The Role of Physical Therapy in Pediatric Hematology/Oncology: More Than Just Lab Values

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Objectives

1. Describe the epidemiology, incidence, pathology, physiology, and clinical manifestation of pediatric hematological disorders in infants, children, adolescents, and young adults, including: bleeding disorders, clotting disorders, anemias, and autoimmune diseases.
2. Recognize common pulmonary, neurologic, cardiovascular, gastrointestinal, musculoskeletal, hematological, and integumentary impairments in individuals with these diseases as they relate to function and participation.
3. Identify the medical and physical therapy management and measurements of pain, functional outcomes, and quality of life in persons living with hematological disorders.
4. Discuss the role of physical therapy in management of these patients including potential complications of bone marrow transplantation and pharmacological interventions.

Hematopoiesis

• Blood cell production

Cells, cells, and more cells...

- Red blood cells: carry oxygen
- Platelets: help blood to clot
- Granulocytes: phagocyte
  - Neutrophils: ingest bacteria
  - Eosinophils: allergic reactions and attack parasites
  - Basophils: release histamine
- Lymphocytes: regulate immune system
  - T-cell
  - B-cell
- Monocytes: phagocytic WBC
  - Dendritic: antigen-presenting
  - Macrophages: larger phagocyte, antigen-presenting (histiocyte)

Clotting Cascade

• Ask the right questions
• Understand the underlying cause of lab value variations
• Advocate indications and role of physical therapy
• Educate patients/families
• Empower patients to take control over their physical and functional potential
Clotting Cascade

Beyond Lab Values:
The Role of the Physical Therapist in Bleeding and Clotting Disorders

Learning Objectives
• Identify multi-system impairments found in bleeding disorders and clotting disorders
• Discuss evaluation tools to use for patients with bleeding and clotting disorders
• Reflect on treatment strategies when working with persons with bleeding or clotting disorders to improve quality of life

Bleeding Disorders
• Hemophilia A
• Hemophilia B
• Factor VII deficiency
• Von Willebrand Disease
• Glanzmann’s Thrombasthenia

What Is Hemophilia?
• Genetics
• Presentation
• Types
  – Factor VII deficiency
  – Hemophilia A
  – Factor IX deficiency
  – Hemophilia B
• Severity
  – Mild (<4%)
  – Moderate (1-4%)
  – Severe (<1%)
• Treatment
• Complications
  – inhibitor

Inactivity
Higher risk of injury and bleed
Hemophilic Arthropathy
Muscle Atrophy
Joint becomes Vulnerable
Carcao 2015
**Joint Bleed**

- Healthy knee:
- The blood starts to enter the joint:
- The joint swells. It may become so large that it's called "swollen knee."

**Development of Hemophilic Arthropathy**

**Evaluation of Joint Health**

- **Hemophilia Joint Health Score**
  - ROM
  - Loss of flexion/extension
  - Swelling
  - Duration of swelling
  - Joint pain
  - Crepitus on motion
  - Atrophy
  - Strength

**Intervention Techniques**

- Joint Preservation
  - PRICE
  - Alignment
  - Range of motion
  - Strengthening
  - Bone Density
  - Proprioception
  - Factor Replacement

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MASAC Guidelines


- Guidelines for treatment of muscle or joint bleed, post surgical

CLOTTING DISORDERS

Epidemiology

- 183 per 100,000 (European ancestry)
- VTE occurs in estimated 1 to 2 per 1000 persons annually in the United States
- Increased incidence in African Americans
- Increased incidence with age

Risk Factors

- High risk neonates
- Pregnancy
- Immobility
- Cardiac disease
- Inflammatory Diseases
- Obesity
- Cancer
- Central Venous Catheter
- Oral Contraceptives
- Inherited Thrombophilia
- Anatomical Risk Factors

Inherited Thrombophilia

- Factor V Leiden
- Antiphospholipid syndrome
- Protein C deficiency
- Protein S deficiency
- Antithrombin deficiency
Thromboembolism

- Venous
  - CNS
  - Non-CNS
  - Assess for Post Thrombotic Syndrome

- Arterial
  - CNS
  - Non-CNS
  - Assess for limb length discrepancy and chronic arterial insufficiency

Anatomical Risk Factors: May Thurner Anomaly

Left iliac vein compression from the contralateral right common iliac artery against posterior fifth lumbar vertebral body

Anatomical Risk Factors: Paget Schroetter Syndrome

- Thoracic Outlet Syndrome:
  - Axillary-subclavian vein thrombosis
  - Scalene tendon hypertrophy
  - Costoclavicular ligament abnormal insertion

Medical Management

- Pharmaceutical Management
  - Low molecular weight heparin
  - Vitamin K antagonist
  - Direct acting anticoagulants (Xarelto)

  - Catheter Directed Thrombolysis

Anticoagulation Therapeutic Levels

<table>
<thead>
<tr>
<th>Medication</th>
<th>Lab Value</th>
<th>Therapeutic Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heparin Drip</td>
<td>Unfractionated Heparin</td>
<td>0.3 - 0.7</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>Low Molecular Weight</td>
<td>0.5 - 1.0</td>
</tr>
<tr>
<td>Warfarin Coumadin</td>
<td>INR</td>
<td>2.0 - 3.0 or 2.5 - 3.5</td>
</tr>
</tbody>
</table>

To Range or not to Range?

- Is it new or old clot?
- In therapeutic range?
- Risk vs benefit?
- Location of clot: Central vs extremity
Precautions if on Anticoagulation

- Sports
- Activity Restrictions
- Diet
  - Vitamin K

Post Thrombotic Syndrome

- Most frequent complication of DVT
  - 30-50% of LE Venous DVT
- Manifestations of PTS
  - Chronic leg pain
  - Edema
  - Leg ulcers
  - Dilated superficial collateral veins
  - Skin discoloration

Standardized PTS Evaluation

- Upper Extremity Girth Measurements
  - Proximal
    - Acromion to elbow crease midpoint
  - Distal
    - Elbow crease to wrist crease midpoint

Bone Density with Anti Coagulation

- Vitamin K participates in bone metabolism and since oral anticoagulants antagonize vitamin K, their use may also increase the risk of osteoporosis.
- LMWH for 3–6 months may not increase the risk of fractures, but longer exposure for up to 24 months may adversely affect BMD.

Physical Therapy Intervention

- Patient Education
- Screen for Recurrent VTE
- Graduated Compression Garment
- Muscle pump
- Positioning
- Fall Risk Assessment
- Hydration
- Aquatics
Clinical Application

- Outpatient referral indicated if
  - Pain
  - Signs of PTS
  - Decline from PLOF

Case Study

- 17 y/o boy with history of R hemi-hypertrophy, RLE DVT, psoriasis and complex mental health issues.
- Anticoagulation: daily Coumadin
- Impairments
  - decreased B LE ROM
  - decreased flexibility of B LE
  - gait deviations
  - increased RLE girth (proximal only)
  - skin discoloration R LE

Case Study: PT recommendation

- Graduated Compression Stocking
- Outpatient PT
- Aquatics
- HEP

PTS Assessment

- Midpoint Girth Measurements of LE
- January 2017
  - R LE Distal 43.5 cm; 60 cm proximal
  - L LE Distal 38.5 cm; 56 cm proximal
- July 2017
  - R LE Distal 37.5 cm; 62 cm proximal
  - L LE Distal 35.5 cm; 55.25 cm proximal
  - January 31, 2018
    - Distally 3 cm difference R > L
    - Proximally 10 cm difference R > L

Take Home Message

- Perform multi-system assessment of patients with bleeding and clotting disorders
- Encourage early mobility with use of graduated compression for VTE
- Collaborate with interdisciplinary team to provide comprehensive care to these complex patient populations

- NHF PT Scholarship
- Questions?
  - ekapoor@childrensnational.org
References Bleeding and Clotting Disorders

- Flora FEARN, M., HILL, K., WILLIAMS, S., MUDGE, L., WALSH, C., Rajachandran V. Chemotherapies Red cell enzyme deficiencies (e.g. G6PD).
- Red cell enzyme deficiencies (e.g. G6PD). Hemoglobin. 2003;27(6):521-530.
- Red Blood Cell Disorders

Anemia

- Blood loss
- Bone marrow malignancies
  - Leukemia, lymphoma, multiple myeloma
- Chemotherapies
  - Platinum (cisplatin, carboplatin)
- Radiation
- Nutritional deficiencies
  - Iron, B12, folic acid
- Hemolytic Anemia
  - Red blood cells destroyed faster than being made
  - Transfusion reaction: immune system destroys transfused cells
- Red blood cell disorders

Red Blood Cell Disorders

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Beyond Lab Values: The Role of the Physical Therapist in Anemias and Autoimmune Diseases

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Red Blood Cell Disorders

- Flora FEARN, M., HILL, K., WILLIAMS, S., MUDGE, L., WALSH, C., Rajachandran V. Chemotherapies Red cell enzyme deficiencies (e.g. G6PD).
- Red cell enzyme deficiencies (e.g. G6PD). Hemoglobin. 2003;27(6):521-530.
Symptoms of Anemia

- Fatigue
- Pallor
- Tachycardia
- Lightheadedness/Dizziness
- Headaches
- Difficulty concentrating
- Chills
- Shortness of breath
- Weakness
- Yellowing eyes/skin

Sickle Cell Disease

- Most common genetically-inherited condition
- Hemoglobin(Hb) S and C - sickle
- 1:350 African American newborns
  - HbSS: homozygous= 65%
  - HbSC: heterozygous 35% (less severe)
- Many states with newborn screen

Sickle Cell Anemia

- Lack flexibility needed to transverse circulation
- Fragile and shortened life span (hemolytic anemia)
- Increased adhesiveness to vascular endothelium
- Vaso-occlusion in small blood vessels
- Local ischemia results in painful "crises"
- Chronic damage to organs/tissues
- Inflammatory cascade – further tissue damage
- Low hemoglobin: average 8gm/dl

Sickle Cell Anemia

- Pain:
  - Acute: Vaso-occlusive crisis (VOC) or vaso-occlusive events (VOE)
  - Chronic
  - Acute on Chronic
- Musculoskeletal:
  - Avascular Necrosis (AVN)
  - Osteomyelitis
- Pulmonary:
  - Acute Chest Syndrome (ACS)
  - Asthma
  - Pulmonary Hypertension
  - Chronic Lung Disease
- Central Nervous System:
  - Stroke
  - Transient ischemic attack (TIA)
  - Silent cerebral infarct
  - Diminished neuropsychological test performance (Wang 2007)
Pain

- Vaso-Occlusive Crisis (VOC) or Events (VOE)
- "Unpredictable and relentless"
- May be provoked by:
  - extremes or changes of temperature
  - infection
  - dehydration
  - high altitude
  - stress
  - fatigue
  - menstruation
  - no identified precipitating cause

Elander et al 1996, Yaster et al 2000

Acute Pain

- "Bone pain"
- Younger children:
  - hands, feet, fingers, toes "dactylitis" (hand-foot syndrome)
- Adolescents:
  - abdominal, chest, low back

Yaster 2000

Pain – Admissions

- 5% of patients account for 30% of hospitalizations
- "Revolving door"
  - frequent admissions
- Up to 10 or more hospitalizations a year
- Earlier death

- Pain intensity scores remain elevated during hospitalization in youth with SCD
- Physical function improves over the course of hospital stay in youth


Acute Care - Pain Management

Goals:
- Decrease Pain
  - Visual Analog Scale (VAS): MCID 0.97 cm
  - Numeric Pain Rating Scale (NPRS): MCID 0.9
  - >7.45 cm (VAS) or 7.5 (NPRS): need for pain medication
- Vasodilation
  - Heat and exercise


Chronic Pain

- May be a result of:
  - avascular necrosis
  - vertebral collapse
  - chronic leg ulceration
  - chronic low back pain
- Goals of management: improve functional capacities while decreasing pain

Yaster et al 2000

Pain Management

Cognitive Therapies:
- Psychological
  - Distraction, guided imagery, hypnotherapy, education, and psychotherapy
- Behavioral
  - Relaxation, biofeedback, behavioral modification, and deep breathing

Physical Therapies:
- Physical therapy, hydration, heat, massage, transcutaneous electrical nerve stimulation (TENS), acupuncture
  - Limited publications

Yaster et al 2000
Avascular Necrosis (AVN)

- As many as 50% have AVN or osteonecrosis
  - Temporary or permanent loss of blood supply to bones
    - head of femur
    - head of humerus
      - Equal occurrence – 2:17%
    - Combo occurring in 8 out of 10
    - temporomandibular, vertebral bodies
- Collapse of femoral head: 90% of patient within 5 years after diagnosis
- Decreased range of motion (ROM), pain with ROM or weight bearing


Avascular Necrosis

Treatment:
- Non-surgical
  - Observation, analgesics, limited weight bearing (WB)
  - Physical Therapy
- Surgical
  - Joint reconstruction
  - Nucleus decompression
  - Bone graft
  - Vascularized bone graft
  - Electrical Stimulation
  - Osteotomy

Martí-Carvajal et al 2016

Avascular Necrosis – PT ± Surgery

Randomized Controlled Trial
  - 176 met inclusion criteria
  - 46 enrolled in study
  - Mean age 26
  - If bilateral more involved hip was included
- Intervention (17 of 23): hip core decompression and physical therapy
- Control (21 of 23): physical therapy alone
- Matched Steinberg staging system
- Outcomes:
  - Children’s Hospital Oakland Hip Evaluation Scale (CHOHES) score
  - Hip survival

Martí-Carvajal et al 2016

AVN – PT ± Surgery (continued)

- Children’s Hospital Oakland Hip Evaluation Scale (CHOHES) score
  - Average follow-up 27 months
  - Intervention: 18 pt (18.1 +/- 19.8)
  - Control: 21 pt (15.7 +/- 19.6)
  - RR 0.95 (95% CI 0.58 to 1.60)

Complications:
- Intervention:
  - 2 re-admissions bilateral hip pain (< 30 days post-op)
  - 1 post-op infection
  - 6 required additional surgical intervention
  - 3 required total hip replacement
- Control:
  - 3 hip core decompression during the study
  - No significant difference between VOC or ACS

Martí-Carvajal et al 2016

3 year – Follow-up Study

- Control (PT only):
  - Hip survival: 86%
  - Harris hip score: 15.7 mean improvement
- Intervention (PT + surgery)
  - Hip survival: 82%
  - Harris hip score: 18.1 mean improvement

“Physical therapy alone appears to be just as effective as core decompression plus physical therapy in improving hip function and postponing the need for additional surgical interventions”

Neumayr et al 2006

Pulmonary

- Accounts for 27% of pediatric SCD hospitalizations
- Acute Chest Syndrome (ACS)
- Pulmonary Hypertension
- Asthma
- Chronic Lung Disease

Ahmad et al 2011, Steiner 2006
Acute Chest Syndrome (ACS)

- Second most common cause of hospitalization
- Most common post-operative complication
- Develops in as high as 50% of admitted patients
- A leading cause of death


Acute Chest Syndrome

- Multifactorial:
  - Infection
  - Fat embolization from bone marrow
  - Sequestration of sickled red blood cells
  - Direct lung infarction “wedge-shaped”
  - Back pain: ACS risk factor


Pulmonary Hypertension

- 11-31% children and adolescents
- Decline in exercise capacity


Asthma

- Incidence: 16.8-53%
- ACS 2x more episodes
- 2x higher mortality


Chronic Lung Disease

- Recurrent ACS Adults:
  - 74% restrictive
  - 20% normal
- Obstructive pattern might start in infancy


Pulmonary Intervention

- Incentive Spirometry!!!
  - Ahmad (2011): mandatory IS for non-pulmonary admissions
  - Decreased requirements oxygen, antibiotics, and blood transfusions
- PEP
- Blowing bubbles
- Ambulation/Activity
- Education
Exercise Assessment

- VO2 max
  - Decreased (less than 80% predicted)
- Anaerobic threshold (AT)
  - Less than predicted
- Low O2 pulse (rate of VO2 to heart rate = mimic stroke volume)
- Low VO2-work
- No mechanical ventilation impairments

Reasons:
- Anemia
  - Low peak VO2, low AT, low O2 pulse, elevated heart rate for level of work, increased respiratory equivalent of CO2.
- Pulmonary vascular disease
  - Gas exchange abnormalities
- Peripheral vascular disease and/or myopathy
  - High heart rate reserve

Connes et al 2011

Exercise Testing

- 6 minute walk test
  - Pulmonary hypertension
  - Pulmonary or peripheral vascular disease (severe SCA)
- Symptom-limited cardiopulmonary exercise testing (CPET)
  - Pulmonary or peripheral vascular disease
  - severe SCA- less than AT
  - Pulmonary hypertension
  - Heart disease (with EKG)
  - Bronchial hyper-reactivity (with spirometry)

Connes et al 2011

Exercise Prescription

- Moderate exercise (50% of maximal aerobic power) of 20 minutes did not cause marked hematological alterations. (Balayssac-Syransy et al 2011)
- Exercise therapy may contribute to a reduction in the length of hospitalization in sickle cell anemia children with painful VOC. (Alcorn et al 1984)
  - Decreased pain, increased respiratory muscles strength, improved quality of life. (Tinti et al 2010)
  - Regular exercise at moderate intensity could decrease the risk of inflammatory reaction related to exercise and could increased exercise intensity (Barbeau et al 2001)
    - Used 60-75% of predicted maximum
    - AT of SCA ranges between 35-60% VO2max (10, 24 exercise)

Connes et al 2011

Central Nervous System

- Stroke
- Transient ischemic attack (TIA)
- “Silent” cerebral infarct

Wang 2007

Stroke

- Children with SCD 500x more likely to have stroke
  - 13% in first 2 decades of life
  - Peak incidence 1st stroke 2-5 years old and 6-9 years old
  - Great risk in HbSS than HbSC (5:1)
- Ischemic – majority
- Hemorrhagic – 38%
  - Moyamoya –collateral circulation related to obstructed anterior portion of Circle of Willis

CNS - Medical diagnosis

• Risk factors:
  – Previous TIA
  – Recent or recurrent ACS
  – Increased blood pressure
  – Overnight oxygen saturation
  – Hemoglobin (low-steady)
  – High leukocytes
  – High platelets


PT Management

• Detailed sensory/motor exam
• Neurological rehabilitation
• Recognize decreased neuropsychological performance

Hydroxyurea (HU)

• S phase-specific chemotherapeutic agent
  – Increased Hb F
  – Decrease adhesion of sickle cells to endothelium
  – Myelosuppressive: decreased WBC and likely number of adherent leukocytes
• Decreased:
  – painful crises
  – ACS
    – BABY HUG (73% reduction)
  – transfusion requirements
  – hospitalization
• Increased
  – Survival
  – Anaerobic and aerobic exercise capacity
• Compliance is an issue


Outcome Measurements

• Youth Acute Pain Functional Ability Questionnaire (YAPFAQ)
  – Self-report measure of physical function in youth experiencing acute pain
  – Measures of physical activity, pain impact, pain location, and quality of life.
  – Pain intensity
• Children's Hospital Oakland Hip Evaluation Scale (CHOHES)
• Functional Independence Measure (FIM)
• Sickle Cell Pain Burden Interview Youth (SCPBI-Y)
• Functional Disability Inventory (FDI)
• Child Activities Limitations Interview (CALI)
• Pediatric Quality of Life Inventory (PedsQL)
  – Acute
  – Sickle cell pain
• Pain
  – Adolescent Pediatric Pain Tool (APPT)
  – Visual Analog Scale (VAS)
  – Numeric Pain Rating Scale (NPRS)

SCD: PT Summary

• Pain
  – Patient-centered: Hot packs, whirlpool, TENS, relaxation/ massage, deep breathing, distraction, impairment-specific exercise
• Musculoskeletal
  – AVN screening and intervention
• Pulmonary
  – Incentive spirometry
  – Bubbles, PEP
• Mobility
• Exercise Tolerance
  – Exercise screening and prescription
  – Outpatient services and monitoring
• Neurological
  – Stroke screening and intervention

Early Detection and Prevention

Integrated Sickle Cell Clinic @ Children's National
• Hematology Providers
• Pain Medicine
• Palliative Medicine
• Psychology
• Physical Therapy
• Social Work

Goal: Comprehensive management and prevention of chronic pain in children/adolescents with chronic pain risk factors
Thalassemia

- Italian, Greek, Middle Eastern, South Asian, and African descent
- Alpha Thalassemia
- Beta Thalassemia
- Major or Minor
- Hemoglobin S associated with Beta thalassemia
- Anemia

Medical Management

- Regular blood transfusions
- Iron chelation
  - Deferoxamine: prevent iron accumulation
- Folic acid
- Hematopoietic stem cell transplantation (HSCT)

Lal 2016

Autoimmune Diseases

- Hemophagocytic lymphohistiocytosis (HLH)
- Lupus
- Severe Combined Immunodeficiency (SCID)
- Immune thrombocytopenia (ITP)
- Autoimmune hemolytic anemia
- Evans syndrome
Hemophagocytic Lymphohistiocytosis (HLH)

- Disordered immune regulation
- Cytokine storm
  - Macrophages
  - T-Lymphocytes
    - Natural Killer T cells (NK-cells)
    - Cytotoxic T-lymphocytes
- Severe cytopenias
- CNS involvement - inflammatory

George 2014

HLH

- 1939 – Scott and Robb-Smith first described
- 1983 – long-term survival 4%, median survival untreated <2 months.
- Children (under 18) = 1 in 100,000

George 2014, Niece et al 2010

HLH diagnosis

- Molecular diagnosis and/or
- Five of the following:
  1. Fever
  2. Enlarged spleen
  3. Cytopenias (2 or more cell lines)
  4. High triglycerides
  5. Partial deficiency of fibrinogen
  6. Elevated ferritin
  7. Hemophagocytosis (bone marrow/spleen/lymph nodes)
  8. Low or absent natural killer (NK)-cell activity
  9. Elevated soluble CD25 (interleukin-2 receptor)

George 2014

Medical Management

- Immune-suppressive and modulatory agents
  - Chemotherapy
    - Etoposide
  - Intrathecal (IT) methotrexate (CNS disease)
  - Corticosteroids
    - Glucocorticoids: dexamethasone, prednisone
  - Cyclosporine (CSA)
  - Immunoglobulins
- Biological response modifiers
  - Rituximab: Epstein-Barr Virus (EBV)
- Treatment of illness (secondary)
  - Antibiotics
- Hematopoietic stem cell transplantation (HSCT)

George 2014, Weitzman 2011
Glucocorticoid Steroids

- **Inhibit glucose uptake** in skeletal muscle
  - Breakdown of muscle proteins
- **Stimulate protein degradation and inhibit protein synthesis**
  - Directly affect protein synthesis
- **Stimulate production of glutamine**
  - Amino acid – generate glucose in the liver
- **Muscle atrophy** – catabolic effects
- **Hyperglycemia**

LaPier 1997

Muscle Atrophy

- **Insidious**
- **Painless**
- **Symmetrical**
- **Type II fibers**
- Locomotion muscles less susceptible
- Diaphragm can be affected

1. Proximal lower extremity
2. Proximal upper extremity
3. Distal extremities

(LaPier 1997), (Falduto et al 1992)

Glucocorticoid Steroids – Exercise

- **Endurance** exercise training
  - **Decrease muscle atrophy** predominately in the most highly recruited type I skeletal muscle fibers
- **Strength**: Fifty days of isokinetic training (3x/week)
  - **Increased** thigh muscle area
  - **Decreased** thigh fat area
  - **Normalized** mean peak torque and total work output


Chart Review

- **Lab values**
  - Blood glucose levels
  - Serum creatine kinase (CK)
- **HLH**:
  - All cell lines
    - Platelets
    - Hemoglobin

LaPier 1997

Exercise

- Individualized
- Hydration – electrolyte imbalances
- Monitor signs/symptoms of hyperglycemia and hypoglycemia
- Resistance training
  - Low weight and high repetitions
- Avoid repetitive shearing forces (skin breakdown)
- Monitor blood pressure

LaPier 1997

Posterior reversible encephalopathy syndrome (PRES)

- Headache
- Altered consciousness
- Visual disturbances
- Seizures
- MRI: vasogenic cerebral edema predominantly in the posterior cerebral hemispheres
- High blood pressure
- Most associated cyclosporine
- Reversible

**Chart Review**

- Chart review
- Monitor lab value trends
- Optimize function
- Adapt/individualize exercise
- Educate on importance of function

**Hematopoietic Stem Cell Transplant (HSCT)**

- Sickle Cell Disease
- Thalassemia
- HLH
- Other immune diseases

**References Anemias and Autoimmune**


**References Hematopoietic Stem Cell Transplant (HSCT)**

- Ashley Braswell, PT, DPT
- APTA Board Certified Pediatric Clinical Specialist
- February 22, 2018

http://scstreatment.com/us/what-are-sickled-red-blood-cells
HSCT or HCT

- Intravenous (IV) infusion of autologous or allogeneic (donor) stem cells in order to restore inadequate bone marrow or immune system
  - Autologous not used to treat hematological disorders

Donor Types

- Matched sibling donor
- Matched unrelated donor (MUD)
- Mismatched unrelated donor
- Single or double umbilical cord
- Haploidentical donor

Source of stem cells

- Bone marrow
- Peripheral blood
- Umbilical cord

Diagnoses

- Bone Marrow Failure/Dysfunction
  - Aplastic anemia
  - Fanconi anemia
  - Shwachman-Diamond syndrome
  - Diamond-Blackfan anemia

*All have an increased likelihood to develop myelodysplastic syndrome or leukemia (usually acute myeloid leukemia)

Diagnoses

- Blood Disorders
  - Beta Thalassemia
    - Decreased production of hemoglobin
  - Sickle Cell Anemia
    - Abnormal hemoglobin

Diagnoses

- Immunodeficiency
  - Severe combined immunodeficiency (SCID)
    - Absence of T-lymphocyte and B-lymphocyte function
  - Severe congenital neutropenia
  - Hemophagocytic lymphohistiocytosis (HLH)
    - Too many immune cells (macrophages and lymphocytes)
  - Wiskott-Aldrich Syndrome
Pre-transplant testing

- History and physical exam
- Liver function, electrolyte, and creatinine
- Viral
  - cytomegalovirus (CMV), herpes virus, HIV, anti-HIV antibodies, hepatitis B and C, syphilis, human T-cell lymphotropic virus 1 and 2 (HTLV-1/2)
- ABO blood typing
- Human leukocyte antigen (HLA) typing

https://emedicine.medscape.com/article/208954-overview#a1

Chest radiography
- Electrocardiography (ECG)/Echocardiogram
- Pulmonary function tests

Performance Evaluation

- Scales used to measure functional capacity
- Found to predict survival in patients with cancer
- Used as entry criteria for clinical trials

Eastern Cooperative Oncology Group (ECOG, Zubrod, World Health Organization) performance scale

<table>
<thead>
<tr>
<th>Performance Status</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Fully active; no performance restrictions</td>
</tr>
<tr>
<td>1</td>
<td>Strenuous physical activity restricted; fully ambulatory and able to carry out light work</td>
</tr>
<tr>
<td>2</td>
<td>Capable of all self-care but unable to carry out any work activities; Up and about &gt;50% of waking hours</td>
</tr>
<tr>
<td>3</td>
<td>Capable of only limited self-care; confined to bed or chair &gt;50% of waking hours</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled; cannot carry out any self-care activities; confined to bed or chair</td>
</tr>
</tbody>
</table>

Preparative/Conditioning Regimens

- Myeloablative
  - Can include total body irradiation
  - Cause immunosuppression for engraftment
- Nonmyeloablative
  - Used for graft-versus-tumor effect which is helpful for cancers
  - Decreased toxicity

Reduced Intensity Regimens

- Can be myeloablative or nonmyeloablative
- Reduced acute and chronic toxicities
- Onset of graft-versus-host disease (GVHD) occurs later
- Incidence of GVHD is similar to myeloablative

Acute complications

- Mucositis
- Infection
- Prolonged, severe pancytopenia
- Acute Graft-versus-host disease (aGVHD)
- Graft failure
- Hepatic veno-occlusive disease (VOD) or sinusoidal obstructive syndrome (SOS)
- Thrombotic microangiopathy (TMA)

Chronic complications

- Chronic graft-versus-host disease (cGVHD)
- Eyes
- Endocrine
- Immune
- Pulmonary
- Musculoskeletal
- Neurological

Infection Prophylaxis

- Hand hygiene, HEPA-filtered positive-air-pressure sealed rooms
  - Facility dependent: isolation
- Antifungal
  - Fluconazole or amphotericin B/voriconazole
- Antibacterial prophylaxis
  - Fluoroquinolone

- Antiviral
  - Acyclovir – herpes simplex positive patients
  - Ganciclovir, intravenous immunoglobulin (IVIg) and CMV negative blood products for CMV negative patients
- Pneumocystis prophylaxis
  - Trimethoprim-sulfamethoxazole/pentamidine
- Gastrointestinal prophylaxis
  - Metronidazole/fluoroquinolones
- Hepatitis B vaccine for all negative patients
Typical Timeline

This diagram reflects a general overview of the transplant process:

- **High Dose Therapy**
- **Admission Here**
- **Stem Cell Infusion**
- **Engraftment**
- **Recovery**
- **Re-evaluation Disease**

- **Before Transplant**
  - Day 0
  - Days 1-10
  - Days 11-30
  - Days 31-90
  - Days 91-180
  - 1 year

- **After Transplant**

http://safepharmacyshop.su/

Acute graft-versus-host disease (aGVHD)

- Multisystem complication
- Donor immune cells recognize recipient cells as foreign, initiating an immune reaction causing disease
- Occurs in allogeneic transplants
- Pathophysiology
  - Tissue injury and up-regulation of inflammatory cytokines with T-cell alloreactivity (Filipovich 2008)

aGVHD definition

- ‘Classic’ within 100 days with symptoms of maculopapular rash, nausea, vomiting, diarrhea, ileus, anorexia and cholestatic hepatitis (rising serum bilirubin concentration)
- Persistent, recurrent or late onset aGVHD without diagnostic manifestations of chronic GVHD (cGVHD) beyond +100 days
  - Often occurs during withdrawal of immune suppression
- Skin, gastrointestinal tract, or liver abnormalities are classified as aGVHD regardless of time

aGVHD risk factors

- Female donor to male recipient
- Mismatched or unrelated donor
- Conditioning regimen intensity
- Prophylactic regimen used
- Peripheral blood and bone marrow > umbilical cord

aGVHD risk factors continued

- Lesser established risk
  - Recipient age, CMV status of recipient and donor, donor Epstein-Barr virus (EBV) status, gut decontamination
- Can differ depending on underlying disease
- Incidence and severity can depend on pre-transplant comorbidities

aGVDH

- Exact incidence is unknown
- 9 to 50% in HLA-identical sibling transplants
- Common in matched unrelated and haploidentical transplants

Chao 2017
Chronic Graft-versus-host disease (cGVHD)

- Immuno-regulatory disorder
- Features of the following:
  - Autoimmunity
    - Similar to Sjögren syndrome, scleroderma, primary biliary cirrhosis
  - Immunodeficiency
    - Thymic injury
    - Poor T-cell immunoreconstitution
- Usually develops within 3 years of HSCT
- Major cause of late non-relapse mortality after allogenic HSCT

Filipovich, 2008

C GVHD Classification

- Classic
  - At least one diagnostic/distinctive manifestation without features of aGVHD
- Overlap syndrome
  - Chronic and acute features appear together
- Both can be present at anytime after allogenic HSCT
- Sometimes diagnosis is missed as patients are at home and do not see their specialty transplant providers but once per year
  - Physical therapy implications

Filipovich, 2008

Diagnostic clinical signs of cGVHD

- Skin
  - Lichen planus-like features: purplish, itchy, flat top bumps
  - Morphea-like features: painless, discolored patches
- Mouth
  - Hyperkeratotic plaques
  - Restriction of opening (sclerosis)
- Genitalia
  - Vaginal scarring/stenosis

Filipovich, 2008

Diagnostic clinical signs of cGVHD

- GI
  - Esophageal web
  - Strictures/stenosis of upper/mid third of esophagus
- Lungs
  - Bronchiolitis obliterans, dx by biopsy
- Muscles
  - Fasciitis
  - Joint stiffness/contractures (sclerosis)

**All listed sufficient to diagnosis cGVHD**

Skin: Lichen planus-like

aGVHD grade 2
cGVHD grade 4

Skin: Morphea-like features

"Localized patchy areas of moveable smooth or shiny skin with leathery-like consistency, often with depigmentation"
Mouth: Lichen-type features


Distinctive Clinical Manifestation by Test

- Skin: depigmentation
- Nails
  - Dystrophy, longitudinal splitting
- Scalp
  - New onset scarring; alopecia (after recovery)
  - Scaling lesions
- Mouth
  - Mucosal atrophy, ulcers, pseudomembranes

Distinctive Clinical Manifestation by Test

- Eyes
  - New-onset dry, gritty, painful
  - Cicatricial conjunctivitis (inflammation/scarring)
  - Keratoconjunctivitis sicca (dry eye)
- Genitalia
  - Erosions, fissures, ulcers
- Lung
  - Bronchiolitis obliterans by PFTs/imaging
- Mandles, facia, joints
- Myositis/polymyositis

Eyes: Keratoconjunctivitis sicca

https://bethematchclinical.org/post-transplant-care/chronic-gvhd/eyes/

Transplant Specific Medications

- Immunosuppression
  - Cyclosporine & Tacrolimus
    - Burning/tingling hands and feet!
  - Granulocyte-colony stimulating factor (G-CSF)
    - Bony pain, fatigue
  - Steroids

Research disclaimer

- Most studies do not separate out malignancies and non-malignancies
- Predominately adult research but some pediatric research exists
- Pilot studies or small number of participants
Role of Physical Therapy

- During transplant, patients have a decline in physical functioning which results in muscle atrophy and a loss of strength (Wolin et al. 2010)
- Mobilization
  - Prolonged isolation reinforces immobility (Baumann et al. 2009)
- Endurance
- Quality of Life (QoL)

Pediatric Program Considerations

- Supervised interventions versus home based program (limited research)
- More intense contact on a regular basis in order to achieve benefit
- If possible, perform in treating hospital
  - Alleviate parent concerns

PT Interventions During HSCT

- Begin during conditioning and continue through discharge
- Supervised, low to moderate intensity exercise addressing:
  - Aerobic endurance training
  - Strength
  - Balance
  - Coordination
  - Flexibility
- Focus on positively affecting QoL
  - Functional mobility, transfers, walking, and stair climbing
- Higher frequency, 5x per week is beneficial to maintain physical performance

Low to Moderate Intensity Exercise Program

- 30-60 minutes with rest breaks as needed
- Aerobic exercise at 50 to 75% of max heart rate with rate of perceived exertion (RPE) at 10 to 13
- Strengthening/stretching – RPE of 10 to 13
- Progressive relaxation exercises at RPE 6 to 9

Discharge from Hospital Recommendations

- Supervised, scheduled moderate intensity exercise program
- Goal of returning to prior level of function
- Designed to address:
  - Fatigue
  - Physical function
  - QoL
- Minimum frequency of 2x per week for 6 to 12 weeks
- Moderate intensity defined as:
  - Aerobic exercise starting at 50 to 60% and progressing up to 70 or 80% max HR with RPE up to 13
  - Strengthening/stretching at RPE of 10 to 13

Wolin et al. 2010

- Systematic Review
- Two studies of kids receiving HSCT
  - Pediatric survivors with ALL/AML, who received HSCT the previous year completed 8 week intervention which showed (San Juan et al. 2008)
    - Improvement in muscle strength, functional mobility, aerobic fitness and QoL
  - An aerobic and resistance training program for 3 weeks during inpatient stay (Chamorro Vina et al. 2010)
    - Increased fitness
    - Increased body mass
    - No negative effects on immune recovery
### Physical Exercise Interventions vs. Treatment Phases, potential effects

<table>
<thead>
<tr>
<th>Phase of Medical Therapy</th>
<th>During HSCT</th>
<th>After HSCT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Endurance performance</strong></td>
<td>Stabilization effect</td>
<td>Performance improving effect</td>
</tr>
<tr>
<td><strong>Strength performance</strong></td>
<td>Stabilization effect</td>
<td>Performance improving effect*</td>
</tr>
<tr>
<td><strong>Psychosocial parameters (QoL, fatigue)</strong></td>
<td>Improving effect</td>
<td>Improving effect</td>
</tr>
<tr>
<td><strong>Body composition</strong></td>
<td>No data available (2008)</td>
<td>Improving effect</td>
</tr>
<tr>
<td><strong>Immune system/function</strong></td>
<td>(+) effect on duration of recovery*</td>
<td>No data available (2008)</td>
</tr>
</tbody>
</table>

*Little data available

### Physical Exercise Interventions, tentative Recommendations

<table>
<thead>
<tr>
<th>Phase of Medical Therapy</th>
<th>Type of Exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Before HSCT</strong></td>
<td>Mixed Exercise (3-5x per week) <strong>Duration:</strong> up to 30 min <strong>Intensity:</strong> Moderate (12-14 Borg, 70-80% max HR)</td>
</tr>
<tr>
<td><strong>During HSCT</strong></td>
<td>Start with endurance training (5x per week up to 7x), adding resistance training with increased platelet counts in last third of hospitalization (2-3x per week) <strong>Duration:</strong> 10-15 min up to 30 min <strong>Intensity:</strong> Moderate (12-14 Borg, 70-80% max HR)</td>
</tr>
<tr>
<td><strong>After HSCT</strong></td>
<td>Mixed Exercise (3-5x per week) <strong>Duration:</strong> up to 30 min or more <strong>Intensity:</strong> Moderate (12-14 Borg, 70-80% max HR)</td>
</tr>
</tbody>
</table>

### Hacker et al 2011

- Pilot study of 19 adults undergoing HSCT
- Exercise intervention versus control group
- Intervention included: strength training including concentric/eccentric exercises, body weight resistance, and elastic band resistance if able
- Assessment included: Timed stair climb (functional quad strength), Handgrip strength (dynamometer), Thirty-Second Chair-Stand Test, Time Needed to stand up from Bed Rest Exam, Fatigue, Health Status Perceptions, QoL
- Strength-training group reported less fatigue compared with usual-activity group was only statistically significant result
Baumann et al 2009

- 64 adults with cancer undergoing allogeneic/autologous HSCT
- Controlled randomized study
- Training group (TG) versus control group (CG)
- TG lost 10% strength; CG lost 24%
- TG maintained endurance, TG decreased
- TG had improved QoL and physical functioning
- CG showed increased fatigue

Take Home

- HSCT is a complicated process that is continually changing as new research and medicines are found
- Physical therapists can be instrumental in stabilizing secondary negative effects of intensive medical treatment and prolonged hospitalizations
- Research to support supervised exercise program improving QoL and fatigue

Resources

- Medscape
  - Overview with specifics
- Bethematchclinical.org
  - Clinicians resource
- UpToDate
- Cincinnati Children’s Best Evidence Statement

References HSCT


