Transplant in the Morbidly Obese Patient

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And
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Objectives
Upon completion of the program, the participants will be able to:
1. State the potential complication risks of the morbidly obese Hematopoietic Stem Cell Transplant (HSCT) patient
2. Explain the nursing implications in the care of the Morbidly Obese HSCT patient
3. Identify the potential drug dosing modifications in the morbidly obese HSCT patient

Definition of Obesity
Obesity is a chronic disease resulting from an imbalance of energy intake and energy utilization leading to the expansion of the size and number of fat cells in adipose tissues and their distribution throughout the body. It is profoundly influenced by the environment, physical activity, psychosocial factors, and even sleep.

“Overweight and obesity are defined as abnormal or excessive fat accumulation that may impair health.”

Weiss BM et al. Trimming the fat: obesity and hematopoietic cell transplantation. BMT. 2013.
The Obesity Problem

WHO (2008)

More than 1.4 billion adults, 20 and older were overweight

Of these overweight adults, over 200 million men and nearly 800 million women were obese

Overall, more than 10% of the world's adult population was obese

8.1% of infants and toddlers have high weight for recumbent length

16.9% of 2 to 19 year olds (age adjusted) were obese

34.9% of adults aged 20 years or older were obese

Overall, no significant change from 2003-2004 through 2011-2012 in high weight for recumbent length among infants and toddlers, obesity in 2 to 19 year olds, or obesity in adults.

There was a significant decrease in obesity among 2 to 5 year old children and a significant increase in obesity among women aged 60 years and older.

WHO global estimates from 2008:

More than 1.4 billion adults, 20 and older were overweight

Of these overweight adults, over 200 million men and nearly 300 million women were obese

Overall, more than 10% of the world's adult population was obese


Measurements of Obesity

Adults: use weight and height to calculate the body mass index (BMI)

Children and adolescents. Use the CDC growth charts to determine the corresponding BMI-for-age and sex percentile.

Overweight corresponds to a BMI > 85th percentile

Obese' corresponds to a BMI > 95th percentile

Rates of obesity vary by country and ethnicity also.

For more information: https://healthyweight.cdc.gov/assessing/bmi/index.html

<table>
<thead>
<tr>
<th>DEFINITION BY WHO</th>
<th>BMI MEASURE</th>
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<tbody>
<tr>
<td>Underweight</td>
<td>&lt;18.5 kg/m²</td>
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<tr>
<td>Normal</td>
<td>18.5 to &lt;25 kg/m²</td>
</tr>
<tr>
<td>Overweight</td>
<td>≥25 to &lt;30 kg/m²</td>
</tr>
<tr>
<td>Obese'</td>
<td>≥30 kg/m²</td>
</tr>
<tr>
<td>Severely Obese</td>
<td>≥40 kg/m²</td>
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</table>

BMI

Body Mass Index (BMI) Chart for Adults

[Graph showing BMI categories: Underweight, Normal, Overweight, Obese']
Other Measurements

<table>
<thead>
<tr>
<th>Waist circumference</th>
<th>Body Shape &amp; Health Risk</th>
</tr>
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<tbody>
<tr>
<td>Truncal obesity worse</td>
<td>Pear shaped = gynoid obesity</td>
</tr>
<tr>
<td>Health risks increase</td>
<td>Osteoporosis</td>
</tr>
<tr>
<td>Waist &gt; 40 inches in men</td>
<td>Vericose veins</td>
</tr>
<tr>
<td>Waist &gt;35 inches in women</td>
<td>Cellulite</td>
</tr>
<tr>
<td>Obese = &gt;88 cm in women and 102 cm in men</td>
<td>Subcutaneous fat traps and stores dietary fat</td>
</tr>
<tr>
<td>Wait-to-hip ratio (WHR)</td>
<td>Trapped fatty acids stored as triglycerides</td>
</tr>
<tr>
<td>Distribution of both subcutaneous and visceral adipose tissue</td>
<td>Apple shaped = android obesity</td>
</tr>
<tr>
<td>Calculated by waist measurement divided by the hip measurement.</td>
<td>Visceral fat more active, causing</td>
</tr>
<tr>
<td>A WHR less than 0.8 is optimal, and a WHR greater than 0.8 indicates more truncal fat</td>
<td>Decrease insulin sensitivity</td>
</tr>
<tr>
<td></td>
<td>Increase triglycerides</td>
</tr>
<tr>
<td></td>
<td>Decrease HDL</td>
</tr>
<tr>
<td></td>
<td>Increase BP</td>
</tr>
<tr>
<td></td>
<td>Increase free fatty acid release into blood</td>
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Case Study

Diane, a 48 year old white female is admitted for a 10:10 matched-related HSCT from her sister. She has a history of AML with poor cytogenetics and is currently in remission. Reports gradual weight gain over the past 10 years. Lives in Studio City, CA. Works as an office assistant in the local grade school. Has two daughters, age 9 and 11 years old. Lives with mother who will be taking care of children while patient in hospital. 

Ht = 172 cm (67.72 inches) 
118.38 KG (260.44 lbs) 
BSA: 2.38m²
BMI = 40kg/m²
BP 135/90, P= 92, RR = 18, Temp 98.8

Activity/Exercise: “walks in the neighborhood around the block with her dog twice a day.”
Diet: “Pretty healthy; I eat pretty much an American Diet.”
No other comorbid conditions.
She had a triple lumen PICC placed just before admission in her left upper arm.
**Question 1**

Is the risk of developing specific hematologic malignancies, including those treated with HSCT elevated in the obese?

A. No, only malignancies like breast and colon cancer
B. Only multiple myeloma
C. Yes, lymphomas, leukemias, and multiple myeloma
D. Only in leukemia with additional occupational exposure to carcinogens

**Results**

**Question 1 ANSWER C**

The risk of developing specific malignancies, including several commonly treated with HSCT is frequently elevated in the obese. Many studies demonstrate increased risk for CML, CLL, non-Hodgkins and Hodgkin Lymphoma and Plasma Cell Myeloma.  


**Question 2**

Is obesity associated with greater overall and cancer-specific mortality?

A. No
B. Yes

**Results**
Question 2 ANSWER B

Among cancer patients, obesity is associated with greater overall and cancer-specific mortality.

Weiss BM et al. Trimming the fat: obesity and hematopoietic cell transplantation. BMT. 2013.

Assessing the Risk Up Front
Variation in Institutional practices:
- different measurements to define obesity
- different dosing strategies
- different calculations for obese patients.

Lack of evidence based practices

Hematopoietic Cell Transplant Co-Morbidity Index

<table>
<thead>
<tr>
<th>Comorbidities</th>
<th>HCT-CI scores</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arrhythmia</td>
<td>1</td>
</tr>
<tr>
<td>Cardiovascular comorbidity</td>
<td>1</td>
</tr>
<tr>
<td>Infections</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes or donor-induced hyperglycemia</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes-related hypoglycemia</td>
<td>1</td>
</tr>
<tr>
<td>Comorbid obesity</td>
<td>1</td>
</tr>
<tr>
<td>Infections</td>
<td>1</td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
<td>1</td>
</tr>
<tr>
<td>Right side</td>
<td>2</td>
</tr>
<tr>
<td>Renal comorbidity</td>
<td>2</td>
</tr>
<tr>
<td>Moderate pulmonary comorbidity</td>
<td>2</td>
</tr>
<tr>
<td>Prior malignancy</td>
<td>3</td>
</tr>
<tr>
<td>Heart valve disease</td>
<td>3</td>
</tr>
<tr>
<td>Moderate/severe hepatic comorbidity</td>
<td>3</td>
</tr>
<tr>
<td>Severe pulmonary comorbidity</td>
<td>3</td>
</tr>
</tbody>
</table>

(Sorror et al., Blood, 2005)
What should we do pre-transplant?

**RECOMMENDED**

Organ function, comorbidities, etc., as other Pre-transplant patients
Health care providers should address healthy behaviors up-front
- Nutrition – high protein, hypo or eucaloric
- Physical Activity
- Psychosocial Evaluation

Oncology Nutrition Evaluation and Ongoing evaluation
Even overweight or obese adults who develop a severe acute illness or experience a major traumatic event are at risk for malnutrition and frequently need and benefit from intensive nutrition intervention. **(JPEN Guidelines)**

Pre-transplant and ongoing exercise program
- Oncology/Transplant Physical Medicine/Rehabilitation Specialist
- Focus on building strength and reduction of sarcopenia.

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What should we do pre-transplant?

**NOT RECOMMENDED**

Extreme diet, weight loss prior to transplant (NIH)

Extreme exercise program

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Etiology-based malnutrition definition (JPEN, White et al)

- Nutritional Risk Identified
  - Compromised intake or loss of body mass
  - Inflammation Present? No / Yes
  - Yes: Moderate Degree
    - Stimulation-Related Malnutrition
      - (psychiatric condition, anorexia, depression, sleep disorders)
    - Chronic Disease-Related Malnutrition
      - (organ failure, cancer, stroke, heart disease)
    - Acute Disease- or Injury-Related Malnutrition
      - (severe infections, burns, burn victims, trauma)
  - No:
    - Minimal Inflammatory Response
EXERCISE IN HSCT PATIENTS

<table>
<thead>
<tr>
<th>AUTHOR &amp; YEAR</th>
<th>METHODS</th>
<th>FINDINGS</th>
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<tbody>
<tr>
<td>Morishita S. et al. SupportCare in Cancer. 2012</td>
<td>116 pts with allo hsct, body composition, handgrip, knee extensor strength, and 6 min walk test. Also fatigue, nutritional status, and health-related QoL.</td>
<td>All pts had sarcopenia prior to allo HSCT r/t low muscle strength, fatigue, and health-related QoL. Male pts may be more susceptible.</td>
</tr>
<tr>
<td>Takekijyo T. et al. Supportive Care in Cancer. 2013</td>
<td>86 pts in Japan who underwent allo SCT Pts performed exercise therapy with pts 5 days a week, starting 2 weeks before allo. Looked at body composition 6 min walk test score, and handgrip strength. Measured again 6 weeks after allo.</td>
<td>Results of 35 pts although upper extremity muscle mass and trunk muscle mass significantly decreased after allo HSCT, lower extremity muscle mass remained unchanged.</td>
</tr>
<tr>
<td>Persoon S, Kersten MJ, et al. Cancer Treatment Reviews. 2014</td>
<td>Electronic databases searched up to 2012. Included randomized controlled trials comparing exercise with usual care in which at least 75% had hematologic malignancies. 8 studies met inclusion criteria.</td>
<td>Exercise had a statistically significant moderately favorable effect on cardiorespiratory fitness, lower extremity muscle strength. Significant small positive effects were found for upper extremity muscle strength, global quality of life, and physical, emotional, and cognitive function. In conclusion, exercise seems to have beneficial effects in patients treated with SCT.</td>
</tr>
</tbody>
</table>

Question 3

Are there specific emotional aspects which might be considered in caring for an obese patient?

A. No
B. Yes

Results

Question 3 ANSWER B

A growing body of evidence suggests a close relationship with psychological components comprising mood disturbances, altered reward perception and motivation, or addictive behavior. Environmental factors, such as low socioeconomic status exert a greater impact on weight gain than genes do.
Psychosocial Aspects

Obesity:
  • If defined as a result of random energy overconsumption, it disregards lifestyle influences, genetic determinants, sociological and psychological factors.
  • A neurological disease

Socioeconomic status
  Altered reward perception and motivation

Obese Person/Patient
  Mood disturbances
  Lifestyle stressors
  Genetics
  Addictive behavior
  Altered reward perception and motivation


Question 4: Are there poorer outcomes in obese allogeneic and autologous HSCT patients?

A. For adult allogeneic
B. For pediatric patients
C. For all allogeneic and all autologous
D. 1 and 2

Results

Question 4 ANSWER D

Generally, obesity results in adverse outcomes in the allogeneic HCT setting and should be incorporated into the risk-benefit assessment in patients being considered.

Pediatric obese patients may do worse.

Autologous HCT for myeloma and lymphoma, obesity does not appear to adversely affect outcomes and should not be considered a contraindication for treatment.
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<tr>
<td>Nikoloussis E, et al. Annals of Hematology. 2010</td>
<td>Retrospective review of 125 (6 obese w/ BMI&gt;30) ALLO adult pts w/ hematologic malignancies treated before 2010 compared with normal or elevated BMIs. Median f/u of 36 months.</td>
<td>Obese pts had equivalent (no sig. diff) in overall survival and progression free survival.</td>
</tr>
<tr>
<td>Navarro WH, Aguas MA et al. Biol Blood Marrow Transplant. 2010</td>
<td>Retrospective review of CIBMTR database of adult patients; 373 AUTO w/ BMIs between 18.5-24.9, 381 MUD, 694 obese across with BMI &gt;30 between 1995 &amp; 2006. Compared underweight BMI&lt;18, normal (18-25), overweight (&gt;25-30), obese (&gt;30-34), and morbidly obese (&gt;35). Median f/u of 51 to 87 months.</td>
<td>No difference in OS between normal and obese for any patient groups. TRM and relapse risk were greater for BMI&lt;18, and relapse risk in the obese and morbidly obese groups. No differences in GVHD between groups.</td>
</tr>
<tr>
<td>Navarro WH, Loberiza JFR, et al. Blood Marrow Transplant. 2006</td>
<td>Retrospective review of 4681 pts undergoing AUTO HCT for Hodgkin or non-Hodgkins Lymphoma between 1990 &amp; 2000. Outcomes evaluated for survival, relapse, transplant-related mortality and lymphoma free survival.</td>
<td>TRM was similar among the normal, overweight, and obese groups; the underweight group had a higher risk of TRM compared with the normal BMI group. No difference in relapse between the normal and obese groups compared with the normal BMI group.</td>
</tr>
<tr>
<td>Vogel, DT, Wang, T. et al. 2011. Biology of Blood and Marrow Transplant.</td>
<td>Retrospective review of 1087 recipients of AUTO HCT of myeloma report to CIBMTR between 1995 and 2003. Categorized pts by BMI as normal, overweight, obese or severely obese.</td>
<td>TRM was similar among the normal, overweight, and obese groups; the underweight group had a higher risk of TRM compared with the normal BMI group. No difference in relapse between the normal and obese groups compared with the normal BMI group.</td>
</tr>
<tr>
<td>Costa, LJ, Micallef IN, Inwards DJ et al. 2008. British Journal Haematology.</td>
<td>Retrospective review of 80 pts in highest dose/weight quartile AUTO adult pts w/ NHL treated between 2001 and 2005 with BEAM. Median f/u of 31.4 months.</td>
<td>Obese pts had less mucositis and shorter LOS. No diff in relapse or survival was reported between groups. Dose based upon BSA based on ABW25 if TBW &gt;IBW. ABW25 = IBW +.25(TBW-IBW)</td>
</tr>
<tr>
<td>Deeg, HJ, Seidel K, et al. Bone Marrow Transplant. 1995</td>
<td>Retrospective review of 1042 adult pts (258 AUTO, 146 ALL, 77 acute and 579 pts w/ home regimen or AML between 1886 &amp; 1985 with BuCy, Cy ATO, or Cy TBI. Median f/u 156 days. Majority based on TBW but some Cutoffs based on ABW25.</td>
<td>Obese pts had less mucositis and shorter LOS. No diff in relapse or survival was reported between groups. Dose based upon BSA based on ABW25 if TBW &gt;IBW. ABW25 = IBW +.25(TBW-IBW)</td>
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Results. Pts with increased BMI had shorter time to engraftment and no difference in OS of LFS.
### NOT WORSE

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<td>Sriharkha, et al. 2009. Journal of Oncology Pharmacy Practice.</td>
<td>Retrospective review of 362 (52 obese) adult patients (max 60 yrs) Heme malign treated with multiple regimens before 2009. ALLO HCT. Only ablative regimens reviewed and actual body weights were adjusted per BMI tables to test the use of large frame weights in place of TBW in obese individuals. Median f/u of 21 to 22 yrs.</td>
<td>Conclusion: Obese pts may experience increase specific toxicities, but when viewed overall did not experience increased treatment-related or relapse-related mortality with ALLO HCT.</td>
</tr>
<tr>
<td>Sucak, GT, Suyani E et al. 2012. Int J Hematology.</td>
<td>Retrospective review of 71 adult ALLO HCT pts (51 Obese) with Heme malignancies or MDS treated between 2003 and 2008 with Allo Cb or 5AC, Cy (53) or CyC (29) numbers not reported. Dosing was on TBW for normal and underweight and based on ABW25 for overweight (BMI 25 to 29.9) and obese (BMI &gt;30).</td>
<td>Obese allo pts had similar outcomes when compared with nonobese pts with regard to mucositis, cardiotoxicity, emesis, and hyperglycemia. Nutritional status did not impact OS, PFS or 100-day TRM.</td>
</tr>
<tr>
<td>Fleming DR, Reyes MM, et al. 1997. American Journal of Medicine.</td>
<td>Retrospective review 322 ALLO (242 adults and 80 peds, 96 obese) pts with heme malignancies, aplastic anemia, or metabolic storage disease. Treated between 1983 &amp; 1995. No specified regimen.</td>
<td>Survival was 35% versus 20% (P=.0045) with a median of 262 days (nonobese) and 120 d (obese) follow-up. Relapse-related mortality was not significantly different between obese and non-obese, but survival difference was significant in adults but not in pediatric controls. Obese pts may have shorter non-relapse-related survival with allogeneic HCT.</td>
</tr>
<tr>
<td>Meloni G et al. 2001. Bone Marrow Transplant.</td>
<td>Retrospectively reviewed AML, AUTO in first CR with BuCy, based on actual body weights. BMI into 3 groups. N-54.</td>
<td>High-BMI predicts increased treatment-related toxicity and mortality. At 30 days, survival for those with BMI &gt;25 was significantly lower compared to BMI &lt;25. Infections were more common among patients with BMI &gt;25 compared to BMI &lt;25 (P=.012 and 0.021). No significant difference in OS and DFS between obese and non-obese groups (P=.012 and 0.021) for high and low BMI.</td>
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<tr>
<td>Nikolousis E, Annals of Hematology. 2010</td>
<td>United Kingdom Retrospective review of 335 NHL cleared of/ or Heme malignancies treated before 2000 compared with normal and elevated BMI. Median f/u of 36 months.</td>
<td>Obese pts had an equivalent (no sig @8) in overall survival and progression-free survival but higher infection rate in the first year after HCT (normal BMI 46 days; high and obese BMI 54 and 61 days).</td>
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<td>Tarella C., Caraciolli D., et al. Bone Marrow Transplant. 2000.</td>
<td>Italy Retrospective review of 205 adult NHL pts treated between 1990 &amp; 1997 with BEAM or HD mitoxantrone and melphalan. BMI &lt;28 compared with BMI &gt;28. Dosed on TBW with a dose adjustment for 6 or 9 pts with a BMI &gt;32. Based on TRM with a dose adjustment for 6 or 9 pts with a BMI &gt;32. 77% had BMI &lt;28, 23% BMI 28-32, 7% overall &gt;32.</td>
<td>No sig diff were in TRM between groups with a nonsignificant decrease in the BMI &gt;28 group. The risk of death (calculated OS of an overweight patient) was 3 times that of a nonobese individual. Conclusion was to exercise caution in treating overweight NHL patients with AUTO HCT as they may have lower survival.</td>
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**Author and Year**

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<tr>
<td>Fuji S, Kim S et al. 2009. <em>Biol Blood Marrow Transplant</em></td>
<td>Japan: Retrospective study from Japan Marrow Donor Program 1998-2005. Total of 20 patients received an unrelated BMT, 3837 pts available for study. Pilot study stratified by BMI.</td>
<td>Higher Pre-transplant BMI was associated with a significantly greater risk of Grade II to IV GVHD. Obesity was associated with an increased risk of infection compared with normal BMI.</td>
</tr>
<tr>
<td>Fuji S., Takano K et al. 2014. <em>Bone Marrow Transplantation</em>. Japan: Retrospective registry data including total of 12050 pts who received allo 2000-2010. Median age 45</td>
<td>Relapse higher in underweight group &amp; lower in the overweight and obese groups vs normal group. GVHD risk higher in the overweight group vs normal group. Risk of NRM was higher in the underweight and obese group vs normal group. Probability of OS was lower in the underweight group compared with the normal group. Obesity was a risk factor for NRM.</td>
<td></td>
</tr>
<tr>
<td>Barker CC, et al. <em>Biology of Blood and Marrow Transplant</em>. 2011.</td>
<td>Retrospectively studied the effect of weight by age-adjusted BMI percentile in 1,281 PEDS pts (2-19) with severe AA who underwent ALLO HSCT 1990-2011. Divided into 5 weight groups: underweight, risk of underweight, normal BMI, risk of overweight, and overweight.</td>
<td>Higher mortality among overweight children (60% adjusted for age). Weight at HSCT did not increase the adjusted risk of grade II-IV GVHD (15% for normal weight and 24% for overweight, not statistically significant). The 1 yr OS 60% and 2 yr OS 59% for overweight children, compared with &gt;70% in children with lower BMI at both time points (P&lt;.001).</td>
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</tbody>
</table>

**Conclusion on HSCT Outcomes with Obese Patients**

Most were retrospective studies.
Differing definitions of obesity.
Adults and children.
Diff preparative regimens.
Heterogeneous patient populations in most.
Generally, obesity results in adverse outcomes in the allogeneic HCT setting and should be incorporated into the risk-benefit assessment in patients being considered.
Pediatric obese patients may do worse.
Autologous HCT for myeloma and lymphoma, obesity does not appear to adversely affect outcomes and should not be considered a contraindication for treatment.
How Do Obese pts differ in terms of dosage of chemo and TBI?

Doses are given to midline
- Separation is more but
- Doses prescribed are the same
Slightly higher dose to the skin and fat
Longer to treat
Possibly more fatigue and nausea*

*TBI contributes to pituitary and gonadal dysfunction; cranial irradiation leads to muscle loss and body fat in children.

What are the nursing care considerations that need to be taken into account as you formulate your plan of care for Diane?

Nursing Care Considerations Upon admission

Physical mobility and safety
- General versus Bariatric bed (possible trapeze), bariatric commode, etc.
- Fall precautions
- PT on board with a mobility plan
VTE prophylaxis
Nutrition

Prevention of infection
- Skin Care
- Oral Care
Emotional support/coping
Potential for sleep apnea with narcotics
Referrals
- Registered Dietitian
- Physical Therapy
- Social Work
**Conditioning**

Diane received Busulfan/Cytoxan conditioning

For Immunosuppression:
- Cyclosporine 2.5 mg/kg IV every 12 hours over 2 hours (starting Day -1)
- Methotrexate 5 mg/m^2 IVP Day +1, Day +3, Day +6, and Day +11

She had mild nausea and vomiting, but otherwise tolerated it well.

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**Infusion and dosing**

Diane received peripheral stem cells:
- $6.5 \times 10^6$ kg CD34
- ABO Compatible (Both O+)

**Question 5:** Are there guidelines/standard dosing of stem cells that apply to the morbidly obese HSCT patient?

A. Yes
B. No

**Results**

**Question 5 ANSWER: B**

The dose of CD34+ cells infused varies widely among centers.

No specific guidelines for obese patients.

Several studies indicate:
- Minimum dose of $2 \times 10^6$ CD34+/kg
- A dose of $5 \times 10^6$ CD34+ or greater ensures engraftment
**Day +1 to Day +16**

Diane had an expected course:
- Neutropenia and fever → antibiotics started
- Thrombocytopenia – severe nosebleed requiring packing by ENT until it resolved
- Anemia

Additionally, she had:
- Grade 3 Mucositis requiring Hydromorphone PCA (bolus only) – duration short so TPN was not started.
- She was at times incontinent of urine and stool, requiring frequent cleaning and turning as she was too weak to get to the commode with staff. She was bedridden for 5 days during her nadir.
- Fluid overload at times, requiring PRN furosemide, electrolyte replacement

She became withdrawn at times and didn’t want to participate in her care, stating “Just leave me alone… I’ll do my mouth care later… give me a minute….!”

<table>
<thead>
<tr>
<th>What should be considered in her care at this point?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monitoring for infection and sepsis – Vital signs at least every 4 hours</td>
</tr>
<tr>
<td>Increased risk of apnea – continuous pulse Ox</td>
</tr>
<tr>
<td>Atelectasis – incentive spirometry</td>
</tr>
<tr>
<td>Skin care</td>
</tr>
<tr>
<td>Cleaning of skin folds</td>
</tr>
<tr>
<td>Assistance with oral care/rinses</td>
</tr>
<tr>
<td>Rectal bag?</td>
</tr>
<tr>
<td>Accurate Intake and Output</td>
</tr>
<tr>
<td>Foley versus no foley</td>
</tr>
<tr>
<td>Accurate bed weights</td>
</tr>
</tbody>
</table>

Nutrition
- Protein dense diet vs. TPN
- Close follow-up by Dietician

Immobility
- Preserving function and maximizing mobility as is safe

Emotional Support
- Careful following of labs
- Liver enzymes
- Glucose

**Diane started to Engraft**

Day +17: started to recover her blood counts
Her mucositis resolved and PCA was tapered off
On day +18
- Mild macular-papular rash on the hands and forearms as well as upper thighs
- Presumed GVHD
- Treatment: Methylprednisolone 1 mg/kg IV Q 12 hours
- During this time she did have glucose intolerance Transitioned to oral medications
Diane started to Engraft

- The rash resolved
- Able to get out of bed with 1 person assistance to the bedside commode and chair.
- Appetite was poor
  - Able to eat 30 to 50% of her meals
  - Kept liquids down.
- Because of her poor mobility, she was discharged to an in-patient Rehabilitation Center for two weeks.

SURVIVORSHIP STUDIES

<table>
<thead>
<tr>
<th>Author &amp; Year</th>
<th>Methods</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chow EJ, et al. Journal of Clinical Oncology. 2014.</td>
<td>Compared HCT survivors &gt; 1 year (1970-2010; N=3833). Surveyed from 2010 to 2011 on smoking, diet, recreational physical activity. Responses for HCT were compared with a matched general population sample (National Health and Nutrition Examination Survey NHANES2005-2006).</td>
<td>HCT survivors (median age 55.9 years) had higher rates of cardiomyopathy, stroke, dyslipidemia, and diabetes. Prevalence of hypertension was similar and survivors were less likely to have ischemic heart disease. Among HCT survivors, hypertension, dyslipidemia, and diabetes were independent risk for ischemic heart disease and cardiomyopathy and smoking was associated with ischemic heart disease and diabetes. Obesity was a risk factor for post-transplantation hypertension, dyslipidemia, and diabetes (P&lt;.001). Healtheir lifestyle characterstics among HCT survivors attenuated risk of all CV conditions assessed.</td>
</tr>
<tr>
<td>Baker KS, et al. Blood. 2007.</td>
<td>Self-reported DM, HTN, CV disease in 1089 HCT survivors (underwent SCT 1974-1998) at least 2 yrs and not on immunosuppressants compared with 383 sibling controls. Mean for 8.6 years and mean age 39.3 years.</td>
<td>HCT survivors more likely to report CM and HTN as compared to siblings. ALLOGraft more likely to develop HTN than autologous pts. TBI was associated with increased risk of DM. HCT survivors have a higher age and BMI-adjusted risk of DM and HTN, potentially leading to a higher than expected risk of CV events with age.</td>
</tr>
</tbody>
</table>

Take-Aways:

- Every interaction/moment Teachable
  - Supportive
- Planning for lifestyle changes are necessary
  - Before transplant
  - During transplant
  - Survivorship
- Higher-acuity nursing care is needed

Drug therapy –please stay tuned – pharmacy on deck....
Pharmacy Management of the Obese Patient

Pharmacy considerations in Diane’s care
- How do we dose her preparative regimen?
- Are there differences in her supportive care medication selection and dosing?
- What if she has had bariatric surgery?

How do we measure the patient?
- Ideal Body weight (IBW)
- Total body weight (TBW)
- Adjusted body weight (ABW)
  - $ABW = IBW + \%(TBW-IBW)$
  - 25% (ABW25), 40% (ABW40), 50% (ABW50) or other adjustment
- BSA based on TBW vs IBW or ABW
  - No preferred BSA formula

Bubelio et al. BMJ 2014;36:00-16
**History of IBW**
- Historical data comparing relative mortality of different height-weight combinations
- 1970s: Devine formula developed

**What is Ideal Body Weight?**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Equation</th>
</tr>
</thead>
</table>
| Devine (1974)¹ | men: \(50 \text{ kg} + 2.3 \text{ kg/m} \text{height} \text{ over} \ 5 \text{ feet}\)  
| | women: \(45.5 \text{ kg} + 2.3 \text{ kg/m} \text{height} \text{ over} \ 5 \text{ feet}\) |
| Robinson et al. (1983)² | men: \(52 \text{ kg} + 1.9 \text{ kg/m} \text{height} \text{ over} \ 5 \text{ feet}\)  
| | women: \(49 \text{ kg} + 1.7 \text{ kg/m} \text{height} \text{ over} \ 5 \text{ feet}\) |
| Miller et al. (1983)³ | men: \(56.2 \text{ kg} + 1.41 \text{ kg/m} \text{height} \text{ over} \ 5 \text{ feet}\)  
| | women: \(53.1 \text{ kg} + 1.36 \text{ kg/m} \text{height} \text{ over} \ 5 \text{ feet}\) |

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**Obesity recommendations for Preparative Regimens in the obese individual**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alemtuzumab</td>
<td>Flat dose (Adults)</td>
</tr>
<tr>
<td>Buzonil</td>
<td>Adult ABW25 or BSA based on TBW with PK monitoring for &gt; 12 mg/kg PO equivalent. Pediatrics on TBW with monitoring</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>BSA based on TBW (Adults)</td>
</tr>
<tr>
<td>Carmustine</td>
<td>BSA based on TBW unless &gt;120% IBW then BSA based on ABW25 (Adults)</td>
</tr>
<tr>
<td>Clofarabine</td>
<td>BSA based on TBW (Adults)</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>Dose on the lesser of TBW or IBW for CY200</td>
</tr>
<tr>
<td></td>
<td>Cy120: dose on IBW (Adults) or TBW until &gt; 120% IBW then ABW25 (Adults)</td>
</tr>
<tr>
<td>Carmustine</td>
<td>BSA based on TBW (Adults)</td>
</tr>
<tr>
<td>Clofarabine</td>
<td>BSA based on TBW (Adults)</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>Adults use ABW25 for mg/kg dosing or TBW for BSA based dosing</td>
</tr>
</tbody>
</table>

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**Obesity recommendations for Preparative Regimens in the obese individual**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fludarabine</td>
<td>BSA based on TBW (Adults)</td>
</tr>
<tr>
<td>Melphalan</td>
<td>BSA based on TBW (Adults)</td>
</tr>
<tr>
<td>Thiotepa</td>
<td>BSA based on TBW unless &gt;120% IBW then BSA based on ABW40 (Adults)</td>
</tr>
<tr>
<td>Anti-thymocyte globulin - equine</td>
<td>Mg/kg based on TBW - Adults and Pediatrics</td>
</tr>
<tr>
<td>Anti-thymocyte globulin - rabbit</td>
<td>Mg/kg based on TBW - Adults and Pediatrics</td>
</tr>
</tbody>
</table>

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Preparative regimen

- Busulfan ABW25 dosing
- Cyclophosphamide IBW dosing

- 67.7 inches tall
- IBW = 45.5 + 7.7(2.3) = 63.2 kg
- ABW25 = 63.2 + 0.25 (118.4 – 63.2) = 77

Busulfan dosing

- Options
  - Oral
    - 1 mg/kg PO Q 6 hrs dose = 78 mg x 16 doses
  - Intravenous
    - 0.8 mg/kg (62 mg) IV every 6 hours
    - 3.2 mg/kg (246 mg) once daily
    - 130 mg/m2 (309 mg) once daily
- Blood draws performed for pharmacokinetic targeting

Pharmacokinetic targeting

- Drawn with first dose or possibly with a test dose prior to beginning the preparative regimen
- Samples used to create a graph of the patients absorption and clearance profile
- Varies widely by individual
Pharmacokinetic targeting

- Allows personalization of the patients drug exposure
- Too high and we see dose limiting and potentially lethal toxicities
  - Sinusoidal Obstruction Syndrome
  - Mucositis
  - Pneumonitis
- Too low
  - Rapid relapse
  - Non-engraftment

Example Target AUC
- AML 3800-5400 micromol*min/day
- CML 4700-6000 micromol*min/day

Cyclophosphamide Dose

- 60 mg/kg/day based on IBW
- 3792 mg IV daily x 2 days
  - Equal dose of mesna given each day for bladder protection
- Provides
  - Adequate disease control
  - Immunosuppression
  - Dose to stay within known organ tolerance for the medication

Challenging patient types

- The large fit individual
- The very obese – BMI >50
- Children (0-15 years old)
- The underweight patient
Supportive Care Medication changes

- Does the medicine have pharmacokinetic monitoring?
  - Tacrolimus, cyclosporine
  - Voriconazole, posaconazole
  - Vancomycin, tobramycin
- Adjusted based on levels
- What do we need to think about if they do not?

Physiological Changes of Obesity

- More fat, less lean tissue per pound of body weight
- Increased
  - Blood volume (~14%)
  - Cardiac output (15-20%)
  - Liver blood flow
- Low-grade inflammation → nonalcoholic steatohepatitis (NASH)


Volume of Distribution
**Volume of Distribution (Vd) Review**

<table>
<thead>
<tr>
<th>Total water:</th>
<th>60% (50-80%)</th>
<th>42 L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracellular volume:</td>
<td>40%</td>
<td>28 L</td>
</tr>
<tr>
<td>Extracellular volume:</td>
<td>20%</td>
<td>14 L</td>
</tr>
<tr>
<td>Plasma volume:</td>
<td>4%</td>
<td>3 L</td>
</tr>
<tr>
<td>Blood volume:</td>
<td>8%</td>
<td>5.6 L</td>
</tr>
</tbody>
</table>

- Small Vd (<10 L), confined to intravascular fluid
  - Warfarin, aspirin, gentamicin, furosemide
- Medium Vd (20-50 L)
  - Vancomycin, phenytoin
- Large Vd (>50 L)
  - Nitroglycerin, digoxin, morphine, lidocaine


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**Factors affecting Vd in Obesity**

- Excess body weight (EBW) ~30% water
  - Lead to a higher volume of distribution
  - Lipophilic drugs = higher Vd
    - TBW dosing
  - Hydrophilic drugs = higher Vd, but to a lesser degree
    - IBW or ABW dosing

Increase blood volume
Poorer peripheral perfusion


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**Vd in PK Studies**

- Uncorrected for weight
- Using Vd corrected for weight is more meaningful
  - Vd/TBW
    - Describes how a drug distributes into excess body weight
    - Lipophilic
    - Similar Vd/TBW for obese and non-obese individuals
    - Dose should be based on TBW
  - Hydrophilic
    - Lower Vd/TBW in obese
    - IBW or LBW dose may be warranted

Hepatic Metabolism

Phase I Metabolism
CYP enzymes → oxidation, reduction, hydrolysis
CYP3A4
- 50% of all drugs are 3A4 metabolized
- Decreased clearance in obesity
Other CYP enzymes
- 2E1, 1A2, 2C9, 2C19, 2D6
- Increased clearance in obesity


Phase II Metabolism
Uridine diphosphate glucouronosyltransferase (UGT)
- Expressed in liver, visceral and adipose tissue
- IV Acetaminophen
  - N = 17 and 25
  - Study design: single dose PK
  - Obese vs. non-obese
  - Higher absolute clearance
    - 484 vs. 323 ml/min p<0.05
    - 312 vs. 227 ml/min p<0.05

Phase II Metabolism
- Lorazepam
  - N = 28
  - Study design: single dose PK
  - 102 vs. 63 ml/min p<0.005
  - Increased ratio of metabolite to drug in urine


What are the general trends seen with phase I and II metabolism in obesity?

A. Decreased clearance of CYP3A4 metabolism
B. Increased clearance of most other CYPs
C. Increased clearance UGT-metabolized drugs
D. All of the above

Results
Liver Blood Flow

High extraction drugs
- Rapidly metabolized, sensitive to liver blood flow
- Insensitive to enzyme changes
- Increased total clearance compared to non-obese
  - Propofol, sufentanil, paclitaxel studies
  - Trend toward difference, but not significant

Renal Clearance

Increased GFR

- Renal vasodilation of afferent arterioles, increased hydrostatic pressure, hypertrophy of nephrons
- Not proportional to increase in weight
- $^{[125]}$I Na iothalomate clearance to reflect GFR
- N=14, mean BMI 46 vs. 22 kg/m²
- 116 vs. 93.5 mL/min in non-obese patients, not significant

When considering other supportive care drugs?

- What is the intended affect?
- What are the potential side effects
- What route will you use to deliver it?
- What is the intended use vs the likely distribution to the site of action?
- Is there a known target blood level?

Other supportive care drugs?

- Antibiotics – may need larger doses (penicillins, cephalosporins especially)
- Antiemetics - standard doses used
- Analgesics – standard doses
  - Be aware if patient has sleep apnea if opioids
- Antifungals – standard doses
- Antivirals – Standard dosing
  - Consider ideal or adjusted body weight for acyclovir
- Acid suppressing agents, antidiarrheals, antihypertensives, heart rate control agents all start at standard doses
What about patients who have had Bariatric surgery

- Issues
  - No literature w/ HSCT
  - There are altered pharmacokinetics for orally administered drugs
  - Bypassing the stomach and a majority of the small intestine results in decreases surface area for absorption...
  - Vitamin deficiencies


Laparoscopic Adjustable Gastric Band

Adjustable silicone band with reservoir port
Inject or remove saline via port to adjust
Promotes early satiety and slows transit
Restrictive

Sleeve Gastrectomy

Greater curvature of stomach resected
~25% of original volume remains as “sleeve”
No longer considered investigational as of 2011
Restrictive
Roux-en-Y Gastric Bypass

15-30mL pouch created from stomach
Small intestine cut after duodenum and attached to pouch
Remainder of stomach and duodenum reattached to small intestine
Restrictive and Malabsorptive

Bariatric Surgery Diet

1. Liquids (1-2 days)
   - 2-3 oz at a time
   - Broths, milk, strained soups
2. Pureed Food (2-4 weeks)
   - Small servings, eat slowly
   - Lean meats, fruits/vegetables, yogurt
3. Soft Food (8 weeks)
   - Able to mash with fork, protein rich
   - Drink 30 minutes after eating
4. Solid Food
   - ½ cup servings several times per day
   - Avoid tough, crunchy, or stringy foods and seeds/nuts

Vitamin and Mineral Absorption Sites

<table>
<thead>
<tr>
<th>Vitamin/Mineral</th>
<th>Stomach</th>
<th>Duodenum</th>
<th>Jejunum</th>
<th>Ileum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intrinsic factor (For B12)</td>
<td>Calcium</td>
<td>Calcium</td>
<td>Vit C</td>
<td></td>
</tr>
<tr>
<td>Iron</td>
<td>Iron</td>
<td>B9, 12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vit A, D, E, K</td>
<td>Vit A, D, E, K</td>
<td>Vit D, K</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phosphorus</td>
<td>Phosphorus</td>
<td>Magnesium</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Magnesium</td>
<td>Magnesium</td>
<td>Bile salts/ acids</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B1, 2, 3, 7, 9</td>
<td>B1, 2, 3, 6, 7, 9</td>
<td></td>
<td>Vit C</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Zinc</td>
<td></td>
<td>Amino Acids</td>
</tr>
</tbody>
</table>
Minimal Daily Nutritional Supplementation

- Adult multivitamin including B-vitamins
  - Crushed tablet twice daily
- Calcium (1200 mg to 1500 mg)
  - Citrate preferred, separate from Iron, crushed tablet
- Vitamin D (≥3000 IU)
  - Titrated to levels >30 ng/ml, crushed tablet
- Vitamin B₂
  - Injection, sublingual, or crushed tablet
  - 1000 mcg IM monthly or 350-500 mcg PO daily
- Iron (45 mg to 60 mg)
  - May need extra vitamin C to increase absorption
  - Liquid or IR tablet

Common Medications (3-6 months post procedure)

- No specific guideline recommended medications or dosing – patient specific
- Whole tablets larger than an M&M risk lodging in surgery sites
  - Can re-open sutures or block passage
- Liquid is the preferred dosage form
- Tablets
  - Crush all tablets
  - Ensure immediate release form tablets
- Capsules
  - Open and sprinkle on sugar-free yogurt

Common Medications

- Bowel Care
  - Senna-Docusate 8.6-50 mg/5mL syrup – 5 mL twice daily PRN
  - Polyethylene glycol 3350 powder – 17 grams once daily PRN
  - Hold for loose stools
- Nausea Prevention
  - Ondansetron 4 mg ODT tablet every 12 hours PRN
  - Prochlorperazine 10 mg tablet three times daily PRN
- Marginal Ulcer Prevention
  - Omeprazole 20 mg DR/EC capsule once daily
  - Continue for 3 months
- DVT Prophylaxis
  - Continue after discharge if high risk (i.e. previous DVT)