• New MOA agents
  – Synthetic analog of amylin
  – Glucagon-like peptide 1 (GLP-1) agonist
  – Dipeptidyl peptidase 4 (DPP-4) inhibitor
  – Sodium-glucose co-transporter 2 (SGLT2) inhibitor
<table>
<thead>
<tr>
<th>Insulin Type</th>
<th>Color</th>
<th>Onset</th>
<th>Peak</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rapid-Acting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lispro Aspart</td>
<td>Clear</td>
<td>15-30 mins</td>
<td>1-2 hrs</td>
<td>3-5 hrs</td>
</tr>
<tr>
<td>Glulisine</td>
<td>Clear</td>
<td>15-30 mins</td>
<td>1-2 hrs</td>
<td>3-5 hrs</td>
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<tr>
<td><strong>Short-Acting</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regular</td>
<td>Clear</td>
<td>30-60 mins</td>
<td>2-3 hrs</td>
<td>4-6 hrs</td>
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<tr>
<td><strong>Intermediate-Acting</strong></td>
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<tr>
<td>NPH</td>
<td>Cloudy</td>
<td>2-4 hrs</td>
<td>4-8 hrs</td>
<td>8-12 hrs</td>
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<tr>
<td><strong>Long-Acting</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glargine</td>
<td>Clear</td>
<td>4-5 hrs</td>
<td>peakless</td>
<td>22-24 hrs</td>
</tr>
<tr>
<td>Detemir</td>
<td>Clear</td>
<td>2 hrs</td>
<td>Slight-peak</td>
<td>14-24 hrs</td>
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</tbody>
</table>
What can happen if hyperglycemia is poorly controlled in hospitalized patients?
Dysglycemia
Mortality and Morbidity
Mortality Benefits

• Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI)
  – Mortality benefits in 620 CCU patients (18.6% vs. 26.1%)
    • Blood glucose goal: 126-196 mg/dL vs. usual care
• Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) 2
  – Group 1 (acute insulin–glucose infusion followed by insulin-based long-term glucose control), group 2 (insulin–glucose infusion followed by standard glucose control, and group 3 (routine metabolic management according to local practice)
  – Mortality benefit was not significant in 1253 CCU patients
    • Group 2 (22.6%) vs. Group 3 (19.3%), p=0.203
    • Blood glucose goal: 90-126 mg/dL vs. usual care

Can a sweet tooth be a good thing?
Hyperglycemia Management Improves Outcomes

- American College of Endocrinology position statement on inpatient diabetes and metabolic control-2004
  - 57% reduction in mortality
  - 46% reduction in sepsis
  - 41% reduction in acute renal failure
  - 44% reduction in critical illness polyneuropathy
  - Decrease of hospital stay by 1 day for every 50mg/dl reduction

Randomized Controlled Trials with Intensive Insulin Therapy

- Van den Berghe et al (2001)
  - Mortality benefit in 1548 SICU patients (4.6% vs. 8%)
  - Blood glucose goal: 80-110 mg/dL vs. 180-200 mg/dL
  - Hypoglycemia (5% vs. 0.8%)

  - Mortality benefit was not significant in 1200 MICU patients (37.3% vs. 40%)
    - Mortality benefit was seen in patients having an ICU stay for ≥ 3 days (31.3% vs. 38.1%)
  - Blood glucose goal: 80-110 mg/dL vs. 180-200 mg/dL
  - Hypoglycemia (18.7% vs. 3.1%)

J-Shaped Relationship Between Blood Glucose and Mortality

Unadjusted Association Between Mean BG and In-Hospital Mortality

NICE-SUGAR

- Randomized controlled trial involving 6104 adult patients admitted to the ICUs of 42 hospitals
- Intensive Glucose Control (81-108 mg/dL) vs. Conventional Glucose Control (≤ 180 mg/dL)
- Primary Outcome
  - Death from any cause within 90 days after randomization
- Results
  - Intensive Glucose Group had a higher percentage of death [27.5% versus 24.9%, p=0.02] and higher incidence of severe hypoglycemia [6.8% versus 0.5%, p=0.001]
## Target Blood Glucose for Hospitalized Patients

<table>
<thead>
<tr>
<th>Patients</th>
<th>American Diabetes Association American College of Endocrinology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Critically Ill</td>
<td>Initiate insulin therapy (&gt;180 mg/dl) Target BG (140-180 mg/dl)</td>
</tr>
<tr>
<td>Non-critically Ill</td>
<td>Target preprandial BG (&lt;140 mg/dl) Target random BG (&lt;180 mg/dl)</td>
</tr>
</tbody>
</table>
Which path leads to sweet success?
ICU Insulin Administration in Critically Ill

- Intravenous insulin infusions are preferred for achieving and maintaining blood glucose control
  - Validated insulin infusion protocols
    - Efficacy
    - Safety
  - Frequent glucose monitoring is essential to minimize the occurrence of hypoglycemia

Insulin Infusion Protocols

• A validated insulin infusion protocol is essential
  – Monitor for efficacy
    • Minimize the number of hyperglycemic events
    • Minimize glycemic variability
  – Monitor for safety
    • Minimize the risk of hypoglycemia
    • Identify clinical scenarios that will predispose patients to having a hypoglycemic event
    • Identify special patient population that are at high risk of hypoglycemia
    • Recognize discrepancy among blood glucose samples
Sedation and Analgesic Management
Sedation and Analgesic

• Intensive care patients are at risk of experiencing pain
  – Preexisting disease, invasive procedure, therapeutic device, blood draws

• Intensive care patients are at risk of experiencing anxiety and agitation
  – Continuous noise and ambient light
  – Sleep deprivation, excessive stimulation

Sedation and Analgesic

- Analgesic agents
  - Fentanyl
  - Hydromorphone
  - Morphine

- Sedative agent
  - Lorazepam, midazolam
  - Propofol
  - Dexmedetomidine

Guideline Recommendation

• Implementation
  – Analgesic and sedation protocols
    • Sedation and analgesic goal
      – Pain assessment
        » Behavioral pain scale (BPS), critical care pain observation tool (CPOT)
      – Sedation scale
        » Riker sedation-agitation scale (SAS), Richmond agitation-sedation scale
  – Light targeted level sedation is often preferred
  – Daily sedation interruption should be considered

Guideline Recommendation

• Treatment of pain
  – Intravenous opioids should be considered as the first line of choice to treat non-neuropathic pain
    • Carbamazepine or gabapentin with intravenous opioids should be considered for the treatment of neuropathic pain

• Choice of sedation
  – Non-benzodiazepine sedative (propofol or dexmedetomidine) is preferred

Barr et al. *Critical Care Med* 2012;41:263-306
How do you like your sleep, continuous versus intermittent?
Intermittent versus Continuous Sedation

• Nassar Junior and colleague compare daily interruption and intermittent sedation during the mechanical ventilation
  – Ventilator-free days in 28 days between daily interruption and intermittent sedation (median: 24 versus 25 days, p=0.16)
  – ICU mortality (40 versus 23.3%, p=0.16), hospital mortality (43.3 versus 30%, p=0.28), incidence of delirium (30 versus 40%, p=0.47)
  – Self-extubation (3.3 versus 6.7%, p=0.51)

Intermittent versus Continuous Sedation

- Tanios and colleagues evaluated risk factors for unplanned extubation in patients receiving mechanical ventilation
  - 92 unplanned extubations occurred (7.5 events/1000 days of mechanical ventilation)
    - Continuous sedation protocol with daily interruption of sedatives had 1.5 events/1000 ventilator days
    - Intermittent sedation protocol had 5 events/1000 days
    - No sedation protocol had 16 events/1000 days
      - $P < 0.05$

Dopamine Therapy
Dopamine

• **Mechanism of action**
  – <3mcg/kg/min (Low Dose)
    • D₁ receptor agonist
    • Vasodilation of the renal mesenteric and coronary beds
  – 3-10mcg/kg/min (Medium Dose)
    • β₁ receptor agonist
    • Increase cardiac contractility and heart rate
  – 10-20mcg/kg/min (High Dose)
    • α₁ receptor agonist
    • Increase arterial vasoconstriction

• **Maximum concentration**
  – 800mg/250ml
Does a little dopamine keep the kidney doctor away?
Low Dose Dopamine

• Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: 2012

• Vasopressor Therapy
  – Low-dose dopamine should not be used for renal protection
    • Grade 1A

Bellomo and colleague performed a randomized multi-centered clinical trial involving 23 intensive care units.

Patients were administered low-dose dopamine (2 mcg/kg/min) versus placebo.

No difference between the dopamine and placebo groups in peak serum creatinine concentration during treatment:
- 2.77 versus 2.81 mg/dL, p=0.93

Durations of ICU stay:
- 13 versus 14 days, p=0.67

Hospital stay:
- 29 versus 33 days, p=0.29

Meta-Analysis-Low Dose Dopamine

- Kellum and colleague performed a meta-analysis to determine whether low-dose dopamine
  - Evaluated the incidence or severity of acute renal failure, need for dialysis, or mortality in patients with critical illness
  - Included 58 studies (n = 2149)
  - Dopamine did not prevent mortality
    - Relative risk, 0.90 [0.44-1.83]; p =0.92
  - Dopamine did not prevent onset of acute renal failure
    - Relative risk, 0.81 [0.55-1.19]; p =0.34
  - Dopamine did not prevent the need for dialysis
    - Relative risk, 0.83 [0.55-1.24]; p =0.42

Low Dose Dopamine-Renal Perfusion

- Lauschke and colleague performed a clinical study to evaluate renal perfusion based on resistive (RI) and pulsatility index (PI)
  - Dopamine (2mcg/kg/min) reduced renal vascular resistance in patients without acute renal failure
    - Median RI/PI from 0.70 to 0.65/1.20 to 1.07, P<0.01
  - Increased resistance indices in patients with acute renal failure
    - Median RI/PI from 0.77 to 0.81/1.64 to 1.79, P<0.01