Transplant in the Morbidly Obese Patient

Sandra Rome, RN, MN, AOCN, CNS
Hematology/Oncology Blood and Marrow Transplant Program
Cedars-Sinai Medical Center
And
Joseph Bubalo PharmD, BCPS, BCOP
Oncology Clinical Pharmacy Specialist
Oregon Health and Science University Hospital

1.15.15

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.

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

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

The World Health Organization. Updated August 2014. http://ww.who.int/mediacentre/factsheets/fs311/en/

The Obesity Problem

WHO (2008)

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 worlds' adult population was obese

The World Health Organization. Updated August 2014. http://www.who.int/mediacentre/factsheets/fs311/en/

NHANES (2011-2012)

N= 9120

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.

Ogden CL et al. Prevalence of Childhood and Adult Obesity in the United States, 2011-2012. *NEJM*. 2014.

Measurements of Obesity

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

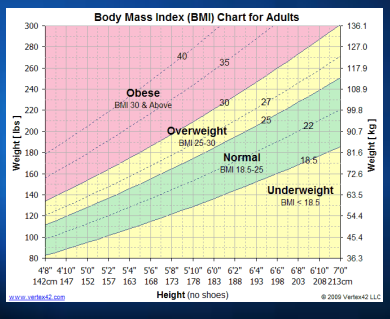
Children and adolescents.

- Use the CDC growth charts to determine the corresponding BMI-for-age and sex percentile.
- Overweight corresponds to a BMI $\geq$ 85th percentile
- Obese' corresponds to a bMI $\geq$ 95th percentile.
- Rates of obesity vary by country and ethnicity also.

For more information: /healthyweight/assessing/bmi/index.html

DEFINITION BY WHO	BMI MEASURE
Underweight	<18.5 kg/m^2
Normal	18.5 to <25 kg/m^2
Overweight	$\geq$25 to <30 kg/m^2
Obese	$\geq$30 to 40 kg/m^2
Severely Obese	$\geq$40 kg/m^2

BMI



Other Measurements

Waist circumference
- Truncal obesity worse
- Health risks increase↑waist
  - > 40 inches in men
  - >35 inches in women.
- Obese = >88 cm in women and 102 cm in men

Wait-to-hip ratio (WHR)
- Distribution of both subcutaneous and visceral adipose tissue
- Calculated by waist measurement divided by the hip measurement.
- A WHR less than 0.8 is optimal, and a WHR greater than 0.8 indicates more truncal fat

Body Shape & Health Risk
- Pear-shaped = gynoid obesity
  - Osteoporosis
  - Vericose veins
  - Cellulite
  - Subcutaneous fat traps and stores dietary fat
  - Trapped fatty acids stored as triglycerides
- Apple shaped = android obesity (worse)
  - Heart disease
  - DM
  - Breast and endometrial cancer
  - Visceral fat more active, causing
    - Decrease insulin sensitivity
    - Increase triglycerides
    - Decrease HDL
    - Increase BP
    - Increase free fatty acid release into blood

Daniels, J Nursing Management: Obesity. In: Lewis SL, et al. *Medical Surgical Nursing 2 ed*. 2014. St. Louis, Elsevier.

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: 2.38m^2

BMI = 40kg/m^2

BP 135/90, P= 92, RR = 18, Temp 98.8

Case Study

Physical exam unremarkable; she walks with a steady gait in spite of her obese body habitus.

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.

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

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

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

Hematopoietic Cell Transplant Co-Morbidity Index

Comorbidities	HCT-CI scores
Arrhythmia	1
Cardiovascular comorbidity	1
Inflammatory bowel disease	1
Diabetes or steroid induced hyperglycemia	1
Cerebrovascular disease	1
Psychiatric disorder	1
Mild hepatic comorbidity	1
Obesity	1
Infection	1
Rheumatologic comorbidity	2
Peptic ulcer	2
Renal comorbidity	2
Moderate pulmonary comorbidity	2
Prior malignancy	3
Heart Valve disease	3
Moderate/severe hepatic comorbidity	3
Severe pulmonary comorbidity	3

(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.

References:
Martin-Salces M, et al. Nutritional recommendations in hematopoietic stem cell transplantation. Nutrition. 2008;24:769-775.
Choban P, Dickerson R, Malone A, et al. A.S.P.E.N. Clinical Guidelines: Nutrition Support of Hospitalized Adult Patients with Obesity. 2013. Journal of Parenteral and Enteral Nutrition. 37:714. (ASPEN = American Society for Parenteral and Enteral Nutrition)

What should we do pre-transplant?

NOT RECOMMENDED

Extreme diet, weight loss prior to transplant (NIH)

Extreme exercise program

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

EXERCISE IN HSCT PATIENTS

AUTHOR & YEAR	METHODS	FINDINGS
Morishita S. et al. *SupportCare in Cancer*. 2012	I164 pts with allo hsct, body composition, handgrip, knee extensor strength, and 6 min walk test. Also fatigue, nutritional status, and health related QOL	83 pts had **sarcopenia prior to allo** HSCT r/t low muscle strength, fatigue, and health-related QOL. Male pts may be more susceptible.
Takekiyo T, et al. *Supportive Care in Cancer*. 2014.	86 pts in Japan who underwent ALLO SCT PT performed **exercise therapy** with pts 5 days a week, starting 2 weeks before ALLO. Looked at body composition 6 min walk test scores, and handgrip strength. Measured again 6 weeks after allo.	Results of 35 pts: although upper extremity muscle mass and trunk muscle mass significantly decreased after ALLO HSCT, **lower extremity muscle mass remained unchanged.**
Persoon S, Kersten MJ, et al. Cancer Treatment Reviews 2013.	**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.	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.**

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

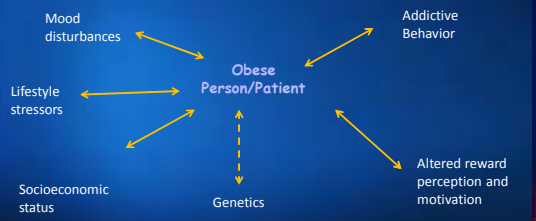
A growing body of evidence suggests a close relationship with psychological components comprising mood disturbances, altered reward perception and motivation, or addictive behavior.

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 neurobiological disease



Jauch-Chara K, Oltmanns, KM. Obesity – A neuropsychological disease? Systematic review and neuropsychological model. Progress in Neurobiology. 2014. 114:84-101.

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.

NOT WORSE

Author & Year	Methods	Findings
Nikolousis E, et al. *Annals of Hematology.* 2010.	In United Kingdom: Retrospective review of 325 (46 obese w/ BMT>30)) **ALLO** adult pts w/ hematologic malignances treated before 2010 compared with normal or elevated BMT. Median f/u of 24 months.	Obese pts had an equivalent (no sig dif) in overall survival and progression free survival.
Navarro WH, Agovi MA et al. *Biol Blood Marrow Transplant.* 2010	Retrospective review of CIBMTR database of adult patients; 373 **AUTO** with 85 obese, 2041 **MRD**, 1801 **MUD**, **654 obese** overall with AML between 1995 & 2004. Compared underweight BMI <18, normal (18-25), overweight (>25-30), obese (>30-34), and morbidly obese (≥35). Median f/u of 51 to 87 months.	No difference in OS between normal and obese for any patient groups. TRM and relapse risk great for BMI <18, and relapse sig less in the obese and morbidly obese groups. No differences in GVHD between groups
Hadjibabaie M, Tabeefar H, limoghaddam K et al. 2012. *Clinical Transplant.*	Retrospective review of 192 MRD **ALLO** adults (61 obese) with acute leukemia treated with multiple regimens between 2006-2009. Median f/u of 15 months. Chemo was based on TBW and the primary regimen was BuCy.	Obese pts have equivalent TRM and survival to those with normal weight patients and may have shorter time to engraftment.

NOT WORSE

Author & Year	Methods	Findings
Navarro WH, Loberiza JFR, et al. 2006. *Biol Blood Marrow Transplant.*	Retrospective review of 4681 pt undergoing **AUTO** HSCT for Hodgkin or non-Hodgkins Lymphoma between 1990 & 2000. Outcomes evaluated survival, relase, transplant-related mortality and lymphoma free survival.	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 difs in relapse were noted. Overall mortality was higher in underweight group and lower in the overweight and obese groups compared with the normal BMI group.
Vogl, DT, Wang, T. et al. 2011. *Biology of Blood and Marrow Transplant.*	Retrospective review of 1087 recipients of **AUTO** HCT of myeloma report to CIBMTR between 1995 and 2003. Categorized pts by BMT as normal, overweight, obese or severely obese.	There was no overall effect of BMI on progression-free survival, overall survival, and progression or nonrelapse mortality.

NOT WORSE

Author & Year	Methods	Findings
Costa, LJ, Micalleff IN, Inwards DJ et al. 2008. *British Journal Haematology.*	Retrospective review of 80 pts (19 in highest dose/weight quartile) **AUTO** adult pts with NHL treated between 2001 and 2005 with BEAM. Median f/u of 31.4 months.	Obese pts had less mucositis and shorter LOS. No dif in relapse or survival was reported between groups. Dose based upon BSA based on ABW25 if TBW >IBW. ABW25 = IBSW +.25(TBW-IBW)
Deeg, HJ, Seidel K, et al. 1995. *Bone Marrow Transplant.*	Retrospective review of 1662 **adult** pts (258 **AUTO**, 1404 **ALLO**, 77 obese) and 576 **peds** (79 **AUTO**, 497 **ALLO**, 13 obese) pts w/ heme maligs or AA tx between 1985 & 1992 with Bu Cy, Cy ATG, or Cy TBI. Median f/u 150 days. Majority based on TBW but some Cytoxan based on ABW50.	Results. Pts with increased BMI had shorter time to engraftment and no difference in OS of LFS.

NOT WORSE

Author & Year	Methods	Findings
Sriharksha, et al. 2009. *Journal of Oncology Pharmacy Practice.*	Retrospective review of 262 (52 obese) adult patients (max 60 yrs) Heme maligs treated with multiple regimens before 2009. **ALLO HSCT.** Only ablative regimens reviewed and actual body weights were adjusted per IBW tables to test the use of large frame weight in place of TBW in obese individuals. Median f/u of 11 to 23 mo.	Conclusion: Obese pts may experience increase specific toxicities, but when viewed overall did not experience increased treatment-related or relapse-related mortality with ALLO HSCT.
Sucak, GT, Suyani E et al. 2012. *Int J. Hematology.*	Retrospective review of 71 adult **ALLO** HSCT pts (11 Obese) with heme malignancies or MDS treated between 2003 and 2009 with Bu(12.8 or 16) cy (120) or CyBu(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≥30).	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.

WORSE

Author & Year	Methods	Findings
Fleming DR, Rayens MK, et al. 1997. *American Journal of Medicine.*	Retrospective review 322 ALLO (242 adults and 80 peds, 91 obese) pts with heme malignancies, aplastic anemia, or metabolic storage disease. Treated between 1983 & 1995 with unreported chemo regimens.	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 and controls. Conclusion: Obese adults but not peds may have shorter non-relapse-related survival with allogeneic HCT.
Meloni G et al. 2001. *Bone Marrow Transplant.*	Retrospectively reviewed AML, AUTO in first CR with BuCy, based on actual body weight. BMI into 3 groups. N-54.	High BMI predicts increase treatment-related toxicity and mortality. 30 pts currently alive in continuous CR, after a median f/u of 76.5 months, statistically sign differences in OS and DFS were detected between obese and non-obese groups (P=0.012 and 0.021); marked increase in infections in obese

WORSE

Author & Year	Methods	Findings
Nikolousis E, *Annals of Hematology.* 2010	United Kingdom: Retrospective review of 325 (46 obese w/ BMT>30) **ALLO** adult pts w/ heme malignances treated before 2010 compared with normal or elevated BMT. Median f/u of 24 months.	Obese pts had an equivalent (no sig dif) in overall survival and progression free survival but higher infection rates (P=0.03) and more inpatient days in the first year after HCT (normal BMI 46 days; high and obese BMI 54 and 61 days)
Tarella C., Caracciolo D., et al. *Bone Marrow Transplant.* 2000.	Italy:Retrospective review of 121 (28 obese) adult **AUTO** NHL pts treated between 1990 & 1997 with BEAM or HD mitoxantrone and melphalan. BMI <28 compared with BMI ≥28. Dosed on TBW with a dose adjustment for 6 or 9 pts with a BMI ≥32. 77% had BMI <28, 23% had BMI ≥ 28, 7% overall ≥32.	No sig dif seen in RRT between groups with a nonsignificant decrease in the BMI ≥28 group. The risk of death (reduced OS) of an overweight adult was 2.9 times that of a nonoverweight individual. Conclusion was to exercise caution in treating overweight NHL patients with AUTO HSCT as they may have lower survival.

WORSE

Author and Year	Methods	Findings
Fuji S, Kim S et al. 2009. *Biol Blood Marrow Transplant*	Japan: Retrospective study from Japan Marrow Donor Program 1998-2005. Total of 3935 pts received an unrelated BMT, 3837 pts available for study. Pts were stratified by BMI	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.
Fuji S., Takano K et al. 2014. *Bone Marrow Transplantation*.	Japan: Retrospective registry data including total of 12050 pts who received allo 2000-2010. Median age 45	Relapse higher in underweight group & lower in the overweight and obese groups vs the 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. The probability of OS was lower in the underweight group compared with the normal group. Obesity was a risk factor for NRM.

WORSE

Author and Year	Methods	Findings
Barker CC, et al. *Biology of Blood and Marrow Transplant*. 2011.	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 1990-2. Divided into 5 weight groups: underweight, risk of underweight, normal BMI, risk of overweight and overweight.	Higher mortality among overweight children (>95% adjusted for age). Weight at HSCT did not increase the adjusted risk of grade III-IV GVHD (15/5 for normal weight and 24% for overweight, not statistically significiant). The 1 yr OS 60% and 2 yr OS 59 for overweight children, compared with >70% in children with lower BMI at both time points (P<.001).

Conclusion on HSCT Outcomes with Obese Patients

Most were retrospective studies.

Differing definitions of obesity.

Adults and children.

Diff preparative regimens.

Heterogeneic 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.

*Communication with Behrooz Hakimian, MD, Radiation Oncology, CSMC (November 21, 2014)

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.

Infusion and dosing

Diane received peripheral stem cells:

- 6.5 x 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 2x10^6 CD34$^+$/kg
- A dose of 5x10^6 CD34$^+$ or great ensures engraftment

Ezzone S. *Hematopoietic Stem Cell Transplantation*. ONS. 2013.

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.
- Incontinence left her skin wet and macerated, requiring frequent cleaning
- 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….!"

What should be considered in her care at this point?

Monitoring for infection and sepsis – Vital signs at least every 4 hours

Increased risk of apnea – continuous pulse Ox

Atelectasis – incentive spirometry

Skin care

- Cleaning of skin folds
- Assistance with oral care/rinses
- Rectal bag?

Accurate Intake and Output

- Foley versus no foley

Accurate bed weights

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

Author & Year	Methods	Findings
Chow EJ, et al. *Journal of Clinical Oncology*. 2014.	Compared HSCT survivors > 1 year (tx 1970-2010; N=3833). Surveyed form 2010 to 2011 on smoking, diet, recreational physical activity. Responses N=2362 were compared with a matched general population sample (**N**ational **H**ealth **a**nd **N**utritional **E**xamination **S**urvey;N=1,192)	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<.001).** Healtheir lifestyle characterstics among HCT survivors attenuated risk of all CV conditions assessed.
Baker KS, et al. *Blood*. 2007.	Self-reported DM, HTN, CV disease in 1089 HSCT survivors (underwent SCT 1974-1998) at least 2 yrs and not on immunosuppresants compared with 383 sibling controls.Mean f/u 8.6 years and mean age 39.3 years.	HCT survivors more likely to report CM and HTN as compared to siblings. ALLO HSCT more likely to develop HTN than autologous pts. TBI was assoc with increased risk of DM. HCT survivors have a higher age and BMI adjusted risk of DM and HTN, potentiallyy leading go a higher than expected risk of CV events with age.

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

Bubalo et al BBMT 2014;20:600-16

What is Ideal Body Weight?

Table 1. Comparison of Ideal Body Weight Equations Using Height

Reference		Equation
Devine (1974)[1]	men:	50 kg + 2.3 kg/each inch over 5 feet
	women:	45.5 kg + 2.3 kg/each inch over 5 feet
Robinson et al. (1983)[2]	men:	52 kg + 1.9 kg/each inch over 5 feet
	women:	49 kg + 1.7 kg/each inch over 5 feet
Miller et al. (1983)[3]	men:	56.2 kg + 1.41 kg/each inch over 5 feet
	women:	53.1 kg + 1.36 kg/each inch over 5 feet

History of IBW

- Historical data comparing relative mortality of different height-weight combinations
- 1970s Devine formula developed

Pai MP, Paloucek FP. The origin of the "ideal" body weight equations. Ann Pharmacother 2000;34:1066-9.

Obesity recommendations for Preparative Regimens in the obese individual

Drug	Dose
Alemtuzumab	Flat dose(Adults)
Busulfan	Adult ABW25 or BSA based on TBW with PK monitoring for > 12 mg/kg PO equivalent. Pediatrics on TBW with monitoring
Carboplatin	BSA based on TBW(Adults)
Carmustine	BSA based on TBW unless >120% IBW then BSA based on ABW25(Adults)
Clofarabine	BSA based on TBW(Adults)
Cyclophosphamide	Dose on the lessor of TBW or IBW for CY200 Cy120 dose on IBW (adults) or TBW until > 120%IBW then ABW25 (pediatrics)
Cytarabine	BSA based on TBW(Adults)
Etoposide	Adults use ABW25 for mg/kg dosing or TBW for BSA based dosing

Bubalo et al BBMT 2014;20:600-16 Cy120 – 60 mg/kg x 2 days, Cy200 – 50 mg/kg x 4 days

Obesity recommendations for Preparative Regimens in the obese individual

Drug	Dose
Fludarabine	BSA based on TBW(Adults)
Melphalan	BSA based on TBW(Adults)
Pentostatin	BSA based on TBW(Adults)
Thiotepa	BSA based on TBW unless >120% IBW then BSA based on ABW40(Adults)
Antithymocyte globulin - equine	Mg/kg based on TBW – Adults and Pediatrics
Antithymocyte globulin - rabbit	Mg/kg based on TBW – Adults and Pediatrics

Bubalo et al BBMT 2014;20:600-16

Preparative regimen

- Busulfan ABW25 dosing
- Cyclophosphamide IBW dosing

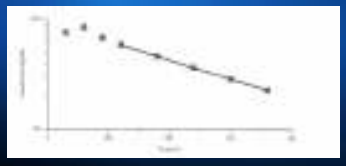
- 67.7 inches tall
- IBW = 45.5 + 7.7(2.3) = 63.2 kg
- ABW25 = 63.2 + 0.25 (118.4 – 63.2) = 77

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

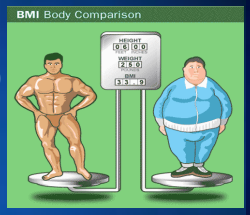
Example Target AUC
AML 3800-5400 micromol*min/day
CML 4700-6000micromol*min/day

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)

Brill JE et al. Impact of obesity on drug metabolism and elimination in adults and children. Clin Pharmacokinet 2012;51(5):277-304.
Zavorsky GS. Cardiopulmonary aspects of obesity in women. Obstet Gynecol Clin North Am. 2009 Jun;36(2):267-84.

Volume of Distribution

Volume of Distribution (Vd) Review

Total water:	60% (50-80%)	42 L
Intracellular volume:	40%	28L
Extracellular volume:	20%	14L
Plasma volume:	4%	3L
Blood volume:	8%	5.5L

- 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

Pharmacokinetics: an online resource for students. Volume of distribution. Universite de Lausanne. http://sepia.unil.ch/pharmacology/index.php?id=61

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

Increased blood volume

Poorer peripheral perfusion

Janson B. Thursky K. Dosing of antibiotics in obesity. Curr Opin Infect Dis. 2012;25:634-649.

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

Hanley MJ, Abernethy DR, Greenblatt DJ. Effect of obesity on the pharmacokinetics of drugs in humans. Clin Pharmacokinet 2010;49(2):71-87.

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

Brill JE et al. Impact of obesity on drug metabolism and elimination in adults and children. Clin Pharmacokinet 2012;51(5):277-304.

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

Brill JE et al. Impact of obesity on drug metabolism and elimination in adults and children. Clin Pharmacokinet 2012;51(5):277-304.

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

Brill JE et al. Impact of obesity on drug metabolism and elimination in adults and children. Clin Pharmacokinet 2012;51(5):277-304.

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

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

A. Decreased clearance of CYP3A4 metabolism
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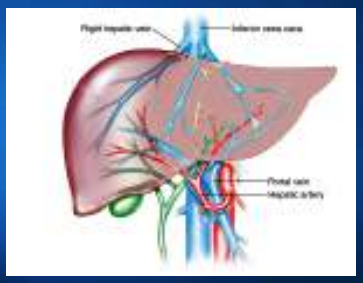
Liver Blood Flow



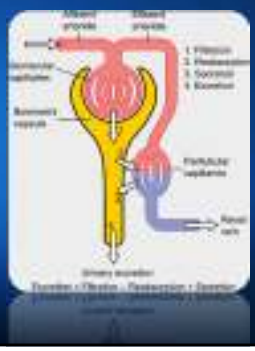
Liver Blood Flow

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

Brill JE et al. Impact of obesity on drug metabolism and elimination in adults and children. Clin Pharmacokinet 2012;51(5):277-304.

Renal Clearance



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

Clin Pharmacokinet 2010;49(2):71-87.
J Antimicrob Chemother 2012;67:1305-1310.
Antimicrob. Agents Chemother. August 2007 vol. 51 no. 8 2741-2747

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

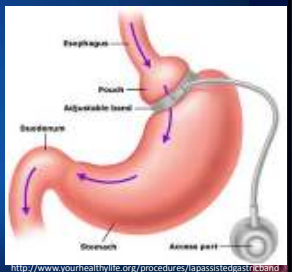
What about patients who have had Bariatric surgery

- 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 are for absorption…
  - Vitamin deficiencies

Weiss BM et al Bone Marrow transplant 2013;48:1152-60.

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



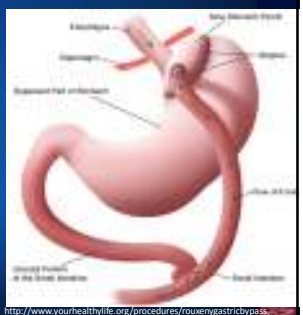
http://www.yourhealthylife.org/procedures/lapassistedgastricband

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



http://www.yourhealthylife.org/procedures/rouxenygastricbypass

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

Mechanick JI, Youdim A, Jones DB, et al. American Association of Clinical Endocrinologists, Obesity Society, American Society for Metabolic & Bariatric Surgery. Clinical practice guidelines for the perioperative nutritional, metabolic, and nonsurgical support of the bariatric surgery patient--2013 update: cosponsored by American Association of Clinical Endocrinologists, the Obesity Society, and American Society for Metabolic & Bariatric Surgery. Endocr Pract. 2013 Mar-Apr;19(2):337-72.

Vitamin and Mineral Absorption Sites

Stomach	Duodenum	Jejunum	Ileum
Intrinsic factor (For B12)	Calcium	Calcium	Vit C
	Iron	Iron	B9, 12
	Vit A, D, E, K	Vit A, D, E, K	Vit D, K
	Phosphorus	Phosphorus	Magnesium
	Magnesium	Magnesium	Bile salts/acids
	B1, 2, 3, 7, 9	B1, 2, 3, 6, 7, 9	
		Vit C	
		Zinc	
		Amino Acids	

Sawaya RA, Jaffe J, Friedenberg L, Friedenberg FK. Vitamin, Mineral, and Drug Absorption Following Bariatric Surgery. Curr Drug Metab. 2012 November ; 13(9): 1345–1355

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 B_{12}
  - 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

Mechanick JI, Youdim A, Jones DB, et al. American Association of Clinical Endocrinologists, Obesity Society, American Society for Metabolic & Bariatric Surgery. Clinical practice guidelines for the perioperative nutritional, metabolic, and nonsurgical support of the bariatric surgery patient--2013 update: cosponsored by American Association of Clinical Endocrinologists, the Obesity Society, and American Society for Metabolic & Bariatric Surgery. Endocr Pract. 2013 Mar-Apr;19(2):337-72.

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

Mechanick JI, Youdim A, Jones DB, et al. American Association of Clinical Endocrinologists, Obesity Society, American Society for Metabolic & Bariatric Surgery. Clinical practice guidelines for the perioperative nutritional, metabolic, and nonsurgical support of the bariatric surgery patient--2013 update: cosponsored by American Association of Clinical Endocrinologists, the Obesity Society, and American Society for Metabolic & Bariatric Surgery. Endocr Pract. 2013 Mar-Apr;19(2):337-72.

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 (ie. previous DVT)


QUESTIONS