Bigger is not always better: Pediatric obesity and its implications for critical care with case study discussions

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Speaker Introductions

• Heather Herrera is a dually certified pediatric nurse practitioner working in a busy PICU at the Children’s Hospital of San Antonio as a clinical instructor with Baylor College of Medicine. She also enjoys being a pediatric acute care updates committee member with the Pediatric Nursing Certification Board. When not working, she enjoys spending time with her husband and two children.
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Disclosures

• Speakers have no disclosures.

Objectives

1. Discuss pharmacological challenges in caring for critically ill obese children.
2. Define ventilator strategies that can be utilized in critically ill obese children.
3. Discuss co-morbidities that can be encountered when caring for critically ill obese children and their impact on care.

Statistics

• CDC - 95th percentile or greater for weight status
• For children aged 2-19 years of age
  • 18.5% (~13.7 million children and adolescents)
  • 18.4% among 2 to 5 year olds
  • 18.4% among 6 to 11 year olds
  • 20.6% among 12 to 19 year olds

Obesity Epidemic
**Obesity Epidemic**

- Estimated that almost 20% of admissions to children’s hospitals involve obese children (Lim et al, 2018)
- 5% to 30% of US 6-17yo (7 to 14 million children) are overweight or obese, with disproportionately high prevalence in ethnic minorities

**Definitions**

- BMI ≥ 95% = obese
- BMI ≥ 85% = overweight

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**Why does size matter?**

- Obesity – alterations in physiology
  - Changes in tissue composition
  - Larger amount of fat body mass and lean body mass
  - Higher proportion of extracellular water compared to total body water
  - Increased circulating blood volume and cardiac output
  - Altered regional flow distribution
  - Impaired liver and kidney function
  - Obese adults have shown increased blood volume, cardiac output and renal blood flow

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**Pharmacokinetics**

- Vd (volume of distribution) and clearance
  - Vd (L/kg) is a theoretical parameter correlated to the total amount of drug distributed in the body and the resulting plasma level
  - Outcome measure most affected by obesity
  - Determined mostly by the physiochemical properties of the drug (lipid partition coefficient and plasma protein binding)
  - Specific to each individual

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**Volume of distribution**

- Drug in the bloodstream distributed to the body:
  - Central (blood vessels, major organs)
    - Low lipid solubility (hydrophilic)
    - Low volume of distribution
  - Peripheral (skin, fat stores)
    - High lipid solubility (lipophilic)
    - High volume of distribution
Pharmacological Challenges

- No standard on how to dose medications in obese children
  - IBW (ideal body weight)
  - TBW (total body weight)
  - BSA (body surface area)
  - Other complex physiologically based formulas

Definitions

- **Ideal Body Weight (IBW):** a weight that is believed to be maximally healthful, based chiefly on height but modified by factors such as gender, age, and build
- **Total Body Weight (TBW):** measure of mass; kilograms or pounds
- **Lean Body Weight (LBW):** the amount of weight that isn’t fat
- **Body Surface Area (BSA):** the area of the external surface of the body, measured in m²
- **Adjusted body Weight (ABW):** reflects lean body mass plus excess fat mass determined by a cofactor
- **BMI:** Older than 2 years; TBW (kg)/height² (m); categorizes the degree of obesity; rarely used for drug dosing

<table>
<thead>
<tr>
<th>Body size descriptor</th>
<th>Population</th>
<th>Formula</th>
<th>Application</th>
</tr>
</thead>
<tbody>
<tr>
<td>TBW</td>
<td>Patient's current weight in kilograms</td>
<td>Used for dosing in pediatric population</td>
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<tr>
<td>BMI</td>
<td>Older than 2 years</td>
<td>TBW (kg)/height² (m)</td>
<td>Categorizes the degree of obesity</td>
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</tbody>
</table>
| IBW in adults        | Man: 49.9 kg + 0.89 x (height in cm – 152.4)  
Woman: 45.4 kg + 0.89 x (height in cm – 152.4) | Considers sex difference |
| IBW in children      | Older than 2 years | Desired weight for a specific height and age; corresponds to 50th percentile age x height | Suggested for hydrophilic drugs and for establishing maintenance dose |
| BSA (m²)            | Children and adults | Height (cm) x weight (kg)/3600 | Frequently used for chemotherapy and fluid therapy |
| ABW                  | Adult males | TBW – drug factor x (TBW – IBW) usual factor 0.3–0.4 | Suggested for aminoglycoside dosage |
| LBW                  | TBW – fat weight | Considers sex difference |
|                      | Child: IBW + 0.29 (TBW – IBW)  
Man: 1.10 x TBW – 0.0128 x BMI x TBW  
Woman: 1.07 x TBW – 0.0148 x BMI x TBW | Considers sex difference |

In the future...

- Bio-electrical impedance analysis (BIA)
  - Non-invasive, practical, portable method of evaluating and trending body composition in children
  - A weak electric current flows through the body and the voltage is measured to calculate impedance of the body
  - Measures how well the body impedes electric current flow
  - Fat has a high resistivity
  - Blood lower resistivity
  - Has not been validated in the PICU environment

How to calculate IBW

- No gold standard for ideal body weight calculation in children exists
- For girls taller than 5 ft (60 in)
  - 42 + [2.27 x (height in inches – 60)]
- For boys taller than 5 ft (60 in)
  - 41 + [2.27 x (height in inches – 60)]
- For children shorter than 5 ft (60 in)
  - IBW = (height in inches)² x 1.63/1000

How to calculate LBW

- Fat-free mass (FFM) (sum of vital organs, extracellular fluid, muscles and bones), then also includes the fat accumulated in cell membranes, bone marrow and nervous system
- Obese children have excess lean body mass, especially in the lower limbs
- On average, 30% of excess weight in obese children corresponds to lean tissue
- Use is not validated
How to calculate ABW

- ABW
  - IBW + 0.4 (TBW – IBW)
  - Must remember that there is no gold standard method for calculating IBW in obese children
  - ABW has not been validated in children (Kendrick et al, 2015)

Pharmacological Challenges

- Important to identify correct dose of medication at the onset of therapy, particularly in critically ill children who need quick improvement

  - Inadequate dosing can lead to:
    - Treatment failure
    - Adverse events

Pharmacokinetic Variables

- In obese children, volume of distribution and clearance are best represented by total body weight (TBW) and lean body weight (LBW)

  - Volume of distribution and clearance
    - Often used to determine dosage of a medication

Pharmacokinetic Variables

- The degree of drug lipophilicity and hydrophilicity should also be considered

  - Consider loading versus maintenance dosing
  - Loading doses of hydrophilic medications in obese children should be based on IBW
  - Partially hydrophilic medications should be based on a percentage of TBW
  - Lipophilic medications should be based on TBW

Dosing

- Loading doses
  - Based on volume of distribution
- Hydrophilic drugs
  - Based on ideal body weight
- Lipophilic drugs
  - Distribute freely into fat and so larger doses may be needed in obese and overweight children, may be calculated on total body weight
- Maintenance doses
  - Based on clearance rate

Pharmacokinetics

- Highly lipophilic drugs
  - Distribute extensively into adipose tissue
  - High Vd
  - Dosage should be estimated based on total body weight
- Hydrophilic drugs
  - Should be based on IBW
  - Remain in the intravascular space and bind to adipose tissue (to a lesser extent)
  - Lower Vd
  - Potential risk for overdose
Analgesia

- Acetaminophen
  - IV commonly given as an adjunctive to opioids during major surgery
  - According to Hakim et al, current recommendations to give the maximum dose of 1000 mg, resulted in serum concentrations below detection limits in all patients within two hours of administration (in obese adolescents); dose is better predicted using total body mass
  - Some data suggests that pregnancy and/or oral contraceptive use can also affect IV Tylenol metabolism
  - Best dosing for obese adolescents remains unclear
  - Risk vs. benefit
    - Higher dose of Tylenol vs. risk of hepatotoxicity; current dosing is limited to 1000 mg q6h

- Morphine
  - Most hydrophilic of opioids
  - Initial dosage should be adjusted by IBW with titration to desired effect
  - Fentanyl
    - Lipophilic, fat soluble, rapid onset of action; increased volume of distribution, increased risk for accumulation and delayed recovery after prolonged administration
  - Remifentanil
    - Lipophilic; use caution in morbidly obese patients secondary to variances in cardiovascular and respiratory physiology

Benzodiazepines

- Highly lipophilic drugs
- Increased Vd
- Single IV dose should be based on TBW
  - May reach high levels rapidly so may need to use mini loading doses due to risk of dose-dependent respiratory depression
- Continuous IV infusion should be based on IBW
  - May consider dosing at fixed rate (mg/hr) in obese adolescents

- Midazolam (Versed)
  - High lipophilicity
  - Short-acting, water soluble
- Diazepam (Valium)
  - High lipophilicity
- Lorazepam (Ativan)
  - Lipophilic
  - Longer acting than versed

Antibiotics/Antivirals/Antifungals

- Acyclovir – IBW; max adult dose 10 mg/kg q8h
- Voriconazole – IBW; max adult dose 300 mg/dose
- Amikacin/Gentamicin – ABW (factor 0.4); plasma levels should be determined
- Clindamycin, Cephalosporins, Linezolid, Meropenem, Metronidazole, Piperacillin/tazobactam, Quinolones (TBW, in the case of ciprofloxacin, some use ABW in case sufficient dose is not achieved)
- Vancomycin is also TBW with the assumption of normal renal function, plasma levels should be obtained

Anticonvulsants

- Valproic acid – TBW; has a wide therapeutic range and drug level monitoring
- Carbamazepine – IBW (loading and maintenance doses)
- Phenytoin – ABW (loading dose), IBW (maintenance dose) or fixed dose of 300 mg/day
- Phenobarbital – TBW; levels should be monitored
- Levetiracetam – ABW; volume of distribution similar to total body water
**Inotropes/Vasoactives**

- **Adrenaline** – TBW; small volume of distribution, max adult dose 1 mg/dose
- **Catecholamines** (dopamine, dobutamine) – IBW; titrate to achieve effect; rapid initiation and short half-life; hydrophilic, small therapeutic window, wide titration window
- **Milrinone** – TBW; risk for insufficient dosing when using lean body mass to calculate dose
- **Nitroprusside** – TBW; obesity may be inversely related to drug response; may require higher doses

**Antihypertensives**

- **ACE inhibitors and Angiotension II receptor antagonist**
  - A small study found that obese and normal weight patients receiving similar doses may have a similar reduction in blood pressure
- **Calcium channel blockers**
  - Small study found that obese individuals response to CCB was 12.5% with a normal weight group response of 52.9%, suggesting that obese children may not respond as well to similar mg/m² doses of CCB and may need higher doses to achieve control of their high blood pressure

**Anesthetics**

- **Dexmedetomidine** – IBW; high risk for bradycardia and other adverse events in critically ill individuals
- **Ketamine** – IBW; using IBW may reduce the risk of adverse events; maximum IV dose in adults is 5 mg/kg
- **Methadone** – IBW; maintenance dose 80–120 mg/day (adult)
- **Morphine** – IBW; intermittent doses preferred over continuous infusion; must have clinical monitoring (respiratory depression)
- **Propofol** – IBW (loading dose), TBW (maintenance dose); the dose should start at 2 mg/kg and then titration is required
- **Rocuronium** – ABW; clinical response should be assessed and titrate dosing
- **Vecuronium** – IBW; kinetic values are similar in both obese and normal weight patients

**Anticoagulants**

- **Enoxaparin** – TBW; if total weight is used, doses above 30% of the standard dose may be required
- **Heparin** – prophylaxis with standard adult dose 5000 – 7500 U three times/day; for treatment, adjust per PT time to goal

**Antidotes**

- **Flumazenil** – IBW; maximum adult dose is 0.2 mg/kg
- **Naloxone** – TBW; maximum adult dose is 10 mg
- **Neostigmine** – ABW (cofactor 0.4); less adverse events and faster action
- **Protamine** – ABW (cofactor 0.4); dose should be based on the heparin dose using ABW

**Electrolytes**

- **Sodium bicarbonate** – IBW; small therapeutic window when used chronically
- **Sodium chloride** – IBW; dose based on either the individual’s requirements, age, weight, or Na plasma levels
- **Potassium chloride** – IBW; small therapeutic window; 20 meq/dose (max)
- **Calcium gluconate** – IBW; hydrophilic with low volume of distribution
- **Magnesium sulfate** – IBW; small therapeutic window
Steroids
- Dexamethasone – TBW
- Hydrocortisone – TBW
- Methylprednisolone – IBW; maximum dose in adults is 1 g (pulse therapy)

Antiarrhythmics
- Adenosine – IBW; hydrophilic drug with a small volume of distribution
- Atropine – TBW; large volume of distribution into the extravascular space
- Amiodarone – TBW; recommended with caution due to potential for reduced clearance in the long term
- Lidocaine – TBW (loading dose), IBW (maintenance dose); high volume of distribution in obese patients; clearance is the same in normal weight and obese patients

Diuretics
- Furosemide – IBW; risk for ototoxicity; maximum adult dose 40 mg
- No studies to guide dosing in obese pediatric patients:
  - Diuril
  - Bumetanide
  - Spironolactone

Immunosuppressors
- Cyclosporine – IBW; monitoring is required due to a small therapeutic window; obese children require lower maintenance doses
- No information found on how to dose the following drugs for obese children:
  - Mycophenolate
  - Tacrolimus
  - Rituximab

Insulin
- Insulin – TBW; conservation initial dosing to prevent hypoglycemia

Bronchodilators
- Ipratropium - TBW
- Salbutamol – TBW; maximum adult dose 10 mg/day (nebulizer), 1.6 mg/day (spray)
- Theophylline – TBW (loading dose), IBW (maintenance dose); plasma levels should be determined; minimal distribution into adipose tissue; volume of distribution decreases as adiposity increases
- Albuterol – no information found for dosing in obese children
Blood components

- Red blood cells – IBW; maximum dose 1 U
- Platelets – IBW; maximum dose for adults is 5-7 platelet concentrates
- Plasma – IBW; maximum adult dose 10 – 20 ml/kg
- Non-specific immunoglobulin – IBW; IBW should be used when TBW is > 20% of the IBW

Chemotherapy

- Typically dose in BSA (m²) using TBW
- Etoposide
- Teniposide
- Busulfan
- Cytarabine
- Methotrexate
- Doxorubicin

- One respective review found compared safety and efficacy outcomes between obese and normal weight children undergoing treatment for ALL
  - All children
  - Found no significant difference on the basis of BMI in the rates of complete remission, overall survival, or cumulative incidence of relapse
  - Found no difference on the basis of BMI in the frequency of grade 3 or 4 toxicity

Vaccines

- Hepatitis B
  - Tested for serum concentrations of antibody to hepatitis B surface antigen –
    - Median anti-HBs concentration were lower in obese children than in those children with normal weight
    - All of the study participants had anti-HBs concentrations that were above the recommended threshold of 10 IU/L
- Tetanus
  - Study examined inflammatory mediators, circulating immunoglobulins, and tetanus antibodies in overweight and normal weight children
    - Found that the mean concentration of antitetanus immunoglobulin G (IgG) was significantly lower for overweight children than the normal weight children
    - Study did find that all study participants had antitetanus IgG concentrations above the recommended threshold of 0.1 IU/mL

Perioperative Management

- Perioperative respiratory adverse events (PRAE) occur more commonly in obese children (Lerman and Becke, 2018)
  - Hypoxemia
  - Upper airway obstruction
  - Difficult bag-mask ventilation
- Obesity and BMI were predictors of overall PRAEs
  - Difficult laryngoscopy, laryngospasm, bronchospasm, major cough and need for O2 were identified but not significant associated with PRAE
- Obesity affects the washin and washout of inhaled anesthetics

Case Study #1

- 15 y/o male with trisomy 21, s/p ASD/VSD closure, T2DM, CHF, morbid obesity and OSA arrived Code 3 EMS after full arrest and aspiration event at home. EMS placed a King airway, had ROSC after 3rd dose of epinephrine: total down time-10 minutes. Discharged 8 weeks ago after a 2 month hospitalization.
- Weight 136kg (Up from 113kg at discharge), Height 149cm, BSA 2.48m², BMI 61.3kg
- Home Meds: Amlodipine, Lasix, Metformin, Lovenox, Abilify, Melatonin and albuterol prn

How Does Obesity affect this child?

- Type 2 Diabetes-takes metformin
- Altered mobility-Specialty Bed
- Obstructive sleep apnea(OSA)/Obesity Related Hypoventilation-Bipap dependent-not compliant
- Cardiomyopathy
- Hypertension
- CHF-lasix dependent
- Obesity related asthma
Case: Need an Airway!

• Unable to be intubated in field or in ER despite good views with laryngoscope due to airway obstruction/aspiration.
• Anesthesia and ENT to bedside O2 saturations 60%.
• Emergent microlaryngoscopy and bronchoscopy in trauma bay by ENT staff.
• Thick dense stenosis found in high trachea region. Distally airway open BUT had thick mucoid secretions and food particles with evidence of pulmonary edema.

Difficult airway?? Glidescope-hints and tips

• Have all size appropriate supplies
• Prepare ETT to mirror the same angle as glidescope with semi-rigid stylet
• Pre-oxygenate
• Sniffing position, lidocaine
• Insert blade midline-avoid sweeping the tongue
• Avoid going to deep-obstructs view
• Insert ETT parallel to blade, gently advance ETT once in view.

OSA (sleep disordered breathing) and Obesity

• Increased incidence of OSA: rates 13-60% in obese children.
• Diagnosed when >5 episodes of hypopnea per hour of sleep.
• Elevated CRP levels are seen in OSA supporting theory that it leads to inflammation.

OSA- Arrhythmias

• Etiology: Hypoxia and or sympathetic innervation occurs that lead to inspiratory efforts against a collapsed pharyngeal area creating negative intrathoracic pressure thought to provoke dysrhythmias.
• Apnea and hypopnea are associated with increase in premature beats and prolongation of Qtc interval.
• Most common: Non-sustained VT, sinus pause/arrest, second degree AV block, frequent PVC’s.
• Literature results vary but some evidence that CPAP support does not reduce dysrhythmia frequency-requires repeat sleep studies.

Vicious OSA Cycle

• O2 Saturations increased to 80’s, bronchoscope retracted and a 6.0 ETT was passed and the airway was cleared of food particles.
• NGT placed for decompression.
• Required significant pressures to be ventilated.
• Remained unresponsive, poor distal pulses, muffled heart tones, persistent hypoxia, hypotensive and cold peripherally.
Pulmonary Considerations-Mechanics

• Obesity leads to reduction in lung volumes, specifically expiratory reserve volume (ERV) and functional residual capacity (FRC) - obese kids will tend to breathe more rapidly and at lower lung volumes.
• These reduced volumes cause lack of stretch in the airway smooth muscle, which alters the actin-myosin bridges and produces "latching" of the muscle.
• The protective effects of deep inspiration are reduced or lost in obesity.
• In >10yr old population there is a lag behind standing height and the growth spurt of the lung and thoracic cavity - so small lungs for stature - must be careful using IBW methods to calculate tidal volume.

Pulmonary Considerations-Ventilation Strategies

• Low protective tidal volumes (TV)
• Peep maneuvers for lung recruitment
• Judicious oxygen use
• Outcomes no different if TV is adjusted to IBW
• Using driving pressure versus TV may be a better parameter in obese children
• Consider NIV as an alternative to intubation - especially when oversedated, have brief etiology of AMS or as a way to improve ventilation while awaiting intubation.
• TV >10ml/kg correlates with poor outcomes
• TV >10ml/kg using IBW-BMI adversely affected probability of extubation and with other methods of calculating BMI there was an increase in mortality in obese children using TV >10ml/kg.

Pulmonary Considerations-Asthma

• Obese children have:
  - higher risk of developing asthma
  - more frequent or significant symptoms
  - higher risk of exacerbations
  - longer exacerbations
  - decreased airway hyperreactivity and airway sensitivities BUT, have increased airway closure. Differing theories in "Obese asthma" blame hormones and "adipokines".

Case: Admit to PICU

• Hypotensive despite fluid boluses and initiation of epinephrine and norepinephrine drips. Milrinone stopped.
• Pleural effusion drained with chest tube
• Fluid restricted to 70% maint. Lasix drip started.
• EKG: Sinus tachycardia, RBBB, PVC's with multiple morphologies, T wave inversion on lateral leads.

Cardiac Effects

• Overweight adolescents are at risk for developing cardiac steatosis due to the accumulation of Intramyocellular Lipids (IMCL) with lipotoxicity.
• Develop cardiac toxicity and dysfunction with increasing insulin resistance.
• Can lead to development of Cardiomyopathy

• Complex development of Hypertension due to inflammation and endothelial dysfunction
• Leads to abnormal LV geometry and LVH

• Subclinical pulmonary hypertension combined with borderline right ventricular heart failure may complicate the combination of increased cardiac output (CO) from obesity and pulmonary hypertension from chronic intermittent hypoxemia, rendering the child vulnerable to acute right heart failure in the face of any stress.
• Obesity study revealed that between 19% and 31% of obese youth had elevated systolic or diastolic blood pressure.
• Overweight youth with BMI >95% ages 5-17 had 11.1% increased risk for hypertension with one study finding an odds ratios of 2.4 for elevated total cholesterol.
• Overweight youth ages 5-10, were found to have at least one risk factor for developing cardiovascular disease.
Nutritional Challenges

- Obesity is an inflammatory state that has weakened response to critical illness.
- Low Vitamin D and increase in oxidative stress leads to alterations in insulin metabolism and resistance which serves to promote airway remodeling.
- Endothelial dysfunction and inflammation.

Measurements

- Measuring caloric needs is challenging in critical care due to variability in anthropometrics, poor or inaccurate measurements, inaccurate resting energy expenditure (REE) and difficulty predicting energy needs.
- Indirect calorimetry can be used, but this is expensive.
- Skinfold measurements are not accurate in critically ill due to fluid shifts and capillary leak.

Nutrition in Pediatric Obesity

- Suffer the same loss of lean body mass during times of critical illness.
- Most studies reveal suboptimal protein delivery the first week. Lower mortality with adequate protein intake. 1.5-3g/kg/day based on age.
- Many NPO for 1/3 of their PICU stay.

Case Neurologic Status

- Encephalopathic with seizures and clonus, no purposeful movement. GCS 3-5.
- EEG: burst suppression pattern off all sedation medications.
- Periods of gasping breaths
- Concern for quality of life—numerous family discussions
- Poor neurologic exam—seizures developed, unable to perform MRI due to body habitus
- Care withdrawn on Hospital day #14 with his PICU family present.
- Removal from home after previous admission change the outcome?
- Aggressive interventions when younger?

Ethics Surgery???

- Surgical interventions—bariatric surgery offers a solution and co-morbid conditions often resolve but long term habits have not been changed.
- Should children have these surgeries?
- Age of assent 8-14 years of age as a general rule—should be provided
- In adolescents bariatric surgery literature surgery was followed by sustained weight loss in 84.8% of 33 adolescents, and obesity-related morbidity generally improved.
- In another study: gastric banding procedure resulted in a median loss of 35.6 kg or 59.3% of excess weight in 17 adolescents.
- Another reported that after mean follow-up of 5.5 years, 18 of 19 adolescents who had undergone bariatric surgery at ages 13 to 17 years had lost adequate weight and all had resolution of comorbid conditions.

Ethics in Obesity

- Complex—Fault entirely on parents? Family issue?
- Interventions—Accusatory, labeling, stigmatizing, threatening
- Can lead to long term psychosocial problems.
- Behavioral therapy aids in weight loss and maintenance.
- Frequent follow up
- Camps and group therapy
Case study #2

15yo male
- Wt: 92.9 kg, BSA 2.09 m², ht 170 cm
- PMH: Obesity (BMI 32.1), fatty liver disease, DM type 2, hypertension, asthma, hypertriglyceridemia
- Presented with three-day history of nausea, vomiting, dizziness, and one day history of severe epigastric pain

Labs:
- CBC: WBC 20.2, Hgb 14.6, Hct 42.1, Plts 277
- Chem: Na 131, K 4.0, Cl 97, CO₂ 12, BUN 9, Creatinine 0.9, Amylase 832, Lipase 1509, HgA1c 8.5
- Initial triglycerides 2536, increased to 3849 in 24 hours
- ABG: 7.40/35.5/45.6/21.6/‐2.4

Primary diagnoses
- Initially admitted to hospitalist service, transferred to PICU for management of severe hypertriglyceridemia and hyperglycemia
- Current diagnoses:
  - Uncontrolled diabetes
  - Hypertriglyceridemia
  - Pancreatitis
  - Obesity

PMH
- Diagnosed with diabetes at age 5; originally started on Metformin, started requiring insulin for management at age 13; also takes Glipizide daily
- Reportedly mostly compliant, MOC states he usually misses 2-3 doses/week
- Noncompliant with diet and exercise
- Hypertension – takes daily Lisinopril
- Fatty liver disease – followed by GI, recommended diet and exercise, noncompliant, at risk for development of pancreatitis secondary to hypertriglyceridemia (> 500); started on Gemfibrozil
- Asthma – mild, no controller medications prescribed

How did obesity affect this patient?
- Diabetes
- Severe hypertriglyceridemia
- Hypertension
- Mechanical ventilation strategies
- Specialty bed
- Dosing of medications

Diabetes
- Children with DM type 2 frequently have a family history
- Acanthosis nigricans and polycystic ovarian syndrome (PCOS) are disorders associated with insulin resistance and obesity and are common co-diagnoses
- Lipid disorders and hypertension are also frequent diagnoses seen in children with type 2 DM.
- Caucasian children and adolescents were asymptomatic at time of diagnosis, whereas other ethnicities demonstrated manifestations of type 2 DM and had high insulin and C-peptide levels
- Syndromes associated with type 2 DM: Klinefelter Syndrome, Bardet Biedl Syndrome, Prader Willi Syndrome and Alstrom Syndrome; also associated with mental retardation and extreme obesity

PMH (cont)
- No prior surgical history
- Immunizations up to date
- No sick contacts
Diabetes

- Obesity is a hallmark of type 2 diabetes mellitus
- Goals of treatment (outpatient) – normalization of blood glucose and HbA1c
- Should also attempt normalization of other comorbidities (hypertension, dyslipidemia)
- Ultimately, goal is to decrease long-term complications associated with DM type 2

Diabetes Mellitus Treatment

- Diet and Exercise
- Metformin
  - Oral agent – may aid in compliance
  - Decreases hepatic glucose output and enhances primarily hepatic and muscle insulin sensitivity without a direct effect on b-cell function
  - Advantage of weight reduction and decrease in lipids
  - Contraindicated in patients with impaired renal function due to risk for lactic acidosis
  - Should not be used in patients with severe infection, alcohol abuse or hepatic disease

Treatment while acutely ill

- Best to manage diabetes with insulin drip and IV fluids during severe, acute illness
  - Hospitalization can interrupt the patient’s typical home balance of medications, diet and exercise and can potentially lead to hypoglycemia or hyperglycemia
  - Also predisposed to develop these conditions secondary to critical illness (infection, drugs, NPO status/reduced PO intake)
  - Stress hyperglycemia has been associated with an increased mortality in adults with acute myocardial infarction (both with and without history of diabetes)
  - Uncontrolled hyperglycemia has been associated with worse clinical outcomes
  - Insulin drip
  - Titrate IV fluids (two bag system) as needed to achieve goal blood glucose

Diabetes and Hypertriglycerides

- Results from either increased production or decreased clearance of triglycerides
- Increases risk of pancreatitis
- Primary vs. secondary
- Acute triglyceride lowering therapy is critical in the initial treatment of hypertriglyceridemia-induced pancreatitis
- Plasma exchange vs. insulin and heparin therapy

Hypertriglyceridemia

- Origin is often multifactorial
- Difficult management due to genetic and secondary causes and lack of evidence-based guidelines
- Primary vs. secondary
  - Dietary restriction of fat is the mainstay of management of primary hypertriglyceridemia
  - Obesity, alcohol abuse, uncontrolled diabetes, hypothyroidism, chronic renal failure, and certain drugs are also secondary factors
Hypertriglyceridemia

• High risk secondary to hypertriglyceridemia
• Acute inflammation of the pancreas
  • Diagnosed with the presence of at least two of the three following factors:
    • Abdominal pain
    • Elevation of pancreatic enzymes over 3 times the upper limit of normal
    • Radiologic evidence of acute pancreatitis
• Mortality as high as 20-25% in severe cases (Jin et al, 2018)
• Hypertriglyceridemia is a well-established cause of acute pancreatitis
  • Associated with high complication rate and poor patient outcome

Pancreatitis

• Mortality as high as 20-25% in severe cases (Jin et al, 2018)
• HYPERTRIGLYCERIDEMIA is a well-established cause of acute pancreatitis

Back to the case...

• Increasing respiratory distress and developed an increasing O2 requirement
• Decision made to intubate due to high risk of ARDS development and to assist with plasmapheresis management
• Initially tachycardia – likely due to intravascular depletion due to capillary leak syndrome; developed hypotension, did not respond to fluid boluses, required initiation of epinephrine
  • Initial echo showed estimated ejection fraction 60% (normal 55% - 70%)
• GI recommended plasmapheresis to lower severely elevated triglyceride levels

Hypertiglyceridemia and Pancreatitis

• Significant risk of pancreatitis when TG are greater than 1000 mg/dL
  • Pancreatic capillary bed ischemia due to TG-rich chylomicron sludge, ultimately leads to pancreatitis
  • If pancreatitis is suspected, hospitalization for rapid lowering of TG levels is required

Pancreatitis – Management

• Initially directed at patient stabilization
• Limited adult data suggests that aggressive fluid hydration in the first 24 hours decreases the risk of multiorgan system failure
• IV fluids boluses should be administered as needed and maintenance fluids should be infused at 1.5x maintenance
• Antiemetics
• Analgesics

Pancreatitis treatment – conservative therapy

• Aggressive IV hydration
• Initial bowel rest
• Pain control
  • Further management should be guided on illness severity of patient and may require management in an intensive care

Management – Insulin and Heparin

• Insulin
  • Insulin activates lipoprotein lipase (LPL) activity which then accelerates chylomicron degradation which then lowers triglyceride levels
  • Insulin also allows the pancreatic tissue to rest and may improve immunoparalysis via upregulating the expression of human leukocyte antigen on monocytes and decreasing cell apoptosis
  • Insulin lowers triglyceride levels by 50-75% over two to three days
• Heparin
  • Releases stored lipoprotein lipase from endothelial cells which then lowers triglyceride levels
  • Combination of insulin and heparin has been used to lower triglyceride levels with a mean decrease of 50% in triglyceride levels within 24 hours
Management – Plasmapheresis

- Rapidly removes triglycerides and chylomicrons from circulation thereby stopping further inflammation and damage to the pancreas
- Lowers lipid levels drastically within a few hours as compared to conservative therapy that can take several days
- Usually only require one session as it has been reported to lower triglyceride levels 50-80%

Plasmapheresis

- May improve outcomes by removing proinflammatory markers and cytokines which then downregulates the inflammatory process
- Multiple adult case series report the benefit of plasmapheresis in the treatment of hypertriglyceride-induced pancreatitis, however, a prospective study failed to show any mortality benefit when compared to conservative management
- Potentially due to delay in initiating plasmapheresis
- However, a different study showed no mortality benefit in early (within 36 hours) vs late (greater than 36 hours) plasmapheresis initiation

Back to the case...

- Underwent plasmapheresis – triglycerides decreased to 419
- Abdominal CT revealed pancreatic necrosis
- Extubated on HD 5 to HFNC, slowly weaned off O2
- Developed pancreatic insufficiency, required pancreatic enzymes, unable to tolerate PO feeds for some time due to large pseudocyst/stomach compression

Discharge

- Discharged home on HD #34
- Discharged home with instructions for vegetarian and low fat diet
- Home discharge medications:
  - Humalog 70/30, 20 Units before breakfast and dinner
  - Lisinopril 10 mg daily
  - Creon 24000, take 4 capsules with meals and 2 capsules with snacks
  - Pantoprazole 40 mg twice a day
  - Gabapentin 300 mg three times per day
  - Vitamin D 5000U daily
  - Pantoprazole 40 mg twice a day
  - Probiotics 1 capful twice a day
  - Melatonin 5 mg at bedtime
- Follow-up with multiple specialists – GI, endocrinology, psychology
- Discharged with instructions for wheelchair for long distances, will need accommodations for return to school
- Developed anxiety about returning to school, offered reassurance and set up outpatient follow-up appointment with child psychologist

Follow-up

- Seven months after discharge – wt 98 kg (BMI 32 kg/m²)
- Continues to have chronic health conditions with multiple subspecialists
  - Severe obesity
  - Depression
  - Chronic necrotizing pancreatitis
  - Type 2 DM
  - Pseudocyst s/p stent placement
  - Fatty liver
Mental health

- Obese teens have a higher incidence of mental health diagnoses
  - Depression
  - Anxiety
  - Poor self-esteem
- Effect of obesity on the development of depression has been shown in studies
  - Obesity is seen as an inflammatory state; inflammation has also been associated with depression

Challenges to overcoming the cycle of obesity

- Access to healthy foods
- Ability to be physically active (safety, neighborhood, safe outdoors)
- Education
- Medication use
- Sleep routines/OSA
- Sedentary activities
- Family practices

What are some barriers to care while in the hospital?

- Specialty beds
- Hoyer lifts
- Imaging machines
- Appropriate-sized equipment
  - BP cuff
  - Diapers/personal hygiene
  - Hospital gowns
  - Emergency equipment (oral airways)
  - Central line kits
  - LP needles

Medications that can lead to weight gain

- Glucocorticoids
- Diabetes medications
- First-generation anti-psychotics
- Neurologic and mood stabilizing
- First-generation antihistamines
- TCA, SSRI, SNRI, tetracyclic and MAO inhibitor antidepressants
- Progestational steroid hormones
- Beta-blocker
- Benzodiazepines

Medications for weight loss

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>(Generic/Brand)</th>
<th>Year of Initial Approval</th>
<th>Note About U.S. Approval</th>
<th>Patient Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orlistat</td>
<td>(Xenical)</td>
<td>1999</td>
<td>Approval: obesity management</td>
<td>Obese individuals ≥18 yrs</td>
</tr>
<tr>
<td>Metformin</td>
<td>(Glucophage)</td>
<td>1995</td>
<td>Off-label as antiobesity therapy</td>
<td>Adult, children</td>
</tr>
<tr>
<td>Topiramate</td>
<td>(Topamax, Trokendi XR)</td>
<td>1996</td>
<td>Approved for epilepsy, migraine prophylaxis</td>
<td>Adults, children, adolescents</td>
</tr>
<tr>
<td>Phentermine</td>
<td>(Seroquel XR)</td>
<td>1997</td>
<td>Approved for ADHD, BED</td>
<td>Adults, youth, adolescents and children (≥16 yrs)</td>
</tr>
<tr>
<td>Phentermine</td>
<td>(Oxycontin)</td>
<td>2000</td>
<td>Approved for short-term use</td>
<td>Obese individuals</td>
</tr>
<tr>
<td>Phentermine</td>
<td>(Proposed)</td>
<td>1997</td>
<td>Approved for short-term use</td>
<td>Obese individuals except ≥65 or &lt; 17 yrs</td>
</tr>
<tr>
<td>Lorcaserin</td>
<td>(Belviq)</td>
<td>2012</td>
<td>Approval: weight management</td>
<td>Adults</td>
</tr>
<tr>
<td>Naltrexone and bupropion XR</td>
<td>(Contrave)</td>
<td>2014</td>
<td>Approval: weight management</td>
<td>Adults</td>
</tr>
<tr>
<td>Phentermine and topiramate XR</td>
<td>(Qsymia)</td>
<td>2012</td>
<td>Approval: weight management</td>
<td>Adults</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>(Saxenda)</td>
<td>2010</td>
<td>Approval in 2014: weight management</td>
<td>Adults</td>
</tr>
<tr>
<td>Sibutramine</td>
<td>(Meridia)</td>
<td>1997</td>
<td>Approved for obesity indication – withdrawn</td>
<td>Obese individuals &lt;66 years</td>
</tr>
<tr>
<td>Rimonabant</td>
<td>(Zimulti)</td>
<td>None</td>
<td>Withdrawn</td>
<td>Adults</td>
</tr>
</tbody>
</table>

Orlistat

- Mechanism of action: gastrointestinal lipase inhibitor
- In a drug interaction study with normal weight young adults, orlistat did not significantly alter oral absorption of the highly fat-soluble drugs fluoxetine and simvastatin – important as these medications can be used to treat common comorbidities in obese adolescents
- GI side effects are common and poorly tolerated, may contribute to poor adherence
  - Oily stools
  - Diarrhea
  - Abdominal pain
  - Fecal spotting
- Poor absorption of certain dietary nutrients requires daily dietary supplementation that includes fat-soluble vitamins
  - Should be several hours apart from orlistat, which is dosed with meals TID
Metformin

• Off label use when used for weight management
• One study cited 3% decrease in BMI
• Tablets display low and variable drug effect
• Mechanism of action: monopronated cation that relies on active transport to cross lipid membranes (intestine, liver, kidney); hepatic uptake is essential for full pharmacologic effect of inhibition of hepatic gluconeogenesis and increased insulin sensitivity
• Typically prescribed for an on-label concurrent condition – Polycystic Ovarian Syndrome (PCOS), Diabetes, and prediabetes

Bariatric Surgery

• Roux-en-Y gastric bypass
  • Allows for weight loss
  • High rate of Diabetes type 2 remission
  • Not a practical option for many adolescents
    • Only consider in mature teenagers with access to skilled surgical centers and insurance coverage
• Reinforces importance of avoiding or slowing adolescent weight gain through lifestyle interventions
  • Physical activity
  • Meal planning – focusing on nutrition
  • Pharmacotherapy

Why is it so hard to lose weight?

• Ongoing research in the gut-brain axis, neurobiology determinants of body fat mass and the interplay between genetics, epigenetics, developmental influences, and environment
• Several key organs and peptide hormones are involved in human energy homeostasis
  • Peptide ghrelin is orexigenic – it signals from the stomach to the brain to stimulate appetite
  • Insulin signals the brain to stop feeding; also promotes nutrient uptake into muscle, liver, and fat

Why it’s so hard to lose weight and keep it off

• Adipose tissue produces hormones
  • Adipocyte hormone leptin – circulates in concentrations proportional to body fat mass
  • Intact leptin-regulated neuronal circuitry is essential for body weight and energy homeostasis
• When weight is lost:
  • Decline in leptin blood concentrations, then alters the brain’s executive function and reward aspects of eating behaviors
  • Consequently, there is both stimulation of feeding and a reduction in energy expenditure

More to come

• Leptin has a direct influence on lipid partitioning into skeletal muscle and adipocytes
  • Theorized that the relative proportion of lipids in fat deposits rather than the absolute amount of lipids may be the main determinant of metabolic risk
  • Gut peptides, neurotransmitters, cytokines, steroid hormones and enzymes also play a role in metabolic homeostasis

In conclusion...

• Obesity has a negative impact on acute and critically ill children
  • Affects pharmacologic metabolism
  • Difficulty with procedures (i.e. obscuring physical landmarks for CVL placement)
  • Redundant airway tissue, may cause difficulty with airway placement when intubating
  • Chronic inflammation associated with obesity may affect the complex pathophysiologic interaction of single or multi-organ system disease in acute and critically ill children
• May be a risk factor for higher mortality in hospitalized children with critical illnesses to include oncologic diagnoses and transplants
• Higher incidence of infection and increase hospital LOS