Surviving the Cure: Guidelines for BMT Long-Term Follow-Up Care

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“It Takes a Village....”

- Meet specialized needs of BMT patients
- Aim for best possible outcomes through:
  - Prevention
  - Early detection
  - Minimizing disabilities
- Requires partnership:
  - Primary care physicians and specialists
  - Nurses, advanced practice professionals, pharmacists, social workers, allied health providers
  - Patients and their families

Objectives

- Understand late effects and known risk factors by organ system
- Understand the 2012 expert panel guidelines for screening and preventive practices for long term survivors
- Be able to implement recommendations for your patients
Risk Factors for Late Complications

Recommended Screening and Preventive Practices for Long-term Survivors after HCT

Late Complications Affect All Organ Systems
Immunity and Infections

- Infectious risk highest in the first 1-2 years after transplantation; allo HCT >> auto HCT
- Risk continues long-term for patients with cGHVD
- Patients and their primary care providers should be educated regarding immune status

Immunity and Infections - Recommendations

- Patients with chronic GVHD:
  - Antibiotic prophylaxis targeting encapsulated organisms for at least as long as immunosuppressive therapy is administered
  - Antiviral and antifungal prophylaxis should be considered
- Screening for CMV reactivation should be based on risk factors, including intensity of immunosuppression.
- Prophylactic antibiotics for oral procedures
  - American Heart Association guidelines for endocarditis prophylaxis.

Immunity and Infections - Recommendations

- Pneumocystis jirovecii prophylaxis
  - Allogeneic HCT
    - Engraftment until as long as immunosuppressive therapy is given
  - Autologous HCT
    - 3 to 6 months for those with substantial immunosuppression (purine analogues, high dose steroids)
### Vaccinations

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Time post-HCT to Initiate</th>
<th>No. of Doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumococcal</td>
<td>3-6 months</td>
<td>3-4</td>
</tr>
<tr>
<td>Tetanus, Diphtheria, acellular Pertussis</td>
<td>6-12 months</td>
<td>3</td>
</tr>
<tr>
<td>Haemophilus influenza</td>
<td>6-12 months</td>
<td>3</td>
</tr>
<tr>
<td>Meningococcal</td>
<td>6-12 months</td>
<td>1</td>
</tr>
<tr>
<td>Inactivated polio</td>
<td>6-12 months</td>
<td>3</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>5-12 months</td>
<td>3</td>
</tr>
<tr>
<td>Inactivated influenza</td>
<td>4-6 months</td>
<td>1-2</td>
</tr>
<tr>
<td>MMR*</td>
<td>24 months</td>
<td>1-2</td>
</tr>
</tbody>
</table>

*Not recommended <24 months post-HCT in patients with active GVHD or on immune suppressive therapy.

### Ocular Late Effects

- **Cataracts**
  - 5-20% without TBI; 40-70% with TBI
  - Risk factors: TBI, age, corticosteroids

- **Ocular sicca syndrome**
  - Incidence 20-60%
  - Risk factors: TBI, chronic GVHD

- **Ischemic microvascular retinopathy**
  - Not seen post auto-HCT
  - Risk factors: TBI, cyclosporine, chronic GVHD

- **Posterior segment**
  - Hemorrhage
  - Optic disc edema
  - Infectious retinitis (CMV, toxoplasma, fungi)

### Ocular Recommendations

- **Routine clinical evaluation of visual history and symptoms at 6 months, 1 year and yearly thereafter for all patients**

- **Ophthalmology evaluation for visual acuity and fundus exam at 1 year for all patients**

- Patients with any visual symptoms should undergo ocular exam immediately

- **cGHVD** – refer to ophthalmology sooner and at first clinical sign of cGHVD
Oral Late Effects

- Sicca syndrome
  - Xerostomia occurs in ~50%
  - Risk factors: TBI, chronic GVHD
- Dental caries
  - Risk factors: TBI, chronic GVHD, dry mouth
- Head and neck malignancies
  - Risk factors: chronic GVHD, head and neck radiation, Fanconi’s anemia

Oral Recommendations

- Educate patients about preventive oral health and routine dental maintenance
  - Pre-HCT dental evaluation for all patients
  - Avoid smoking and chewing tobacco
  - Decrease intake of sugar containing beverages
  - Avoid intraoral piercing
- Clinical oral evaluation at 6 months, 1 year and yearly
  - Patients at high risk: every 6 months, and educated on meticulous oral hygiene and taught self oral inspection
  - Include history of xerostomia, review high risk habits, perform oral, head and neck and oral exam
- Dental evaluation at 1 year for all, then yearly
  - More frequent for those with oral GVHD or Fanconi’s anemia

Pulmonary Late Effects: BOS

- Bronchiolitis obliterans syndrome (BOS)
  - Incidence 2-14% (allogeneic HCT)
  - Risk factors: chronic GVHD (“pulmonary GVHD”)
  - Clinically manifests as DOE, cough, wheezing
  - Obstructive lung defect on PFTs
  - CT findings: Bronchiolar obstruction & air trapping
  - May respond to steroids, azithromycin; high mortality
Pulmonary Late Effects: COP

- Cryptogenic organizing pneumonia (COP; BOOP)
  - Rare, no specific early screening tests
  - Risk factors: variety of toxic, immunological, inflammatory injuries
  - Usually presents in first 6-12 months post-HCT; later onset may occur in patients with chronic GVHD
  - Clinical presentation: non-productive cough, DOE, low grade fevers
  - CT findings: Patchy infiltrates: restrictive PFTs
  - Responsive to corticosteroids; 80% of patients recover

Pulmonary Recommendations

- Routine clinical assessment at 6 months, 1 year and yearly
- Some recommend more frequent clinical assessments including PFTs in patients with chronic GVHD
- Counseling regarding risks of smoking and smoking cessation

Cardiovascular Late Effects

- Any cardiac dysfunction (cardiomyopathy, valvular anomaly, conduction anomaly)
- Vascular: Cerebrovascular disease, ischemic heart disease, peripheral arterial disease
- Metabolic syndrome (hypertension, abdominal obesity, diabetes)
- Incidence and Risk Factors:
  - 2-3% of late deaths; may be underestimated and may increase with longer follow-up
  - Risk factors: Radiation to chest and neck, cumulative anthracycline dose, iron overload, cardiac function pre-HCT
  - General population risk factors (e.g., smoking, lipids, diabetes)
Cardiovascular Recommendations

• Routine clinical assessment and CV risk factor evaluation for all at 1 year and yearly
  – More frequent evaluations for high-risk (e.g. mediastinal radiation; amyloidosis; pre-existing abnormalities)
• Education and counseling on “heart” healthy life style
  – Regular exercise, dietary counseling, healthy weight, no smoking
• Treat risk factors, including diabetes, hypertension and dyslipidemia (for patients on therapy: fasting lipid panel every 6-8 weeks until treatment goal is achieved, then every 4-6 months)
• Endocarditis prophylaxis per AHA recommendations

Hepatic Late Effects

• Medication toxicity
• Chronic GVHD
  – Major cause of liver toxicity post-HCT
  – Liver biopsy should be done for diagnosis if only manifestation
• Iron overload
  – Prevalence: 25%
  – Risk factors: Red cell transfusions; ineffective erythropoiesis; carrier state for hereditary hemochromatosis
• Viral hepatitis
  – Prevalence: 3-6%
  – Hepatitis B – mild to moderate liver disease
  – Hepatitis C – often asymptomatic; cumulative incidence for cirrhosis is 11% at 15 yrs and 24% at 20 yrs; extrahepatic disease and genotype 3 are associated with progression to cirrhosis

Hepatic Recommendations

• LFTs every 3-6 months for first year, then yearly thereafter; more frequent on individual basis
• Iron overload
  – Serum ferritin at 1 year for all patients who received RBCs either pre- or post- transplant
  – Additional diagnostic testing (liver bx, MRI) if therapy contemplated
• Hepatitis B and C patients
  – Monitor viral load
  – Consult liver and infectious disease specialists
  – May recommend liver biopsy, particularly at 8-10 years post-HCT
Renal and Genitourinary Late Effects

• Chronic kidney disease (GFR less than 60 ml/min)/1.73m²
  – Incidence: 5-65%
  – Common manifestations
    • Progression of early onset acute renal failure
    • Thrombotic microangiopathy
    • Glomerulonephritis
    • Nephritic syndrome
    • Interstitial fibrosis
  – Risk factors: older age, radiation (TBI, involved field), GVHD, drugs, hypertension, infections (CMV)
• Bladder wall scarring and contraction
  – Risk factors: substantial hemorrhagic cystitis
• Recurrent urinary tract infections
  – Risk factors: immunosuppressive therapy; women with GVHD of vulva/vagina

Renal and Genitourinary Recommendations

• Check blood pressure at every clinic visit and treat hypertension appropriately
• Avoid nephrotoxins
• Evaluate renal function at 6 months, 1 year and at least yearly thereafter for all patients (more frequently for high risk patients)
  – BUN, creatinine, urine protein
  – Early referral to nephrologist for any sign of CKD or progressive disease
  – Further w/u: renal ultrasound, renal biopsy as clinically indicated

Muscle and Connective Tissue Late Effects

• 35% of 10-year survivors report musculoskeletal stiffness, cramps, weakness and joint swelling
• Steroid myopathy
  – Proximal muscle weakness (quadriceps muscle most severely affected) secondary to long-term steroid use
  – May be associated with increased risk of mortality
  – Easy test: observe patient changing position from supine to sitting or sitting to standing
Muscle and Connective Tissue Late Effects

- Fasciitis/scleroderma
  - Diagnostic feature of chronic GVHD
  - Early involvement of fasciae and tendons manifests clinically as edema; progresses to fibrosis and joint contractures
  - Most common in fingers, wrists, shoulders, elbows and ankles

- Myositis or polymyositis
  - Rare; distinctive feature of chronic GVHD; usually occurs 2-5 years post-HCT
  - Majority of patients have elevated serum creatinine kinase; myopathic pattern on EMG; peri-fascicular lymphocytic infiltration on muscle biopsy
  - Responds favorably to immunosuppressive therapy

Muscle and Connective Tissue Recommendations

- All HCT recipients should follow age-specific guidelines for physical activity

- Patients with chronic GVHD
  - Frequent joint ROM assessment
  - Patients should be instructed on self-assessment of ROM

- Patients on steroids
  - PT consult to establish baseline function and provide ROM and muscle strengthening exercises
  - Frequent clinical evaluation for myopathy

Bone Issues Osteopenia and Osteoporosis

Decrease in bone mass and increased risk for fracture

- Normal
- Osteoporosis
Numerous mechanisms of bone loss in HCT recipients

<table>
<thead>
<tr>
<th>Contributing factor</th>
<th>Mechanism</th>
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<tbody>
<tr>
<td>Increase in bone resorption</td>
<td>Decrease in 1,25 (OH) vitamin D3 production, secondary hyperparathyroidism</td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td>Decrease in renal function, osteoclast activation, hyperparathyroidism causing decrease in estrogen and testosterone</td>
</tr>
<tr>
<td>Calcineurin inhibitors</td>
<td>Osteoclast activation, secondary hyperparathyroidism</td>
</tr>
<tr>
<td>Chemotherapy/irradiation</td>
<td>Decrease in renal function, osteoclast activation</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Decrease in renal function, osteoclast activation, secondary hyperparathyroidism</td>
</tr>
<tr>
<td>Malabsorption (e.g. GVHD, mucositis)</td>
<td>Decrease in calcium and vitamin D absorption</td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td>Magnesium and calcium wasting</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>Direct inhibitory effect on osteoblast formation and activity</td>
</tr>
<tr>
<td>TBI/cranio-spinal irradiation</td>
<td>Direct inhibitory effect on osteoblast formation and activity, decrease in growth hormone and IGF-1 production</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Apoptosis of osteoblasts, inhibition of osteoblastogenesis; decrease in calcium levels due to inhibition of gastrointestinal absorption and increase in renal excretion</td>
</tr>
</tbody>
</table>


Avascular Necrosis/Osteonecrosis

- Avascular necrosis
  - 4-19% of survivors
  - Risk factors: same as for post-HCT bone loss PLUS inflammatory microvascular changes related to GVHD
  - Joint pain is first clinical sign
  - Hip most common (over 60% of cases/bilateral in >60%; other joints include knees, wrists, and ankles)
  - MRI is test of choice
  - Surgical approaches: core decompression in early cases; joint replacement

Skeletal Recommendations

- Bone Loss
  - Screening dual photon densitometry at 1 year in adult women, all allogeneic HCT recipients, and sooner in high risk patients
  - Evaluate gonadal function in patients with bone loss
  - Counsel patients about preventative measures
    - Maintain high level of suspicion in patients at risk
    - Weight-bearing exercise
    - Fall prevention
    - Vitamin D and calcium supplementation
    - Hormone replacement therapy considered
    - Consider bisphosphonates for patients with osteopenia, at high risk for bone loss, and for evidence of progressive bone loss
  - Screening for AVN is not recommended on routine basis
Central and Peripheral Nervous System Late Effects

- Manifestations
  - May be subtle
  - Memory loss, cognitive and learning problems in up to 10-20% of patients
  - Long term deficits in >40% of survivors
  - Leukoencephalopathy
  - Peripheral neuropathy
- Risk factors
  - Age, prior cognitive and learning problems
  - Chemotherapy/TBI and immunosuppressive drugs
  - Infections
  - More common in allogeneic HCT than auto
  - Growing evidence for GVHD effect on CNS (cerebral angiitis like syndrome; Guillain-Barre like syndrome)

Central and Peripheral Nervous System Recommendations

- Clinical assessment for symptoms and signs at 1 year and yearly
- Evaluation for cognitive developmental milestones at least annually in pediatric patients; adults should be queried annually
- Earlier and more frequent evaluations in high-risk patients

Endocrine Late Effects

- Hypothyroidism
  - Subclinical: 7-15% in first year
  - Median time to diagnosis is 4 years
  - Risk factors: TBI, busulfan/acy
- Autoimmune thyroiditis
  - Risk factor: radiation
- Hypogonadism
  - Some degree in >90% survivors (male and female)
  - Risk factors: age, gender, TBI, busulfan
- Low incidence of primary adrenal failure
- Growth disturbance in children
**Endocrine Recommendations**

- Thyroid function tests (TSH, T3 and free T4) at 1 year and yearly thereafter.

- Clinical and endocrinologic gonadal assessment:
  - At 1 year for all women post-pubertal at HCT with annual gynecologic evaluation.
  - In men (FSH, LH, testosterone) if symptoms warrant.
  - At 6 months for pre-pubertal boys and girls; endocrinologist care vital.

- Slow terminal tapering of steroids; give stress doses during acute illness.

**Muco-Cutaneous Late Effects**

- Nearly 70% of patients with chronic GVHD (skin, alopecia, nail dystrophy, sweat impairment).

- Women with hypo-estrogenism due to premature menopause.

- Genital chronic GVHD:
  - Develops in 12% of women with OR without associated systemic GVHD.
  - Initial symptoms may be mild and nonspecific.
  - Excoriated or ulcerated mucosa, fissures.
  - Narrowing of introitus.
  - Vaginal scarring or obliteration.
  - Less common in men.
  - Phimosis.

**Muco-Cutaneous Recommendations**

- Skin:
  - Patients should be instructed in self examination, and in avoiding excess sunlight and use of sunscreens.

- Genital:
  - All women post allo-HCT should be instructed about self examination, general hygiene, early recognition of symptoms; annual gynecologic exam.
  - Women with established chronic GVHD should have gynecological exam to screen for genital involvement.
Psychosocial Adjustment

- Depressive symptoms and psychological distress are frequent
  - Both in patients, caregivers, spouses and family members
- May increase at transition from acute convalescence to long-term follow-up
  - Changes in roles
  - Employment situations
  - Financial difficulties
- Caused by multiple factors
  - Anemia, drugs, endocrine dysfunction, emotional distress, change in sleep patterns, sexual dysfunction
  - Underlying medical cause has to be ruled out

Psychosocial Adjustment

- Screen for depression throughout recovery period, at 6 months, at one year, and yearly thereafter
- Mental health professional assessment if needed
- Inquire as to level of spousal/caregiver psychological adjustment and family functioning
- Query sexual function in adults at 6 months, 1 year, and yearly thereafter

Secondary Cancers

- Devastating late complication
- Allo HCT recipients have a 2- to 3- fold increased risk of solid tumors
  - Risk factors: radiation therapy (sarcoma, breast, thyroid), immunosuppression, chemotherapy, cGVHD
  - Risk increased with time, and continue to increase even after 10 years post HCT
- Auto HCT = risk of tAML/MDS; 4% at 7 years; median onset 2.5 years
  - Risk factors: alkylators, prolonged conventional chemotherapy, pre-transplant irradiation
- PTLD – rare; 1% at 10 years; usually early (6 months) but may be late; EBV association
Secondary Cancers - Recommendations

- Advise patients of risk
- Avoid high risk behaviors
- Screening clinical assessments yearly should include symptom review for secondary malignancies
- Women with radiation exposure (>800 cGy to chest) - begin screening mammography age 25 or 8 years post radiation, whichever is later, but no later than age 40
- Pay particular attention to oral exam for patients with history of cGHVD of the mouth and Fanconi’s anemia pts

Additional Topics

- General screening guidelines and preventive health
- Fertility
- Sex-specific screening guidelines
- Healthy lifestyle guidelines
- Implementation of guidelines in resource limited countries
- Variety of links and tables for easy access, including screening and prevention of late complications by selected exposures and risk-factors

Free Guidelines for Patients

- Recommended screening/preventive practices for:
  - 6-months post-transplant
  - 12-months post-transplant
  - 24+ months/annual appointments

- Patient guidelines include:
  - Simple medical descriptions
  - Checklist to take to physician visits
  - Glossary of medical terms

Visit: BeTheMatch.org/careguide
Free Guidelines for Careproviders

Recommendations for autologous and allogeneic patients, including:

- Timing for transplant consultation for 16 diseases, plus outcomes data
- Post-transplant screening and vaccinations
- GVHD screening (with photo atlas)

Available through mobile app, online and print
- From your mobile store, search "transplant"

Visit: marrow.org/md-guidelines

Conclusions

- Late complications may affect any organ system
- Increased risk for patients with cGHVD
- Heightened vigilance, prevention, therapy are imperative
- Develop a partnership with "patients and their villages" for life-long preventative and therapeutic medical care