Hot Topics in Pediatric Hematopoietic Stem Cell Transplantation

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Pediatric Heme/Onc and Stem Cell Transplantation

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Presentation Information

- This presentation was delivered during the BMT Pharmacists Conference as part of the *American Society for Blood and Marrow Transplantation (ASBMT) and Center for International Blood & Marrow Transplant Research (CIBMTR) Tandem Meetings Annual Conference* in Orlando, FL, February 24-28, 2010

Disclosures

- I have received honoraria for services (Speakers' Bureau participation and CE programming) from Enzon Pharmaceuticals, Genzyme Oncology and sanofi-aventis
- I am a member of the Pediatric Central Institutional Review Board through the National Cancer Institute/National Institutes of Health
- Most of the products mentioned in this presentation are not currently FDA-approved for use in patients under the age of 18 years

Objectives

- Identify current trends in the field of pediatric hematopoietic stem cell transplantation with respect to transplant procedures, supportive care practices and long-term surveillance
- Analyze selected data recently published on current trends in pediatric hematopoietic stem cell transplantation
- Incorporate recent published data to augment current institutional practice standards for the care of pediatric hematopoietic stem cell transplant recipients

Disease States

Acute Lymphoblastic Leukemia (ALL)

Acute Lymphoblastic Leukemia (ALL)

- Most common malignancy in childhood
  - Accounts for approximately 1 in 4 cancer diagnoses in children less than 15 years old
  - Peak incidence: 2 to 5 years old
  - Five-year survival rates 85-90%
- Risk determination
  - Age, gender and white blood cell count at diagnosis
  - Cytogenetics
    - Favorable – hyperdiploid; presence of t(12,21)
    - Unfavorable – hypodiploid ; presence of t(4,11) or t(9,22)

Pui CH, et al. *New Engl J Med.* 2006;354:166-78. Silverman LB. *Pediatr Blood Cancer.* 2007;49:1070-3. Krance RA. *Bone Marrow Transplant.* 2008;42:S25-S27. Jeha S, et al. *Hematol Oncol Clin N Am.* 2009;23:973-90.

Acute Lymphoblastic Leukemia (ALL)

- Role of stem cell transplantation (USA)
  - Matched related donor allogeneic SCT is recommended over chemotherapy in very high-risk Ph+ patients in 1st complete remission
  - Matched related donor allogeneic SCT in 2nd or subsequent remission may be equivalent to or better than chemotherapy alone
  - Some patients with late relapses achieve extended leukemia-free survival with autologous purged SCT (but insufficient evidence to determine if better than chemotherapy alone)

Hahn T. et al. *Biol Blood Marrow Transplant.* 2005;11:823-61. Hahn T, et al. *Biol Blood Marrow Transplant.* 2006;12:370-1.

Acute Lymphoblastic Leukemia (ALL)

- There is insufficient evidence to:
  - Support a recommendation for unrelated donor allogeneic SCT vs. chemotherapy in 2nd or subsequent remission
  - Support the use of autologous unpurged SCT
  - Compare outcomes of related vs. unrelated donor allogeneic SCT
  - Support a recommendation of autologous versus allogeneic SCT

Hahn T. et al. *Biol Blood Marrow Transplant.* 2005;11:823-61. Hahn T, et al. *Biol Blood Marrow Transplant.* 2006;12:370-1.

Acute Lymphoblastic Leukemia (ALL)

- Role of stem cell transplantation (Europe)

Disease Status	Sibling donor	Well matched unrelated	> 1 antigen mismatched related	Autologous
Complete Remission (CR) 1 (low risk)	Generally not recommended	Generally not recommended	Generally not recommended	Generally not recommended
CR1 (high risk)	Standard of care	Standard of care	Clinical option	Generally not recommended
CR2	Standard of care	Standard of care	Clinical option	Clinical option
> CR2	Standard of care	Standard of care	Clinical option	Clinical option

Ljungman P, et al. *Bone Marrow Transplant.* 2009 Jul 6. Epub ahead of print.

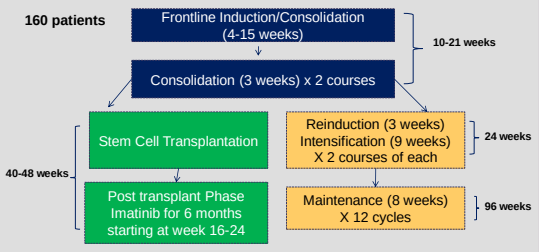
Acute Lymphoblastic Leukemia (ALL)

- Philadelphia-chromosome positive (Ph+) ALL
  - Occurs in only 3-5% of children with ALL compared to 25% incidence in adults
  - Associated with a poor outcome (< 40% survival)
  - Daily oral doses of imatinib have found to be safe and effective in children
    - Doses: 260 – 570 mg/m^2/day
    - Well tolerated: adverse events similar to adults
  - What is the utility of imatinib given in combination with multi-agent chemotherapy?

Champagne MA, et al. *Blood.* 2004;104:2655-60. Guilhot F. *Oncologist.* 2004;9:271-81.
Schultz KR, et al. *J Clin Oncol.* 2009;27:5175-81.

Acute Lymphoblastic Leukemia (ALL)

Children's Oncology Group AALL0031 Study



Schultz KR, et al. *J Clin Oncol.* 2009;27:5175-81.

Acute Lymphoblastic Leukemia (ALL)

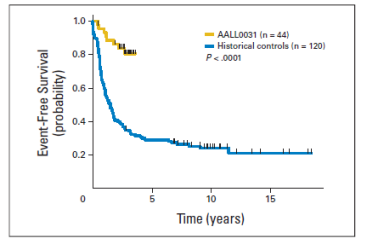
Imatinib Therapy for Non-Transplant Patients

Therapy	Cons 1 (3 wk)	Cons 2 (3 wk)	Reind 1 (3 wk)	Intens 1 (9 wk)	Reind 2 (3 wk)	Intens 2 (9 wk)	Maint 1-4 (8-wk cycles)	Maint 5-12 (8-wk cycles)
Cohort 1 N = 7				Imatinib × 3 wk		Imatinib × 3 wk	Imatinib × 3 wk	Imatinib × 2 wk every 4 wk
Cohort 2 N = 12		Imatinib × 3 wk	Imatinib × 3 wk		Imatinib × 3 wk		Imatinib × 3 wk	Imatinib × 2 wk every 4 wk
Cohort 3 N = 12	Imatinib × 3 wk	→	→		Imatinib × 3 wk		Imatinib × 3 wk	Imatinib × 2 wk every 4 wk
Cohort 4 N = 12	Imatinib × 3 wk	→	→	→	→	→	→	Imatinib × 2 wk every 4 wk
Cohort 5 N = 50	Continuous dosing of imatinib							Imatinib × 2 wk every 4 wk

Schultz KR, et al. *J Clin Oncol.* 2009;27:5175-81.

Acute Lymphoblastic Leukemia (ALL)

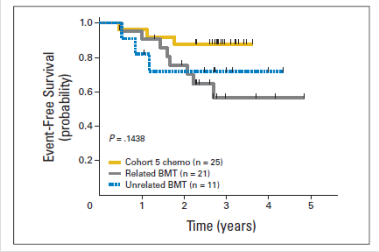
Outcome of adding imatinib to standard chemotherapy regimens



Schultz KR, et al. *J Clin Oncol.* 2009;27:5175-81.

Acute Lymphoblastic Leukemia (ALL)

Chemotherapy + imatinib compared to stem cell transplantation + imatinib



Schultz KR, et al. *J Clin Oncol.* 2009;27:5175-81.

Acute Lymphoblastic Leukemia (ALL)

- Summary & Conclusions
  - Preliminary data suggests outcome with continuous administration of imatinib in combination with chemotherapy is as good as results with imatinib and stem cell transplantation
  - Safety profile of imatinib therapy is acceptable
    - Hepatotoxicity can be augmented by breaks in therapy
    - Cardiac toxicity not seen in children as reported in adults
  - Follow-up study using dasatinib is ongoing
  - **Issues**
    - Long-term efficacy and safety data
    - Incorporation of tyrosine kinase inhibitors
    - Role of transplantation

Schultz KR, et al. *J Clin Oncol.* 2009;27:5175-81.

Transplant Process

Reduced Intensity Conditioning Regimens

Reduced Intensity Conditioning Regimens

- Role of reduced intensity conditioning (RIC) regimens in adults is well established
- Exact place in therapy of RIC is not clear in pediatrics
  - Tolerance to transplant process is usually greater in children
  - Stem source of umbilical cord blood or bone marrow has been preferred in children
    - Survival data
    - Ethical issues
  - Safety and efficacy data is limited to single institutional center experiences

Pulsipher MA, et al. *Blood.* 2009;114:1429-36.

Reduced Intensity Conditioning Regimens

- What are our experiences?
  - Non-malignant diseases (66-100% overall survival)
    - Sickle cell disease
    - β Thalassemia
    - Congenital neutropenia
    - Langerhans cell histiocytosis
    - Severe aplastic anemia
    - Fanconi's anemia
    - Hemophagocytic lymphohistiocytosis
    - Severe combined immunodeficiency disorder
  - Malignant diseases (66-93% overall survival)
    - Acute lymphoblastic leukemia
    - Acute myeloid leukemia
    - Chronic myeloid leukemia
    - Neuroblastoma
    - Non-hodgkin's lymphoma
    - Hodgkin's disease
  - Complications

Satwani P, et al. *Pediatr Blood Cancer.* 2008;50:1-8. Yaniv I, et al. *Bone Marrow Transplant.* 2008;41:S18-S22.

Reduced Intensity Conditioning Regimens

Commonly Used Transplant Regimens in Pediatrics

Non-myeloablative	Reduced Intensity	Ablative	
	Busulfan16mg/Fludarabine/ Alemtuzumab	TBI/Cyclophosphamide ± Etoposide	Haplo
		TBI/Cyclophosphamide ± Thiotepa	
	Busulfan 8mg/Fludarabine/ Antithymocyte globulin	Busulfan/Cyclophosphamide	MUD
2 Gy TBI/Fludarabine	Melphalan 140mg/ Fludarabine/ Antithymocyte globulin		
2 Gy TBI	Cyclophosphamide/ Fludarabine/ Antithymocyte globulin		MRD

Immunosuppression ↑

Myelosuppression

Storb RF, et al. *Hematol Am Soc Hematol Educ Program.* 2001;375-91.

Reduced Intensity Conditioning Regimens

- Pediatric Blood and Marrow Transplant Consortium (PBMTC) ONC0313 Study
  - Enrollment of patients with malignancies at high risk for transplant related mortality with traditional ablative regimens
    - Organ system dysfunction or severe systemic infections

Organ system	"Dysfunction"
Pulmonary	Pulmonary function tests <60% but >30%
Hepatic	Transaminases > 4x up to 10x normal; Total bilirubin 2-3 mg/dL; evidence of synthetic dysfunction with an INR > 2
Renal	Creatinine clearance < 60 but at least 30 ml/min/1.73 m^2
Cardiac	Ejection fraction less than 50% but at least 30%

    - History of previous autologous or myeloablative transplant
    - MUD for a CR3 or greater disease status
    - Combination of toxicities

Pulsipher MA, et al. *Blood.* 2009;114:1429-36.

Reduced Intensity Conditioning Regimens

- Disease status and treatment
  - ALL – morphologic remission AML – M1/M2 acceptable
  - JMML/MDS – less than 5% blasts
  - CML – first chronic phase, accelerated phase, or subsequent chronic phase with less than 5% blasts
  - NHL/HD – responsive disease /no persistent masses > 5 cm

Treatment	Related		Unrelated/Cord	
Busulfan -- targeted dose AUC/Dose 900-1100 µM/min	D-7 D-3, -2	0.8 mg/kg IV x 7 doses	D-10 D-6, -5	0.8 mg/kg IV X 7 doses
Fludarabine (30 mg/m2/dose)	D-7 → D-2	180 mg/m^2	D-10 → D-5	180 mg/m^2
Thymoglobulin (2.5 mg/kg/dose)	D-1	2.5 mg/kg	D-4 → D-1	10 mg/kg
Cyclosporine (IV/PO Q 12 hrs)	D-3 → D+42 Trough 250-350 ng/mL		Day-3 → D+100-180 Trough 250-350 ng/mL	
Mycophenolate mofetil (15 mg/kg IV/PO Q 12 hours)	Day 0 → Day+30		Day 0 → Day+40-96	

Pulsipher MA, et al. *Blood.* 2009;114:1429-36.

Reduced Intensity Conditioning Regimens

- Results – 47 patients (25 males)
  - Median age 11 years (range 2-20)
  - 60% qualified with prior myeloablative transplant
  - 10 patients had organ toxicity/3 invasive fungal infections
  - Median follow-up 24 months (range 11-53)
    - 2 year EFS and OS were 40.2% and 44.5%

	Related donor		Unrelated donor		
	BM	PBSCs	BM	PBSCs	CB
Median time to neutrophil engraftment, d (range)	24 (5-33)	20 (14-26)	19 (12-27)	18 (11-28)	20 (13-42)
Median time to platelet engraftment, d (range)	0 (0-22)	0 (0-17)	19 (0-40)	18 (11-71)	43 (0-251)
Outcome/condition (no. of patients)					
Rejection	1	0	2	0	1
Death/relapse before engraftment	0	0	1	0	2
Partial chimerism	1	0	1	2	1
Full chimerism	6	8	6	7	7
Chimerism data missing	0	0	0	0	1*

*One cord blood patient with AML in PR3 engrafted but relapsed at day 81. Chimerism data were not available.

Pulsipher MA, et al. *Blood.* 2009;114:1429-36.

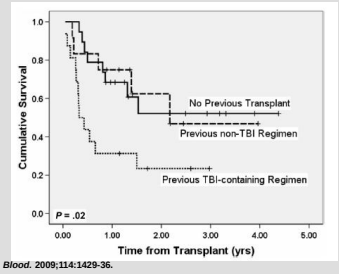
Reduced Intensity Conditioning Regimens

Toxicity	Related donor BM	Related donor PBSCs	Unrelated donor BM	Unrelated donor PBSCs	CB	Overall, no. (%)
N	8	8	10	9	12	47
Acute GVHD						
No. evaluable	7	8	8	9	9	41
No. with acute GVHD, grades 1 or 2	1	1	2	5	2	11 (27)
No. with acute GVHD, grades 3 or 4	0	0	1	0	0	1 (2)
No. with no acute GVHD	6	7	5	4	7	29 (71)
Chronic GVHD						
No. evaluable	5	7	6	7	6	31
No. with chronic GVHD	2	3	1	2	0	8 (26)
No. with no chronic GVHD	3	4	5	5	6	23 (74)
Other events						
No. (%) with transplantation-related mortality	0	0	3 (30)	2 (22)	1 (8)	6 (13)
No. (%) with relapse	4 (50)	5 (63)	3 (30)	4 (44)	5 (42)	21 (45)

Pulsipher MA, et al. *Blood.* 2009;114:1429-36.

Reduced Intensity Conditioning Regimens

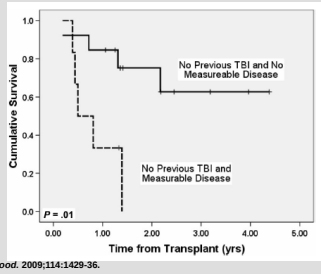
Survival in relation to history of myeloablative transplantation



Pulsipher MA, et al. *Blood.* 2009;114:1429-36.

Reduced Intensity Conditioning Regimens

Survival in relation to disease status



Pulsipher MA, et al. *Blood*. 2009;114:1429-36.

Graft-Versus-Host Disease (GVHD)

Pentostatin in Steroid-Refractory Chronic GVHD

Graft-versus-Host Disease

- Chronic graft-versus-host disease
  - Leading cause of late morbidity and non-relapse mortality following HSCT
  - Different disease and process in children
    - Recovery of the immune system
    - Stem cell source utilization patterns
    - Response to and effects of immunosuppression
  - Treatment options
    - Standard of care: corticosteroids ± calcineurin inhibitor
    - Salvage regimens
    - Need remains for well-tolerated therapy that is easy to administer and monitor

Higman MA, et al. *Brit J Haematol*. 2004;125:435-5 4. Jacobsohn DA, et al. *Blood*. 2009;114:4354-60.

Graft-versus-Host Disease

- Pentostatin
  - Potent inhibitor of nucleoside deaminase
  - Markedly reduces CD4 and CD8 cells as well as B–cells with IgG levels
  - Results in chronic GVHD favorable in adults
    - Phase II study: 55% objective response in 58 heavily pre-treated patients
  - Phase II study in children conducted by the Pediatric Blood and Marrow Transplant Consortium recently published

Jacobsohn DA, et al. *Blood*. 2009;114:4354-60.

Graft-versus-Host Disease

- Pediatric Blood and Marrow Transplant Consortium study
  - Allogeneic HSCT of any stem cell source in patients less than 21 years of age
  - Treatment-refractory cGVHD
    - Development of 1 or more new sites while on active therapy
    - Progression of existing site(s) while on active therapy
    - Failure to improve while on standard therapy for at least 1 month [at least 1 mg prednisone (or other steroid equivalent)/kg every other day or other immunosuppression regimen if intolerant of steroids]
  - Could not have failed more than 2 prior regimens and must have reasonable performance status and organ function

Jacobsohn DA, et al. *Blood*. 2009;114:4354-60.

Graft-versus-Host Disease

- Therapy
  - Pentostatin 4 mg/m^2 IV every other week
  - Duration of therapy was 6-12 months
  - Other immunosuppression therapy
    - Corticosteroid taper started 8-12 weeks after starting study
    - Calcineurin inhibitor continued throughout study
    - All other therapies tapered starting at 3 months from study entry
  - Infection prophylaxis strongly recommended
    - Penicillin
    - Acyclovir
    - Fluconazole
    - Trimethoprim-sulfamethoxazole

Jacobsohn DA, et al. *Blood*. 2009;114:4354-60.

Graft-versus-Host Disease

- Evaluation occurred at baseline and every 3 months
  - Grading in 9 domains: rash, sclerosis, oral, fasciitis, joint, liver, lung, gastrointestinal and ocular
- Monthly toxicity grading
- Results
  - 51 patients treated (53% male)
    - Median age 9.8 years (range 0.9-20.7)
    - Median time from HSCT to GVHD 5.0 months (1.4-26.1)
    - Median time from GVHD to study entry 6.2 months (0.1-42.1)
    - Myeloablative transplants 73%
    - 96% subjects on corticosteroids at study entry for a median time of 3.9 months (range 0-24.9)

Jacobsohn DA, et al. *Blood*. 2009;114:4354-60.

Graft-versus-Host Disease

- Response by domain

	Involved, n (%)	Complete, n (%)	Partial, n (%)	Stable, n (%)	Worse, n (%)	Response rate, % (95% CI)*
Rash/lichenoid changes	40 (78)	13 (33)	7 (17)	10 (25)	10 (25)	50 (36-64)
Sclerosis	27 (53)	11 (41)	5 (18)	6 (22)	5 (19)	59 (42-75)
Oral	30 (59)	9 (30)	8 (27)	7 (23)	6 (20)	57 (40-72)
Fasciitis	7 (14)	2 (29)	1 (14)	2 (29)	2 (29)	43 (18-71)
Joint	20 (39)	5 (25)	4 (20)	5 (25)	6 (30)	45 (27-64)
Liver	5 (10)	0	0	2	3	0
Lung	2 (4)	0	0	1	1	0
Gastrointestinal	21 (41)	8 (38)	1 (5)	7 (33)	5 (24)	43 (25-62)
Ocular	28 (55)	5 (18)	2 (7)	13 (46)	8 (29)	25 (13-41)

CI indicates confidence interval.
*Response rate included CR + PR.

Jacobsohn DA, et al. *Blood*. 2009;114:4354-60.

Graft-versus-Host Disease

- Toxicity

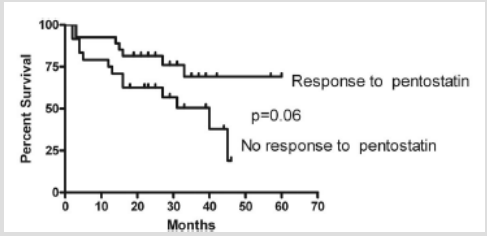
	Months on study	
	0-6, no. of subjects	6-12, no. of subjects
Infections		
Documented bacterial requiring infection	2	—
Presumed bacterial infection	1	—
Documented fungal infection	—	1
Documented viral infection	1	—
Central nervous system (leukoencephalopathy)	1	—
Renal	2	—
Gastrointestinal/liver (pancreatitis/abdominal pain)	1	—
Hematologic(autoimmune hemolytic anemia)	2	1
Allergic reaction	1	—

Subjects with adverse events that required them to be removed from study, separated by two 6-month time periods on the study.
— indicates no event.

Jacobsohn DA, et al. *Blood*. 2009;114:4354-60.

Graft-versus-Host Disease

- Overall survival (secondary endpoint)



Jacobsohn DA, et al. *Blood*. 2009;114:4354-60.

Graft-versus-Host Disease

- Study importance
  - Confirmation of response in children
  - Response to sclerotic manifestations of cGVHD
  - Tempo of response
  - Largest reported pediatric cGVHD trial to date
  - Tools for staging and assessing response to cGVHD
  - Next step → assessment in newly diagnosed, high risk pediatric patients with cGVHD
- **Incorporation of pentostatin in treatment algorithms**

Jacobsohn DA, et al. *Blood*. 2009;114:4354-60.

Other Complications

Invasive Fungal Infections:

Focus on Echinocandins

Invasive Fungal Infections

- Frequency and severity of invasive fungal infections steadily increasing over the past two decades
  - Estimated that 10-40% of pediatric patients will experience at some point during allogeneic HSCT
    - Susceptibility of the host
    - Use of broad-spectrum antibiotics
  - Most common causes *Candida* spp and *Aspergillus* spp
  - Leading cause of morbidity and mortality in children
    - Candidemia 16-31% mortality rate
    - Aspergillosis mortality rate as high as 77%
  - Newer treatment options

Arendrup MC, et al. *Clin Microbiol Infect.* 2009;15:613-24. Zaoutis TE, et al. *Pediatrics.* 2009;123:877-84

Invasive Fungal Infections

Echinocandin Pharmacokinetic Parameters in Children 2-17 Years of Age

Parameter	Caspofungin	Micafungin	Anidulafungin
FDA approval	January 2001	March 2005	February 2006
Pedi approval	Yes in July 2008	No	No
Vd	No data	0.24-0.42 L/kg	0.42-0.58 L/kg
Cl	5.2-8.6 mL/min/m^2	14.2-24.3 mL/hr/kg	13.2-21.7 mL/hr/kg
T ½	8.2-16.5 hr	12.1-17.3 hr	18.9-26.0 hr
Metabolism	Hydrolysis & *N*-acetylation	Arylsufatase & catechol-*O*-methyl transferase	Hydrolysis
Elimination	35% feces; 41% urine (1.4% unchanged)	71% feces	30% feces
Dosing	Load: 70 mg/m^2 Maint: 50 mg/m^2/day Perhaps 25 mg/m^2/day in neonates	1-4 mg/kg/day; Perhaps 5-7 mg/kg/day or higher in neonates	Load: 1.5 or 3 mg/kg Maint: 0.75 or 1.5 mg/kg/day Data lacking in neonates
Dose ↓	Moderate hepatic insufficiency	None	None

VandenBussche HL, et al. *Pharmacotherapy.* 2009 December 15 [Epub ahead of print].
Benjamin Jr., DK, et al. *Clin Pharmacol Ther.* 2009 November 4 [Epub ahead of print].

Invasive Fungal Infections

- Prophylaxis in pediatric HSCT
  - Only evaluation has been with micafungin in this setting
  - Evaluated versus fluconazole up to a month after HSCT
    - ≥ 50 kg: 50 mg/day micafungin vs. 400 mg/day fluconazole
    - < 50 kg: 1 mg/kg/day vs. 8 mg/kg/day
  - Micafungin more successful than fluconazole in preventing systemic fungal infections prior to and through first four weeks after transplantation
  - Rates of candidal colonization more with micafungin (except for *C. glabrata*)
  - Micafungin found to be as effective as fluconazole and may be an alternative agent for antifungal prophylaxis
  - Study limitations

Van Burik JA, et al. *Clin Infect Dis.* 2004;39:1407-16. Kusuki S, et al. *Pediatr Blood Cancer.* 2009;53:605-9.

Invasive Fungal Infections

- Treatment of pediatric invasive candidiasis
  - Evaluations with caspofungin and micafungin
  - Largest randomized double-blind comparative trial evaluated use of micafungin
    - Micafungin vs. Ambisome®
      - 2 mg/kg/day (100 mg/day if > 40 kg) vs. 3 mg/kg/day
      - 4 mg/kg/day (200 mg/day if > 40 kg) vs. 5 mg/kg/day if persistent fever after 5 days or positive infection
      - Minimum treatment for 14 days to a maximum of 4 weeks (in some cases up to 8 weeks)
      - Similar safety and efficacy
    - Micafungin as safe and effective as liposomal amphotericin B in pediatric invasive candidiasis
  - Patients < 8 years old may need 1.3-1.5 times higher doses

Odio CM, et al. *Pediatr Infect Dis J.* 2004;23:1093-7. Natarajan G, et al. *J Perinatol.* 2005;25:770-7.
Queiroz-Telles F, et al. *Pediatr Infect Dis J.* 2008;27:820-6. Kuse ER, et al. *Lancet.* 2007;369:1519-27.
Seibel NL, et al. *Antimicrob Agents Chemother.* 2005;49:3317-24.

Invasive Fungal Infections

- Treatment of pediatric invasive aspergillosis
  - Evaluations with caspofungin and micafungin
  - Largest prospective study was with micafungin alone or in combination
    - Micafungin dosed as 75 mg/day (1.5 mg/kg/day if ≤ 40 kg) with maximum doses of 225 mg/day (4.5 mg/kg/day if ≤ 40 kg)
  - Micafungin alone or in combination was safe and effective
  - Caspofungin – open label noncomparative study
    - 49 patients (3 months – 17 years)
      - 38 patients with invasive candidiasis (81% response rate)
      - 10 patient with invasive aspergillosis (50% response rate)

Denning DW, et al. *J Infect.* 2006;53:337-49. Zaoutis TE, et al. *Pediatrics.* 2009;123:877-84.

Invasive Fungal Infections

- International Pediatric Fungal Network (Duke University) (pfn.pediatrics.duke.edu)
- **Recent safety concerns**
  - Liver toxicity associated with micafungin
    - Micafungin shown to induce irreversible foci of altered hepatocytes and liver tumors in rats after 3 months of treatment
    - European Medicines Agency (EMEA)
    - "Black box warning" on micafungin labeling
      - Use micafungin only if other antifungal agents are not appropriate
- **Role and dose of echinocandins in therapy**

Pappas G, et al. *Clin Ther.* 2009;31:1595-1603. Pappas PG, et al. *Clin Infect Dis.* 2009;48:503-35.
Walsh TJ, et al. *Clin Infect Dis.* 2008;46:327-60. Tomblyn M, e tal. *Biol Blood Marrow Transplant.* 2009;15:1143-238.
Hope WW, et al. *Antimicrob Agents Chemother.* 2007;51:3714-19.

Invasive Fungal Infections

- Dosing "equivalents" for micafungin
  - Hope WW, et al
    - 100 mg/day → 3.38 x weight$^{(-0.25)}$ mg/kg/day
    - 150 mg/day → 5.07 x weight$^{(-0.25)}$ mg/kg/day
    - 200 mg/day → 6.77 x weight$^{(-0.25)}$ mg/kg/day
  - Seibel NL, et al
    - 50 mg/day → 1 mg/kg/day
    - 100 mg/day → 2 mg/kg/day
    - 150 mg/day → 3 mg/kg/day
    - 200 mg/day → 4 mg/kg/day
    - Children 2-8 years of age may need 1.5 times higher dosing

Hope WW, et al. *Antimicrob Agents Chemother.* 2007;51:3714-1. Seibel NL, et al. *Antimicrob Agents Chemother.* 2005;49:3317-24. Benjamin Jr., DK, et al. *Clin Pharmacol Ther.* 2010;87:93-9.

Long-Term Surveillance

Metabolic Syndrome

Avascular Necrosis

Survivorship and Follow-Up in Adulthood

"Pediatric SCT survivors may have decades of life to live following transplant, thus making this lasting support critical for ensuring survivors are able to become well adjusted, functioning members of society."

Dreyer ZE. *Bone Marrow Transplant.* 2009:43:433.

Physical Functioning After SCT

- 214 SCT survivors (> 5 years) analyzed
  - April 1972 – November 1994
  - Mean age 28.7 years (range: 18-8-45.9 years); 55% male
    - Mean age at transplant: 11.9 years (range: 1.8 – 17.9 years)
  - Medical Outcome Study Short Form 36 Health Survey (SF-36)

Measurement	SCT Mean Score	Control Mean Score	P value
Physical component (PCS)	51.1	55.1	<0.001
Physical function	89.1	94.5	<0.001
Role physical	84.5	91.0	0.02
Bodily pain	79.2	82.9	0.05
General health	70.1	81.4	<0.001

Sanders JE, et al. *Bone Marrow Transplant.* 2009 Aug 31 [Epub ahead of print].

Metabolic Syndrome

- Originally described by Reaven in 1988 as "Syndrome X"
- Constellation of complications which predispose patients to the development of cardiovascular disease (CVD) and diabetes
  - Dysglycemia
  - Obesity (central adiposity)
  - Elevated blood pressure
  - Elevated triglycerides
  - Decreased high-density lipoprotein (HDL) cholesterol
  - Pro-inflammatory and pro-thrombotic states
- Exact pathogenesis remains ill-defined
  - Relation to insulin resistance
  - Role of leptin, adiponectin, growth hormone and C-reactive protein

Grundy SM, et al. *Circulation.* 2005;112:2735-52. Kavey REW, et al. *Circulation.* 2006;114:2710-38. Siviero-Miachon AA, et al. *Vasc Health Risk Manag.* 2008;4:825-36. Lusis AJ, et al. *Nat Rev Genet.* 2008;9:819-30.

Metabolic Syndrome

- Definition and diagnostic criteria more ill-defined
  - World Health Organization (WHO) first definition in 1998
    - European Group for the Study of Insulin Resistance (EGIR)
    - National Cholesterol Education Program (NCEP)
    - American Association of Clinical Endocrinologists (AACE)
    - International Diabetes Federation (IDF)
    - American Heart Association/National Heart, Lung and Blood Institute (AHA/NHLBI)
  - In 2008, 27 articles identified 46 "definitions" for pediatric patients
    - 28 ~ NCEP 9 ~ WHO 3 ~ EGIR 1 ~ AACE 5 unique
    - Difficulties with definitions

Ford ES. *J Pediatr.* 2008;152:160-4. Siviero-Miachon AA, et al. *Vasc Health Risk Manag.* 2008;4:825-36.

Metabolic Syndrome

- Example of a pediatric-specific criteria

International Diabetes Federation criteria for metabolic syndrome in children. Diagnosis requires the presence of central obesity plus any two of other criteria

Age Group	Obesity (WC)	Triglycerides (mg/dl)	HDL (mg/dl)	Blood Pressure (mmHg)	Glucose (mg/dl)
6 < 10	≥90th percentile				
10 < 16	≥90th percentile or adult cut-off if lower	≥150	<40	Systolic BP >130 or diastolic BP > 85	FPG >100 or T2D
>16 Adult criteria	WC ≥94 cm for males and ≥80 for females	≥150	<40 in males, <50 in females	Systolic BP >130 or diastolic BP >85	FPG >100 or T2D

WC, waist circumference; HDL, high-density lipoprotein; BP, blood pressure; FPG, fasting plasma glucose; T2D, type 2 diabetes

D'Adamo E, et al. *Endocrinol Metab Clin N Am.* 2009;38:549-563.

Metabolic Syndrome

Measure (any 3 of 5 constitute diagnosis of metabolic syndrome)	Categorical Cutpoints
Elevated waist circumference*†	≥102 cm (≥40 inches) in men ≥88 cm (≥35 inches) in women
Elevated triglycerides	≥150 mg/dL (1.7 mmol/L) or On drug treatment for elevated triglycerides‡
Reduced HDL-C	<40 mg/dL (1.03 mmol/L) in men <50 mg/dL (1.3 mmol/L) in women or On drug treatment for reduced HDL-C‡
Elevated blood pressure	≥130 mm Hg systolic blood pressure or ≥85 mm Hg diastolic blood pressure or On antihypertensive drug treatment in a patient with a history of hypertension
Elevated fasting glucose	≥100 mg/dL or On drug treatment for elevated glucose

Example of adult criteria

American Heart Association/National Heart, Lung and Blood Institute (AHA/NHLBI)

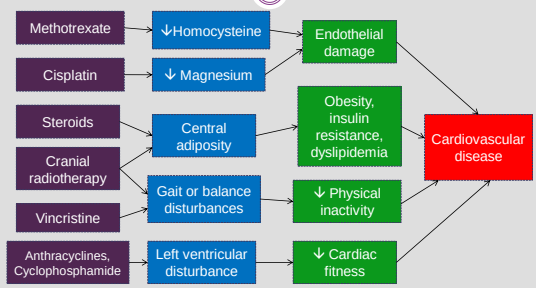
*To measure waist circumference, locate top of right iliac crest. Place a measuring tape in a horizontal plane around abdomen at level of iliac crest. Before reading tape measure, ensure that tape is snug but does not compress the skin and is parallel to floor. Measurement is made at the end of a normal expiration.

†Some US adults of non-Asian origin (eg, white, black, Hispanic) with marginally increased waist circumference (eg, 94–101 cm [37–39 inches] in men and 80–87 cm [31–34 inches] in women) may have strong genetic contribution to insulin resistance and should benefit from changes in lifestyle habits, similar to men with categorical increases in waist circumference. Lower waist circumference cutpoint (eg, ≥90 cm [35 inches] in men and ≥80 cm [31 inches] in women) appears to be appropriate for Asian Americans.

‡Fibrates and nicotinic acid are the most commonly used drugs for elevated TG and reduced HDL-C. Patients taking one of these drugs are presumed to have high TG and low HDL.

Grundy SM, et al. *Circulation.* 2005;112:2735-52.

Metabolic Syndrome



Gregory JW. *Endocri Dev.* 2009;15:59-76.

Metabolic Syndrome

	Annaloro et al	Majhail et al	Taskinen et al
Study features	N = 85 (35 allo) Med age = 46 yr (26-63) > 5 years from HSCT	N = 86 (only allo) Med age = 50 yr (21-71) > 1 year from HSCT 79% active GVHD	N = 31 (only allo) Med age 15 yr (7-34) > 1 year from HSCT No steroids allowed
What was seen	29 (34%) cases (17 auto) 83% hypertriglyceridemia 72% abdominal obesity 72% hyperglycemia 66% hypertension 62% low HDL-C	49% incidence 58%hypertriglyceridemia 41% abdominal obesity 41% hyperglycemia 56% hypertension 41% low HDL-C	39% incidence 42% hypertriglyceridemia 48% abdominal obesity 42% hyperglycemia ? hypertension 23% low HDL-C
Risk factors	Insulin resistance Leptin levels	Nothing clearly identified	Growth hormone deficiency

RISKS

More common to see high triglycerides and low HDL-C
Not common to see hypertension or obesity
Does not appear to associate with GVHD
High leptin levels appear predictive but family history does not

Annalora C, et al. *Bone Marrow Transplant.* 2008;41:797-804. Majhail NS, et al. *Bone Marrow Transplant.* 2009;43:49-54. Taskinen Me, et al. *J Pediatr Hematol Oncol.* 2007;29:529-34.

Metabolic Syndrome

- **Updated criteria**

Measure	Categorical Cut Points
Elevated waist circumference*	Population- and country-specific definitions
Elevated triglycerides (drug treatment for elevated triglycerides is an alternate indicator†)	≥150 mg/dL (1.7 mmol/L)
Reduced HDL-C (drug treatment for reduced HDL-C is an alternate indicator†)	<40 mg/dL (1.0 mmol/L) in males; <50 mg/dL (1.3 mmol/L) in females
Elevated blood pressure (antihypertensive drug treatment in a patient with a history of hypertension is an alternate indicator)	Systolic ≥130 and/or diastolic ≥85 mm Hg
Elevated fasting glucose‡ (drug treatment of elevated glucose is an alternate indicator)	≥100 mg/dL

*** Recommended that International Diabetes Federation (IDF) cut points be used for non-Europeans and either IDF or American Heart Association (AHA) cut points be used for people of European origin until more data is available.**

† Most common drugs for elevated Triglycerides and reduced HDL-C are fibrates and nicotinic acid. A patient taking one of these drugs can be presumed to have high triglycerides and low HDL-C. High-dose ω-3 fatty acids presumes high triglycerides.

‡ Most people with type 2 diabetes will Have the metabolic syndrome by the Proposed criteria.

HDL-C, high-density lipoprotein cholesterol

Alberti KGMM, et al. *Circulation.* 2009;120:1640-5.

Metabolic Syndrome

Current Recommended Waist Circumference Thresholds for Abdominal Obesity

Population	Organization	Men	Women
United States	AHA/NHLBI	≥ 102 cm	≥ 88 cm
Canada	Health Canada	≥ 102 cm	≥ 88 cm
European	European Cardiovascular Societies	≥ 102 cm	≥ 88 cm
Japanese	Japanese Obesity Society	≥ 85 cm	≥ 90 cm
Middle East, Mediterranean	IDF	≥ 94 cm	≥ 80 cm
Caucasian	WHO	≥ 94 cm ↑ risk ≥ 102 cm ↑↑ risk	≥ 80 cm ↑ risk ≥ 88 cm ↑↑ risk
Europoid	IDF	≥ 94 cm	≥ 80 cm

Alberti KGMM, et al. *Circulation.* 2009;120:1640-5.

Metabolic Syndrome

GOALS

Risk factors/Co-morbidities
Fasting lipid profile, smoking history, family history, blood pressure, BMI, fasting glucose, physical activity

YES ***≥ 2 co-morbidities?*** ***NO***

Moderate Risk
BMI ≤ 90%ile for age/sex
BP ≤ 95%ile for age/sex/ht%ile
LDL-C ≤ 130 mg/dL
Fasting glucose < 100 mg/dL
$HgbA_{1C}$ < 7%

At Risk
BMI ≤ 95%ile for age/sex
BP ≤ 95%ile + 5 mm Hg for age/sex/ht%ile
LDL-C ≤ 160 mg/dL
Fasting glucose < 100 mg/dL
$HgbA_{1C}$ < 7%

Kavey REW, et al. *Circulation.* 2006;114:2710-38. Siviero-Miachon AA, et al. *Vasc Health Risk Manag.* 2008;4:825-36.

Metabolic Syndrome

- **Interventions**
  - **A** Assessment/Aspirin
  - **B** Blood pressure control
  - **C** Cholesterol management
  - **D** Diabetes prevention/diet
  - **E** Exercise

Blaha MJ, et al. *Mayo Clin Proc.* 2008;83:932-43. Grundy SM, et al. *Circulation.* 2005;112:2735-52.
Kavey REW, et al. *Circulation.* 2006;114:2710-38. Siviero-Miachon AA, et al. *Vasc Health Risk Manag.* 2008;4:825-36.

Avascular Necrosis

- Exact pathogenesis is poorly understood
  - Subchondral bone ischemia
- Estimated to develop in 4-10% of HSCT survivors
  - Median time of onset is 12 months (range 2-132 months)
- Most likely to occur in the hip
- Identifiable risk factors
  - Steroids?
  - Age > 16 years
  - Diagnosis of aplastic anemia or acute leukemia
  - GVHD
  - TBI-based conditioning regimen

Carpenter PA. *Best Prac Res Clin Haematol.* 2008;21:309-31.

Avascular Necrosis

- Recent examination of risk factors
  - Retrospective review of 1346 patients transplanted 1976-1997
    - > 1 year out from HSCT
    - Median age at HSCT was 34 years (range 7 months – 69 years)
    - 59% males
    - Median length of follow-up was 8.2 years (range 1-25.3 years)
    - Type of transplant (TBI was used in 75% of patients)
      - 44% autologous (594 patients)
      - 50% matched related donor (671patients)
      - 6% matched unrelated donor (81 patients)
    - Incidence of GVHD was 56% (419 patients)

Campbell S, et al. *Cancer.* 2009;115:4127-35.

Avascular Necrosis

- 75 patients developed AVN
  - Cumulative incidence : 3.7% at 5 years and 5% at 10 years
  - Type of transplant (Cumulative incidence at 5 and 10 years)
    - 20 autologous (2.5% and 2.9%)
    - 44 matched related (3.6% and 5.4%)
    - 11 unrelated (13.2% and 14.7%)
  - 160 joints affected (median per patient = 2; range 1-8)
    - 106 hips
    - 26 knees
    - 19 shoulders
    - 2 ankles
    - 4 wrists
    - 3 elbows
  - Latency
    - Median 3.2 years (range 1-16.6 years)

Campbell S, et al. *Cancer.* 2009;115:4127-35.

Avascular Necrosis

Demographic and Clinical Factors and Risk of AVN: Multivariate Analysis

Factor	Overall Relative risk (95% CI)	Allogeneic Relative risk (95% CI)
Type of transplant		
Autologous	1.00	---
Related donor	2.39 (1.30-4.36)	1.00
Unrelated donor	5.82 (2.58-13.11)	1.67 (0.82-3.43)
Sex		
Female	1.00	1.00
Male	2.26 (1.33-3.85)	2.10 (1.12-3.95)
Presence of GVHD		
No	---	1.00
Yes	---	2.22 (1.02-4.82)

Campbell S, et al. *Cancer.* 2009;115:4127-35.

Avascular Necrosis

Demographic and Clinical Factors and Risk of AVN: Multivariate Analysis

Factor	Allogeneic Relative risk (95% CI)
Drugs used for GVHD prophylaxis/treatment	
No cyclosporine (CSA)	1.00
CSA alone	2.26 (0.46-11.32)
CSA + prednisone (pred)	5.17 (0.78-34.39)
CSA + pred + tacrolimus (FK506)	9.83 (2.34-41.23)
CSA + pred + FK506 + mycophenolate mofetil	7.98 (1.76-36.18)
P for trend	< 0.001

Campbell S, et al. *Cancer*. 2009;115:4127-35.

Avascular Necrosis

- **Role of bisphosphonates**
  - Studies in children in the setting of HSCT
  - Several challenges
    - Risk to benefit ratio favors the use in existing conditions rather than prevention
    - Establishment of dosing thresholds remains to be completed
    - Effects of normal growth and development on efficacy and outcomes
    - Number of patents to complete a trial is excessively large
    - Safety and long-term data lacking

Bachrach LK, et al. *J Clin Endocrin Metabol*. 2009;94:400-9.

What's Going to Be Hot?

- COG ASCT0431/PBMTC ONC051
  - Sirolimus-based GVHD prophylaxis in select CR1/CR2 ALL
- COG ASCT0521/PBMTC SUP051
  - Etanercept for treatment of idiopathic pneumonia syndrome
- COG ASCT0631/PBMTC SCT051
  - Phase III randomized trial of filgrastim-stimulated BM vs. conventional BM as a stem cell source in MSD transplants
- BMT CTN 0601
  - MUD HSCT using a RIC regimen for severe sickle cell disease
- PBMTC NMD0901
  - MUD HSCT using a RIC regimen for severe thalassemia

Pulsipher MA, et al. *Biol Blood Marrow Transplant*. 2010 January 14 [Epub ahead of print].

Questions

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Self Assessment Questions

1. In the recently published study by Campbell et al (*Cancer* 2009), the development of avascular necrosis (AVN) is a recognizable complication following hematopoietic stem cell transplantation (HSCT). Which one of the following risk factors was not identified by the authors in predisposing patients to developing AVN after allogeneic HSCT?
   A. Male gender
   B. Female gender
   C. Development of chronic graft versus host disease
   D. Exposure to at least three of the following drugs: prednisone, cyclosporine, tacrolimus and/or mycophenolate mofetil

Self Assessment Questions

2 Although micafungin remains to be studied across the pediatric continuum, there is data to suggest that neonates require higher daily doses compared to adult patients. Which of the following micafungin dose ranges may be most appropriate for a neonate with mild hepatic insufficiency?
   A. 1-3 mg/kg/day
   B. 3-5 mg/kg/day
   C. 5-7 mg/kg/day
   D. 7-9 mg/kg/day

Self Assessment Questions

3. What is the role of allogeneic hematopoietic stem cell transplantation in pediatric patients with high-risk ALL?
   A. It is the standard of care for all patients achieving a CR1
   B. It should be offered only to those patients with a matched-sibling donor after CR1
   C. It is the standard of care for all patients only after CR2 when disease relapse occurs on therapy or within 6 months of completing initial therapy
   D. Its use remains controversial and individual patient situations should be carefully assessed