Hematopoietic Stem Cell Transplant Survivorship Care

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Disclosures

- None*

*except I will be focusing on adult allo HSCT recipients

Objectives

- By the end of this session, participants will be able to:
  - Identify secondary effects of allogeneic bone marrow / stem cell transplant in adults
  - Describe surveillance for late effects in this population
  - Summarize follow-up guidelines in BMT survivorship care

Primer: 2 types of SCT

Allogeneic	Autologous
Donor cells	Patient's own cells
Used if bone marrow cancer	Replace damaged cells after high intensity chemo given to kill cancer
High intensity chemo given to wipe out marrow	
Stem cell "rescue"	
Graft vs. leukemia effect	

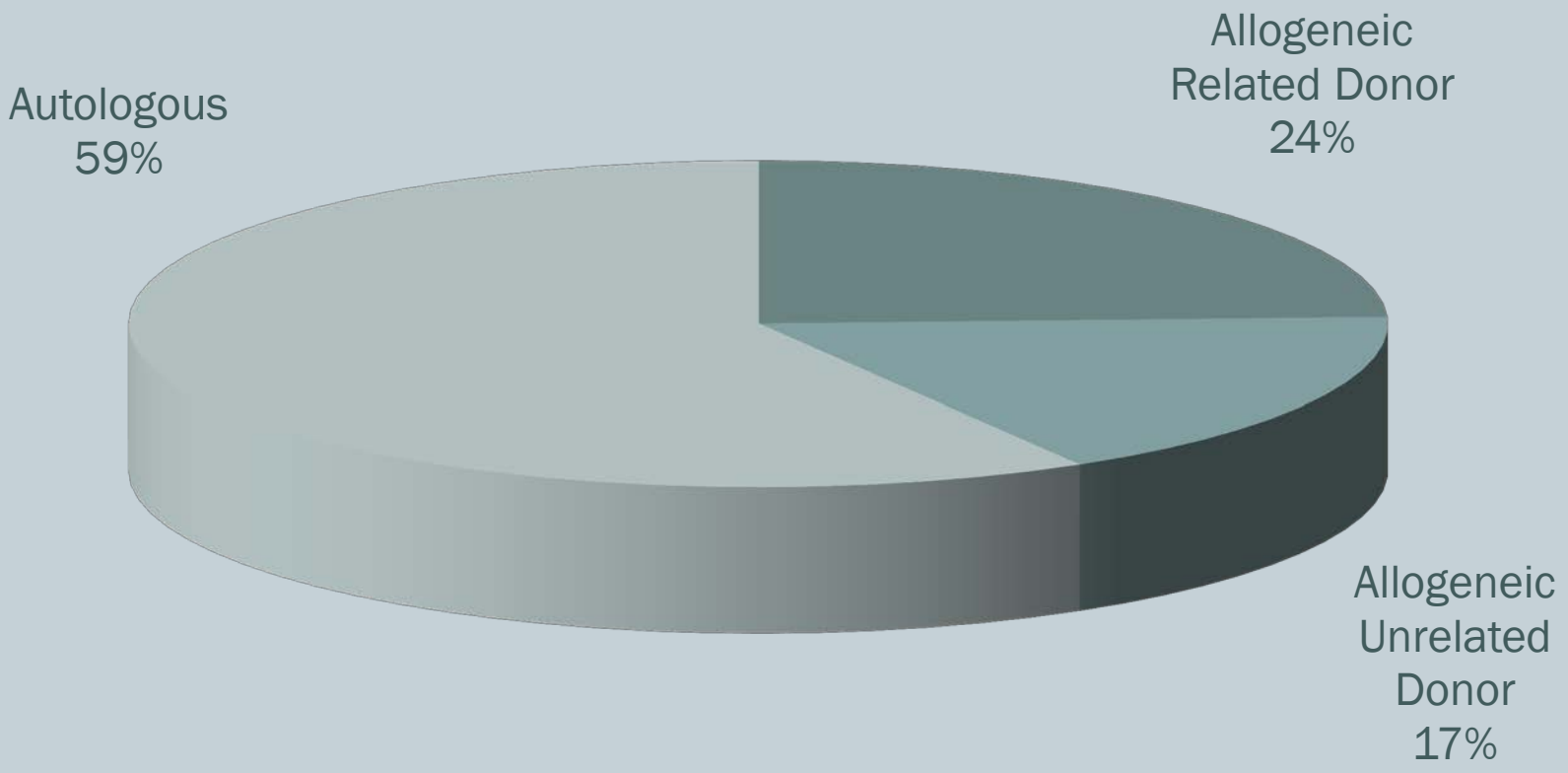
Primer: Donor sources

- Bone marrow
- Peripheral blood
- Umbilical cord blood

- Related
  - Fully matched siblings
  - Haploidentical (“half match”)
    - parents/children
    - siblings 50% chance
- Unrelated
  - Matched / mismatched

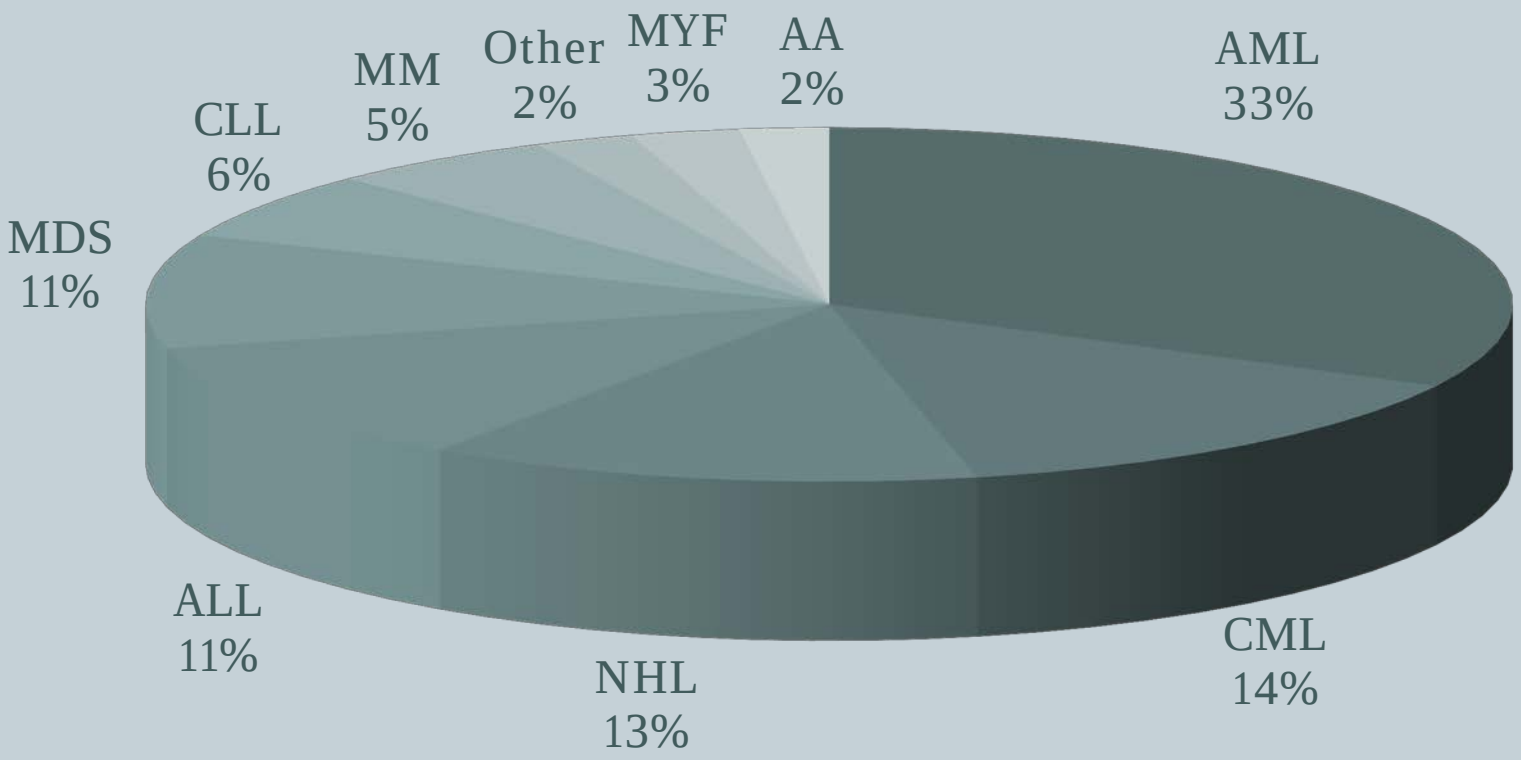
Allogeneic & Autologous HSCT

Aug 1981 - Dec 2018 (Total = 5136)



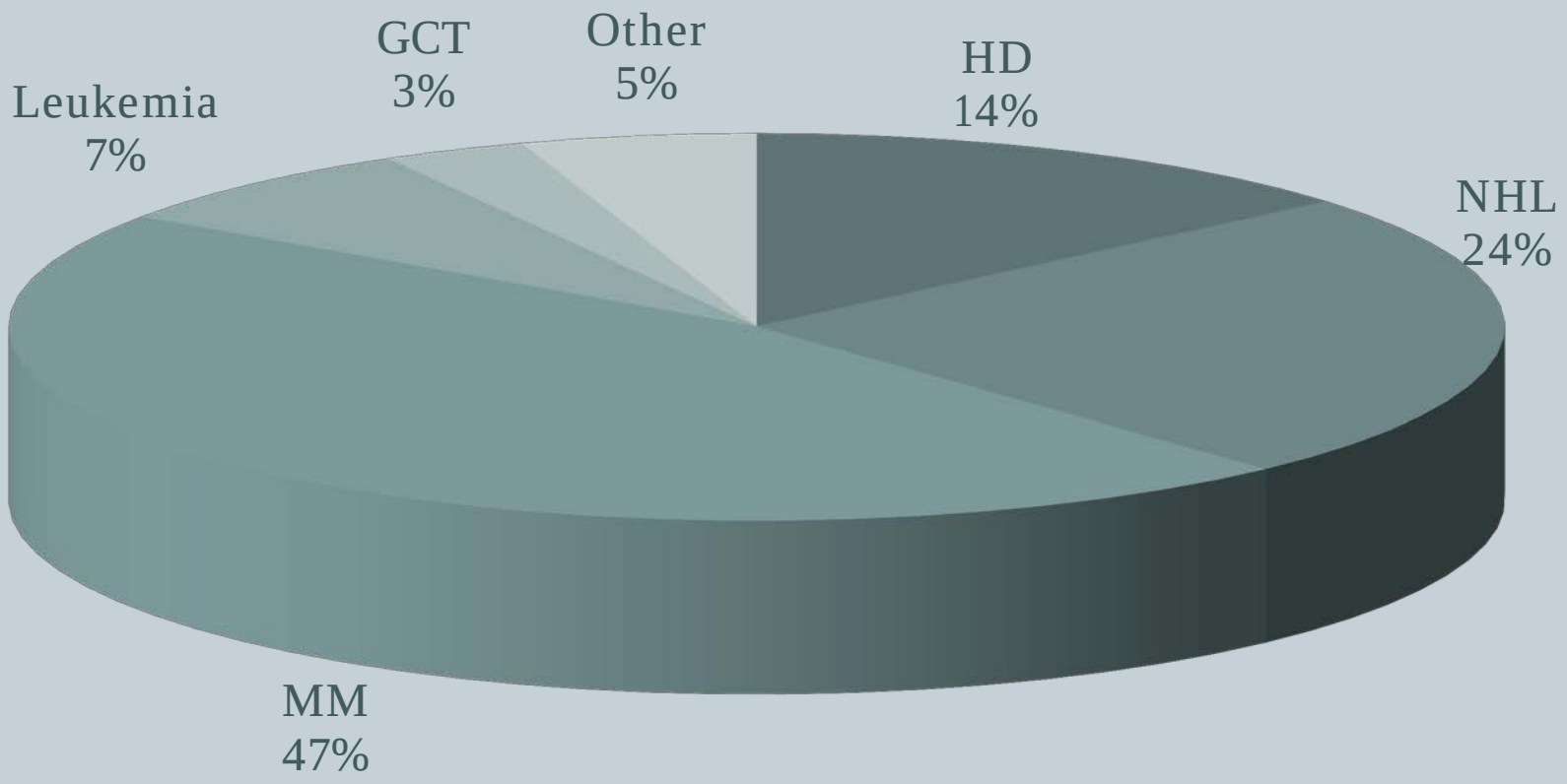
Allogeneic HSCT by Diagnosis

Aug 1981 - Dec 2018 (Total = 2132)



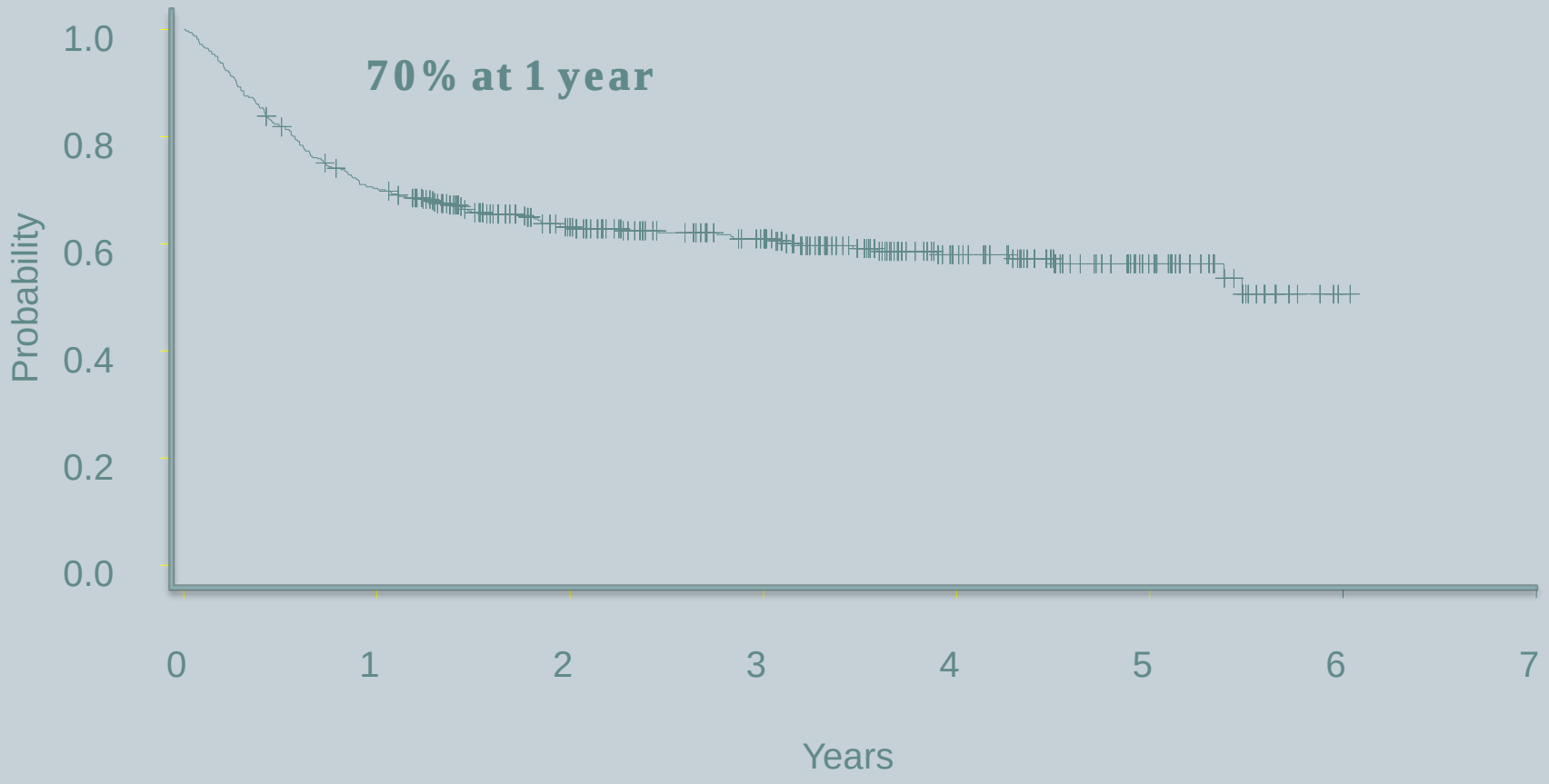
Autologous HSCT by Diagnosis

Aug 1981 - Dec 2018 (Total = 3004)



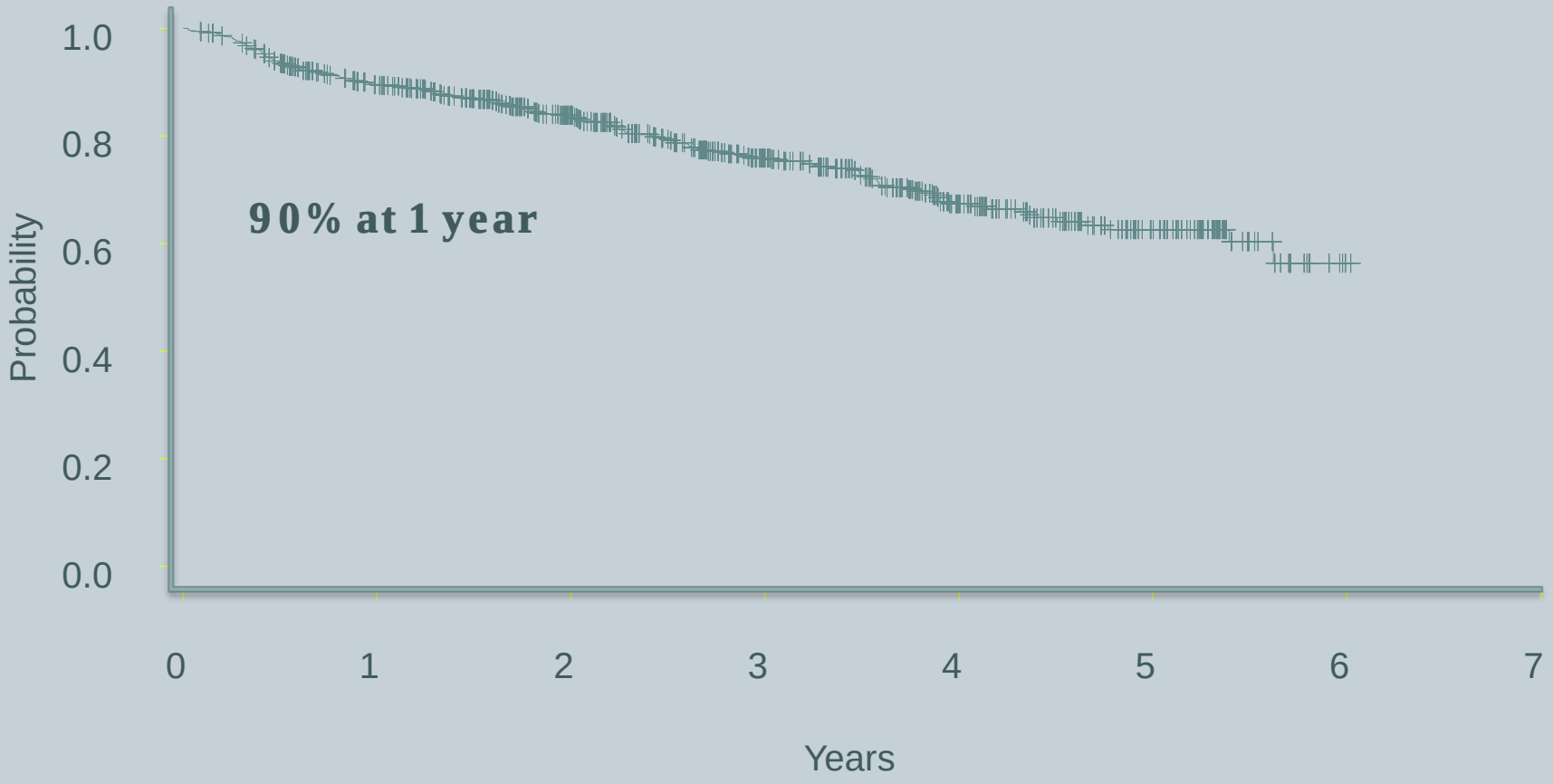
ALLO HSCT

Jan 1, 2013 - Dec 31, 2017 Overall Survival (n = 403)

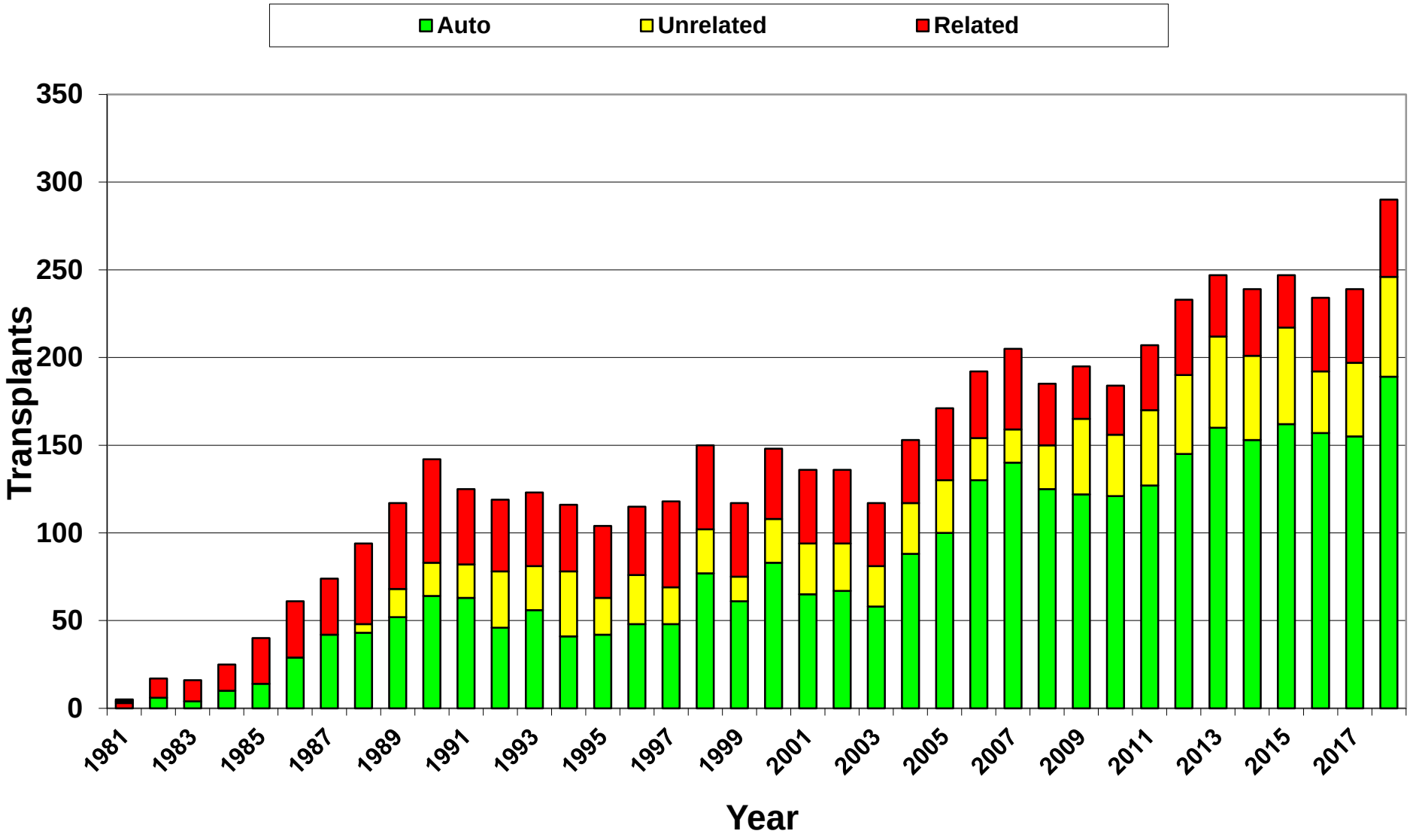


AUTO HSCT

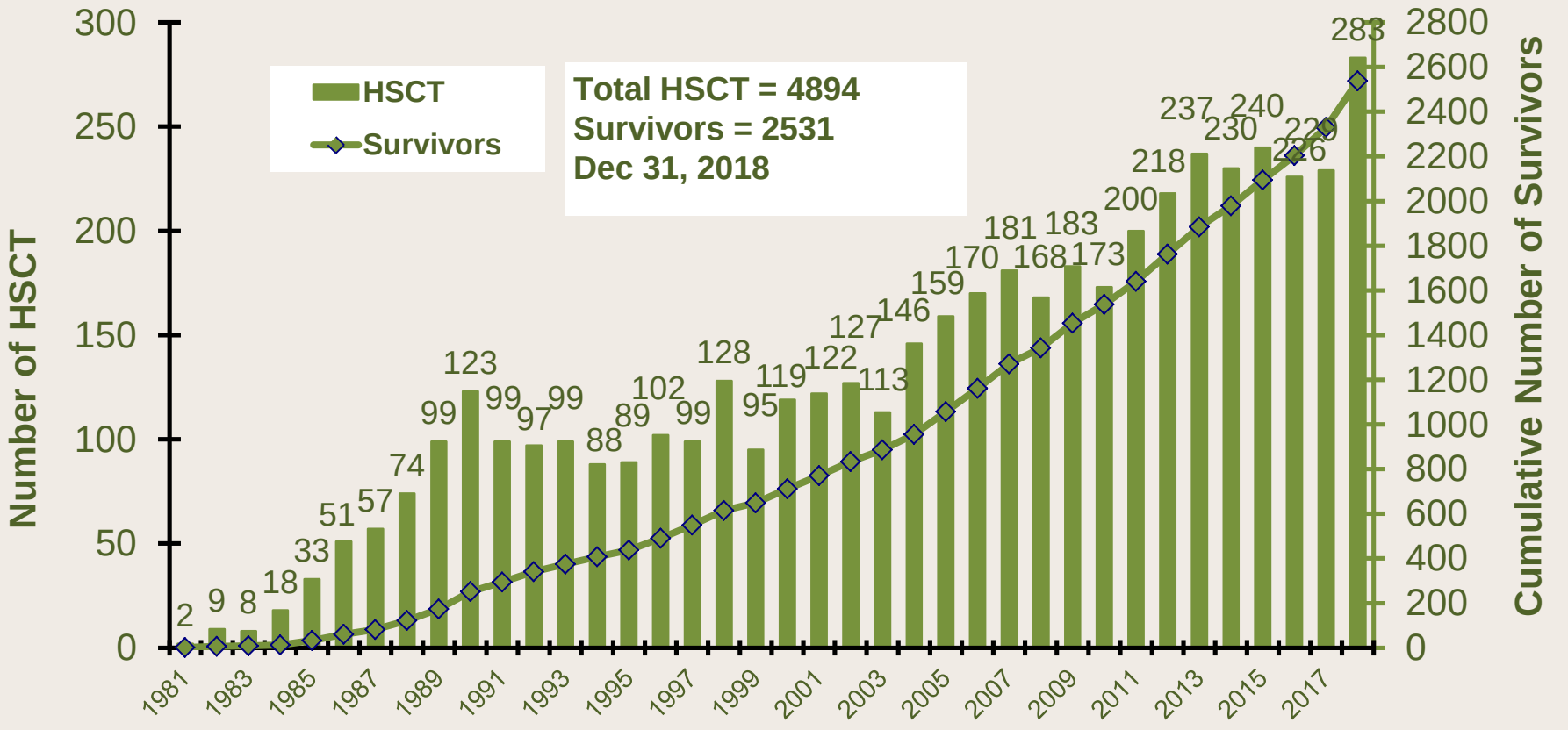
Jan 1, 2013 - Dec 31, 2017 Overall Survival (n = 759)



Leukemia/BMT Program of B.C. - Transplants by Year and Type (1981 - 2018)



HSCT PER YEAR AND CUMULATIVE NUMBER OF SURVIVORS



Case

Andrew M. L.

June 2013

- 32M healthy, married, no children, full time software engineer
- Unwell x 4 weeks → walk-in clinic, CBC shows pancytopenia and circulating blasts
- Admitted to L/BMT
- BMBx confirms poor risk AML
- Standard “7+3” induction (anthracycline) → remission
- Only potential cure is SCT, no related matches
- Consolidation HIDAC x 2 cycles (outpatient)

Case - Andrew

Sept 2013

- Admitted for transplant
- Cyclophosphamide and TBI conditioning
- Donor: PB from matched unrelated multiparous female

Early in-hospital course

- Platelet and RBC transfusion support
- Culture neg febrile neutropenia →broad spectrum antibiotics
- Cyclosporine-related hypertension and renal dysfunction (fluids, amlodipine)
- Acute GVHD skin → prednisone 1 mg/kg then slow taper begins
- Engrafment (counts rise)
- Discharged to outpatient unit D+30 post-transplant for 3x/wk visits

Case - Andrew

December 2013 (~D100 assessment)

- Coming once weekly to daycare unit
- Prednisone tapered off
- BMBx shows ongoing remission
- Cyclosporine taper commenced
- Discharged from daycare unit to L/BMT Attending physician for ongoing care

February 2014 (+5 months)

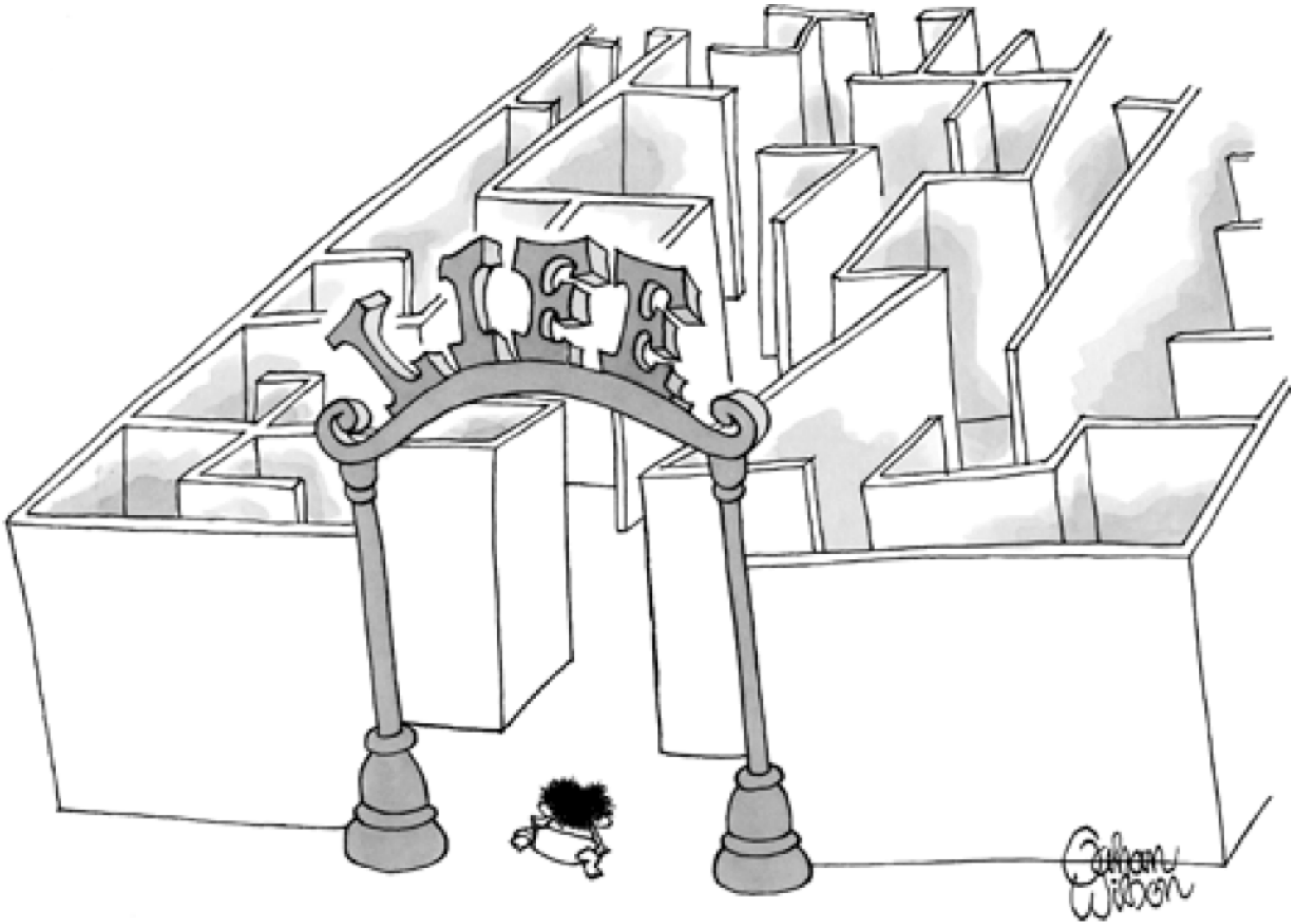
- Chronic GVHD skin, mouth, eyes
- Prednisone 1 mg/kg x 1 month, then taper

Case - Andrew

September 2014

- Comes to LTFU clinic for 1 year assessment

What are long-term follow up considerations for Andrew?


LIFE
Gillian Wilson

Goals of long-term survivors

- Relapse-free survival
- Recover initial health status
- Normal quality of life
- Social integration (work and home)

Why are Late Effects Important?

- Patients disease-free at 2 or 5 years have > 80% 10 year survival rate
- Late effects have adverse effects on
  - Morbidity
  - Mortality
  - Working status
  - Quality of life

Late Effects

- Khera et al. J Clin Oncol. 2012
- Retrospective study (n=1087)
- Cumulative incidence at 5 years post SCT
- Any non-malignant late effect at 5 years
  - 79% allo, 45% auto
- 3 or more late effects
  - 26% allo, 2.5% auto

Life Expectancy is Lower

- Martin et al. J Clin Oncol. 2010
- Life expectancy among 5 year survivors remains 30% lower than general population
  - Regardless of current age and years since HCT

Late Effects post Allo-HSCT

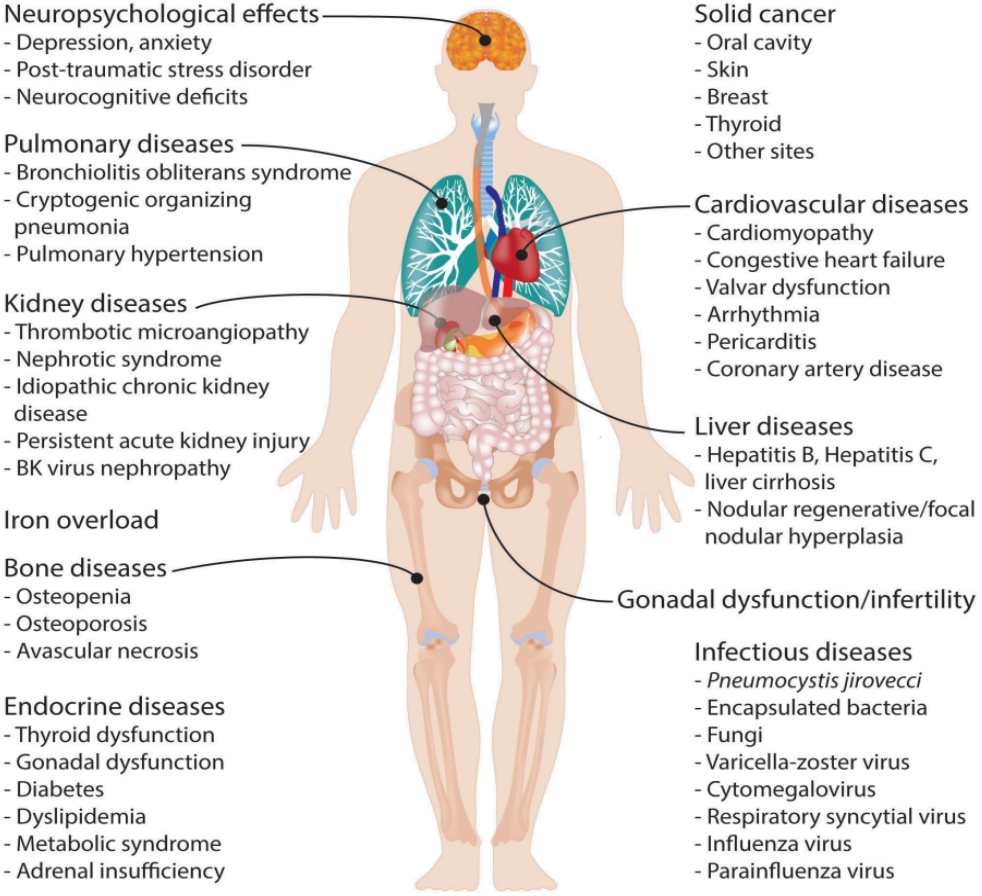
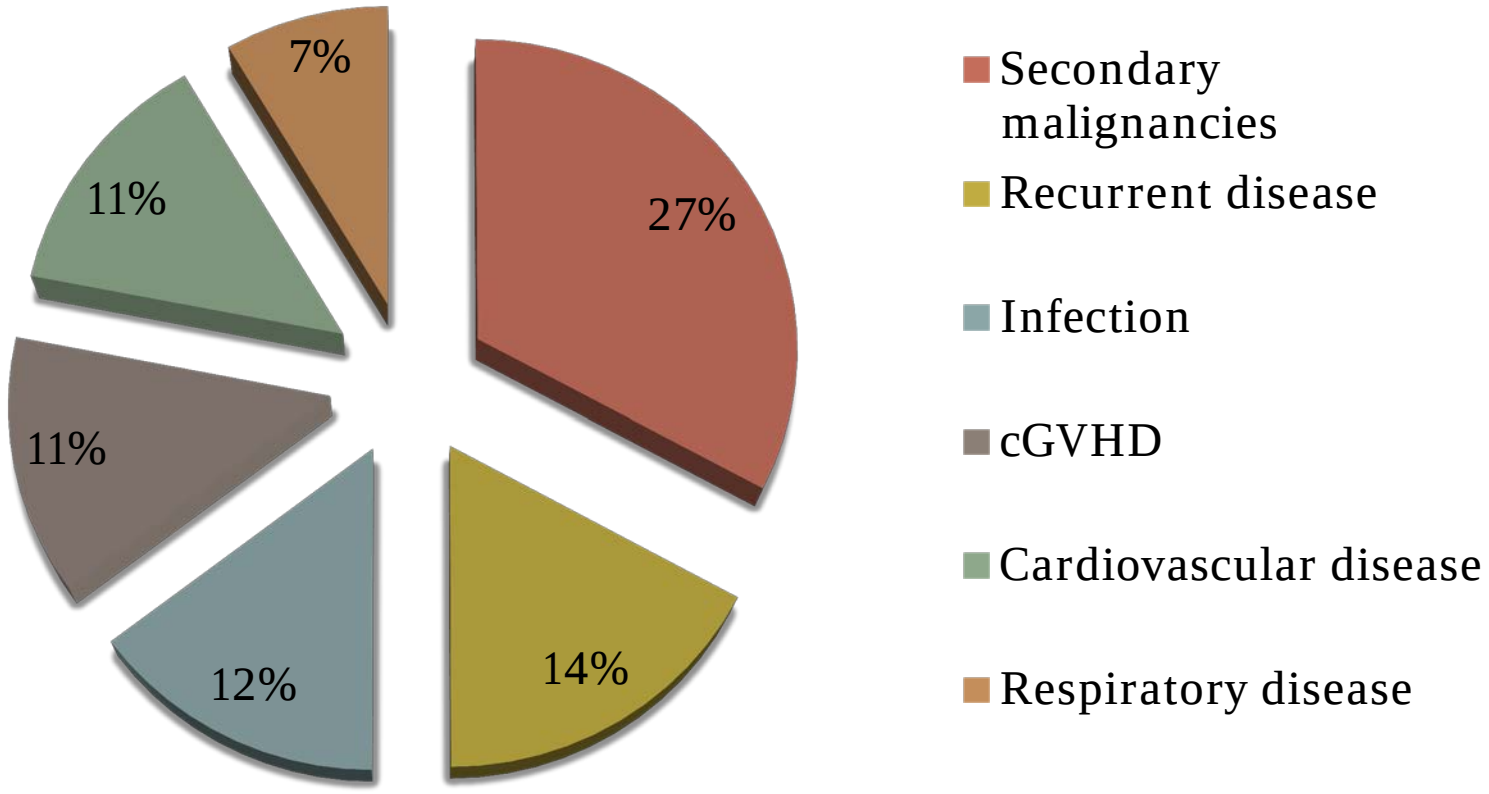


Figure 1. Late effects of blood and marrow transplantation.

Inamoto et al. Haematologica 2017; 102(4)

Leading Causes Excess Death in 5-year Survivors



Martin et al. J Clin Oncol. 2010; 28(6):1011

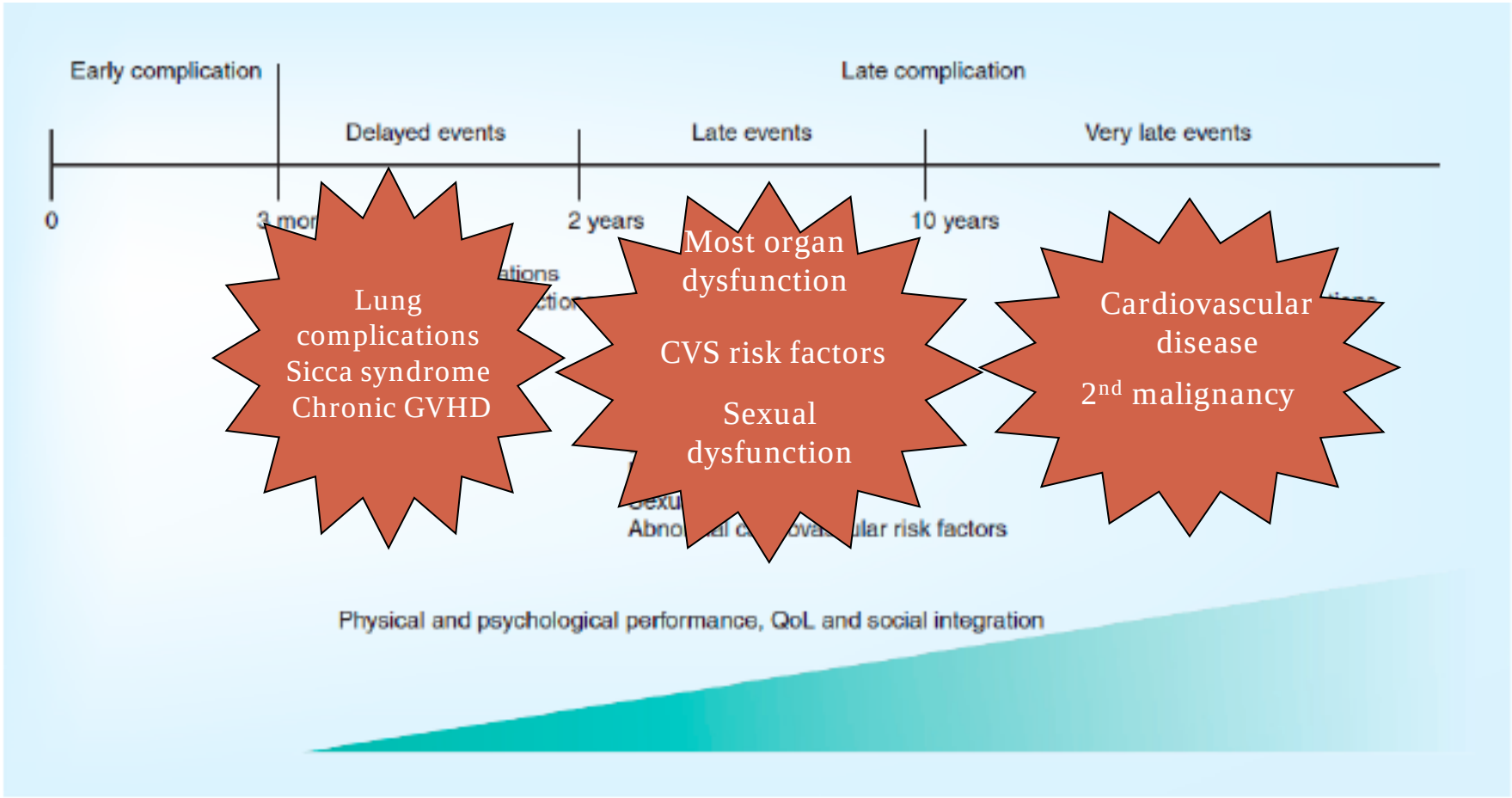
Late Effects post Allo-HSCT

Late effect	Incidence	Mortality	Morbidity	Treatable	Preventable
Cardiovascular	+	+	+	+	+
Pulmonary					
Bronchiolitis obliterans syndrome	+	++	++	+	-
Cryptogenic organizing pneumonia	+	+	+	++	-
Pulmonary hypertension	+	++	++	+	-
Endocrine					
Thyroid dysfunction	++	-	-/+	+++	-
Diabetes	++	+	+	+++	-
Dyslipidemia	++	-	-/+	+++	-
Adrenal insufficiency	+	-	-/+	+++	-/+
Gonadal dysfunction/ infertility	+++	-	-	-/+	-/+
Iron overload	++	-	-	++	-
Liver					
Hepatitis B	+	-	+	++	+
Hepatitis C and cirrhosis	+	-	+	++	-/+
Nodular regenerative hyperplasia	+	-	-	-	-
Focal nodular hyperplasia	+	-	-	-	-
Kidney					
Thrombotic microangiopathy	+	+	++	-/+	-
Nephrotic syndrome	+	-	++	++	-
Idiopathic chronic kidney disease	+	-	++	+	-
Bone					
Osteoporosis/osteopenia	++	-	-	++	+
Avascular necrosis	+	-	++	++	-
Infection	++	+	+	+++	+
Solid cancer	+	++	+++	-/+	-
Neuropsychological	++	-	++	+	-
Recurrent disease	++	+++	+++	-/+	-
Chronic graft-*versus*-host disease	++	+	++	+	-

+ : <20%; ++ : 20%-50%; +++ : >50%.

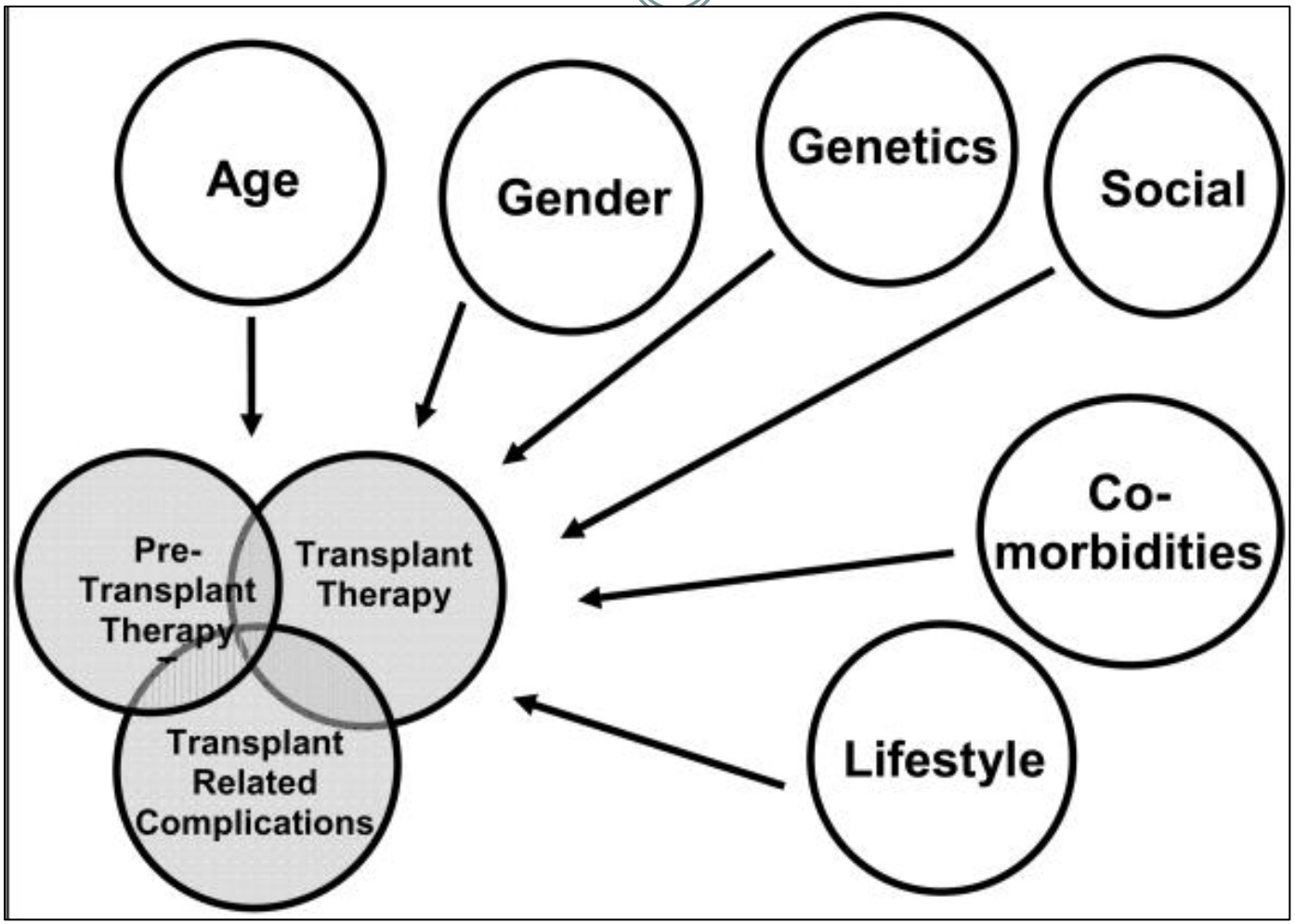
Inamoto et al. Haematologica 2017; 102(4)

Late Effects – Time to Appearance



Tichelli et al. Expert Review Hematology 2009; 102(4)

Late Effects – Complex Interplay



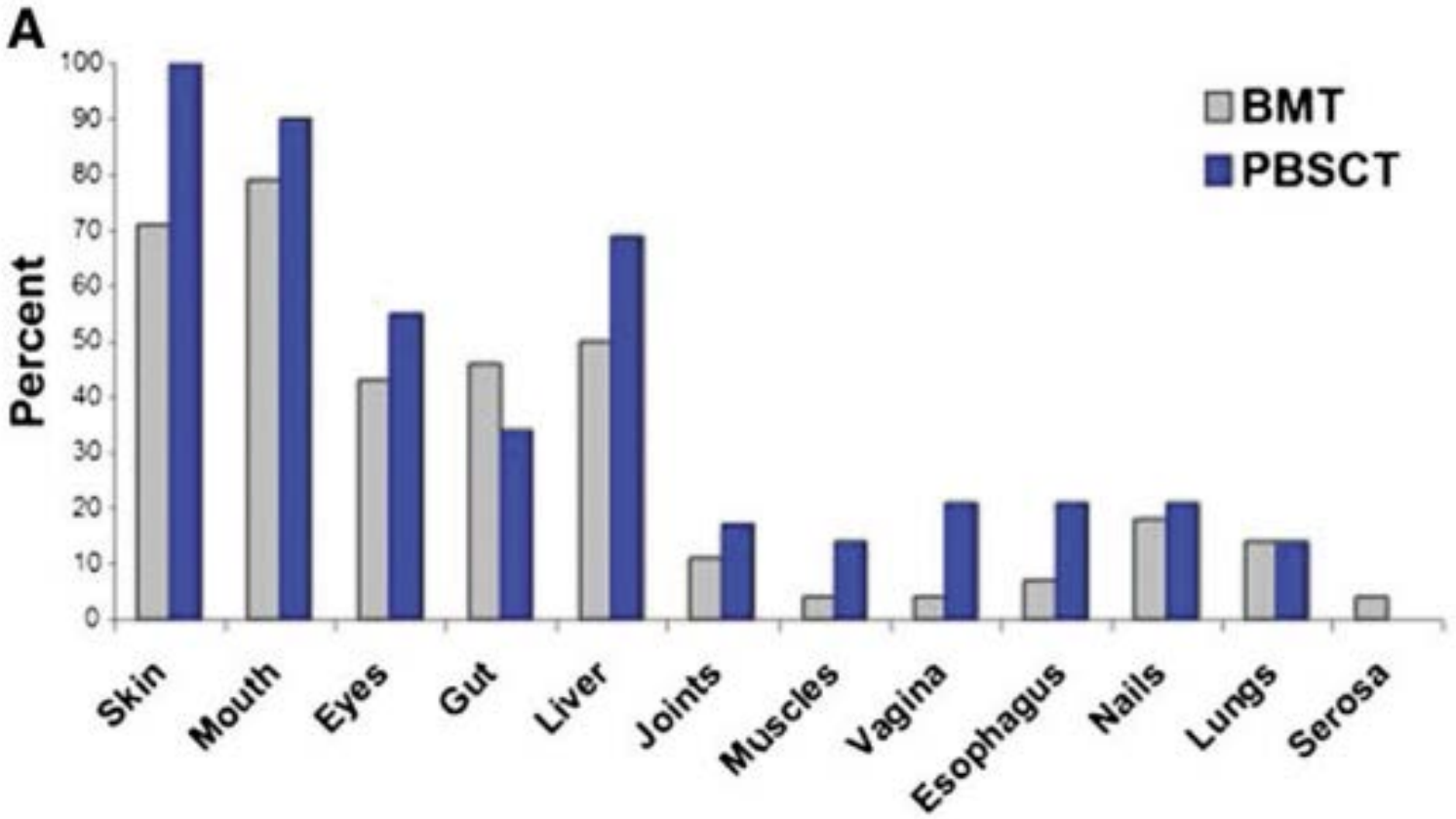
Pulsipher et al. BBMT 2012; 18

Primer: Graft vs. Host Disease

- Donor immune system reacting to recipient's organs

Acute (<100 days)	Chronic (>100 days)
Skin	Almost
Liver	any
GI tract	organ!

Primer: cGVHD Organ Involvement



Flowers et al. Blood 2015; 125(4)

Primer: cGVHD Manifestations

Organ or site	Diagnostic (sufficient for diagnosis)	Distinctive (insufficient alone for diagnosis)	Other	Features seen in both acute and chronic GVHD
Skin	Poikiloderma Lichen planus-like Sclerosis Morphea-like Lichen sclerosis-like	Depigmentation Papulosquamous		Erythema Maculopapular Pruritus
Nails		Dystrophy Onycholysis Nail loss Pterygium unguis		
Scalp and body hair		Alopecia (scarring or nonscarring) Scaling		
Mouth	Lichen planus-like	Xerostomia Mucoceles Mucosal atrophy Pseudomembranes or ulcers*		Gingivitis Mucositis Erythema Pain
Eyes		New dry, gritty, or painful eyes (sicca) Keratoconjunctivitis sicca Punctate keratopathy		
Genitalia	Lichen planus-like Lichen sclerosis-like Female: Vagina scarring or stenosis Clitoral or labial agglutination Male: Phimosis Urethral scarring or stenosis	Erosions* Fissures* Ulcers*		
GI tract	Esophageal web Esophageal stricture			Diarrhea Anorexia Nausea or emesis Failure to thrive Weight loss
Liver				Total bilirubin, alkaline phosphatase or ALT >2× ULN
Lung	Bronchiolitis obliterans diagnosed by biopsy BOS§		Cryptogenic organizing pneumonia† Restrictive lung disease†	
Muscles, fascia, joints	Fasciitis Joint stiffness or contractures due to sclerosis	Myositis Polymyositis		
Hematopoietic and Immune			Thrombocytopenia Eosinophilia Hypo- or hypergammaglobulinemia Autoantibodies Raynaud phenomenon	
Others			Effusions‡ Nephrotic syndrome Myasthenia gravis Peripheral neuropathy	

Flowers et al. Blood 2015; 125(4)

Primer: cGVHD

- Onset 2 mo – 7 years post-transplant
  - Presentation > 1y in <10%
- Risk factors
  - Unrelated donor
  - HLA-mismatch
  - PB source
  - Female donor → male recipient
  - Older age (donor and recipient)
  - Prior acute GVHD
- Treatment = immunosuppression
  - 1st line: corticosteroids
  - Risk for toxicity
- Long term treatment goal: immune tolerance

Immunity and Infections

- Cytopenias
- Immune ablation
- Immunosuppression
- Impaired opsonization
  - hyposplenism (cGVHD or anatomic)

- Immune reconstitution takes ~24 months

Immunity and Infections

- Bacterial, fungal, viral infections
  - Typical or atypical / opportunistic
- General considerations
  - Clinical vigilance for infectious symptoms
  - Avoidance of sick contacts
  - Diligent hand hygiene
  - Low threshold to investigate / treat, especially in first 2 years or if on systemic immunosuppression

Immunity and Infections

- Prophylactic antimicrobials
  - Valtrex and Septra for all
    - VZV and PCP prophylaxis
    - Minimum 1 year or until off all systemic I/S
    - *daily Septra for impaired functional hyposplenism (cGVHD)
  - Special considerations
    - Mold prophylaxis if high dose steroids
    - Lamivudine if Hep B core Ab pos
- Immunoglobulin replacement
  - If recurrent sinopulmonary infections and IgG < 4
    - Lower threshold if cord source
  - Intravenous or subcutaneous

Immunity and Infections

- Post-transplant immunizations
  - Ab levels to vaccine-preventable disease decline 1-4 years after HSCT if not re-immunized (allo and auto)
  - Commence 6-12 months post-transplant
    - Patients w/ cGVHD can mount immune responses and are at risk for infection, so do not delay!
- Flu vaccine annually (household contacts too)
- NO LIVE VACCINES (MMR/Varicella) until all criteria met:
  - 2 years post-transplant
  - Off all immunosuppression for at least 3 months
  - No active chronic GVHD
  - Written authorization from L/BMT physician

BCCDC Immunization Schedule for HSCT

1st Visit (6-12 months after HSCT) [A]	2nd Visit (1 month after 1st visit)	3rd Visit (2 months after 1st visit)	4th Visit (8 months after 1st visit)	5th Visit (12 months after 1st visit)	6th Visit (> 24 months after HSCT)
Date given:	Date given:	Date given:	Date given:	Date given:	Date given:
DTaP-IPV-Hib [B]	DTaP-IPV-Hib [B]	DTaP-IPV-Hib [B]		DTaP-IPV-Hib [B]	
Hepatitis B [C, D]		Hepatitis B [C, D]		Hepatitis B [C, D, E]	
	Hepatitis A			Hepatitis A [E]	
PCV13 [F]	PCV13 [F]	PCV13 [F]	PPV23 [F]		
	Men-C-A,C,Y,W-135 [G]		Men-C-A,C,Y,W-135 [G]		
Influenza [H]					
		HPV [I]	HPV [I]		HPV [I]
					MMR [J, K]
					Varicella [K, L]

Ocular Complications

- Keratoconjunctivitis sicca
  - May be associated with chronic ocular GVHD
- Cataracts
  - TBI: 40-70% at 10 years
  - Prolonged steroid: 45% at 10 years
  - Older age at transplant
- Ischemic microvascular retinopathy
  - TBI, calcineurin inhibitors

Recommendations

- Frequent routine clinical assessments
- Screening ophthalmology ax at least annually

Oral Complications

- Common
- Risk factors
  - Oral cGVHD
  - Radiation of the head/neck
  - Underlying Fanconi's anemia
  - Age at transplant
- Salivary gland dysfunction / xerostomia
  - Even w/o cGVHD (chemo, radiation, medications)
  - Risk for dental caries, oral infections, peridontal disease, oral cancer

Oral Complications

- Recommendations
  - Avoid offending medications
  - Artificial saliva / oral rinses, sugar free candies, +/- sialagogues
  - Treat cGVHD
  - Avoid smoking / chewing tobacco
  - Decreases sugar-containing beverages
  - Avoid intraoral piercing
  - Aggressive mx oral infections
  - Dental hygiene checks q6 mo
  - Oral malignancy screening q6-12 mo

Cardiovascular diseases

- 5-10% cumulative incidence at 10 years post HSCT
- Incidence up to 3.5x higher c/w general pop'n

- Cardiomyopathy
- CHF
- Valve dysfunction
- Arrhythmia
- Pericarditis
- CAD

- Major risk factors:
  - Anthracycline
  - Chest radiation
- Other factors: weight gain, medications, inflammation, inactivity

Cardiovascular diseases

Management

- Lifestyle counseling
  - Smoking cessation
  - Maintain healthy weight
  - Diet/exercise recommendations
- Early diagnosis and treatment of modifiable risk factors
  - Survivors more likely to have conventional risk factors → at least once annual monitoring
  - Low threshold for treatment
- Screening for late cardiotoxicity
  - Clinical vigilance
  - Echo for anthracycline/TBI at 1 year
  - +/- echo q5y if TBI

Pulmonary Diseases

- Infectious
- Non-infectious
  - Bronchiolitis obliterans syndrome (BOS)
  - Cryptogenic organizing pneumonia (COP)

  Associated with cGVHD

  - Pulmonary HTN (rare but potentially fatal)

Pulmonary Diseases

Monitoring

- Clinical vigilance
- Lung function testing q3mo for first 2 years
  - Asymptomatic decline in FEV1 often the first sign of BOS

Liver Diseases

- Medications
- cGVHD
- HBV, HCV
- Iron overload

- Liver function monitored through routine regular blood testing

Renal Dysfunction

- Incidence of CKD 5-65%
- Numerous risk factors
  - Older age at transplant
  - Acute or chronic GVHD
  - TBI
  - Medications
- Monitored through routine regular tests (creatinine, UACR)

Endocrine Diseases

- Hypothyroidism
  - 30% by 25 years
  - Risk factors: age < 10y, radiation, busulfan, cyclophosphamide, heme malignancies
  - Action: annual TSH +/- fT4
- Diabetes
  - 8-41% patients
  - 3.65x higher incidence vs. sibling
  - Action: annual A1C
    - More frequent glucose monitoring if on steroids

Endocrine Diseases

- Dyslipidemia
  - 9-61% patients
  - Action: annual non-fasting lipids
    - Follow CCS lipid guidelines
    - Low threshold to treat eg. intermediate risk group
    - May reassess if considered pred/Csa-driven once tapered off
- Adrenal insufficiency
  - 13% patients
  - Action: monitor for symptoms
    - Alternate day steroid dosing may reduce risk
    - Slow terminal steroid taper
    - Cortisol-stim test if suspect

Male Gonadal Dysfunction and Infertility

- Erectile dysfunction and low libido common
  - Physical and psychosocial factors
- Consider T replacement if sx and low T
- BC Centre for Sexual Medicine referral if indicated

- Risk of azoospermia: 70%
- Spermatogenesis may recover
  - 90% cyclophosphamide
  - 50% cyclophosphamide + busulfan / thiotepa
  - 17% TBI
- **semen banking or cryopreservation of testicular tissue should be discussed *before* HCT if fertility desired
  - Ideally before initial chemotherapy when feasible
  - Olive / PCRM referral

Female Gonadal Dysfunction

- Ovarian failure, vaginal changes, and low libido common
- Individualized decision re: hormone replacement in POF
  - All females see endocrinologist ~3-4 months post-HSCT
- Vaginal changes
  - Gynecology assessment to differentiate b/w genital cGVHD and menopause
- BC Centre for Sexual Medicine referral if indicated

Female Infertility and Pregnancy

- Ovarian failure > 90%
  - 10% in reduced-intensity
- Recovery possible
  - 92% cyclophosphamide alone
  - 24% in cyclophosphamide + TBI
- **discuss cryopreservation of oocytes, ovarian tissues, or embryos *before* HSCT if fertility desired
  - Ideally before initial chemotherapy when feasible
  - Olive / PCRM referral

Pregnancy

- 0.87% of patients or their partners have pregnancies after allo HSCT
  - Retrospective survey by Salooja N, et al. Lancet. 2001;358(9278):271-276
- General recommendation to wait 2-5 years before TTC
  - Relapse rates highest in first two years post-HSCT
  - Theoretical risk of recurrent malignancy d/t disturbance of GVL effect
- Pregnancy outcomes generally good
  - No increase in fetal malformations
  - Considered high risk pregnancies b/c higher maternal risk of pregnancy complications

Iron Overload

- 30-60% long term survivors have elevated ferritin
  - Risks: prior transfusion load; ineffective iron metabolism in some blood disorders
- 25-50% have elevation LIC on T2* MRI

- Action: Annual ferritin and iron saturation
  - Liver biopsy or MRI T2* if diagnostic uncertainty
  - HFE genotyping if FHx HC or pts of Northern or Western European ancestry
  - Consider phlebotomy or iron chelation if Tsat > 45%-50%
    - If Hct > 35%: 250-300 mL q3-4 weeks until ferritin < 1000
    - If Hct < 35%: oral chelation
  - If normal Tsat, consider inflammation, metabolic syndrome, liver disease, alcohol, etc.

Bone Diseases

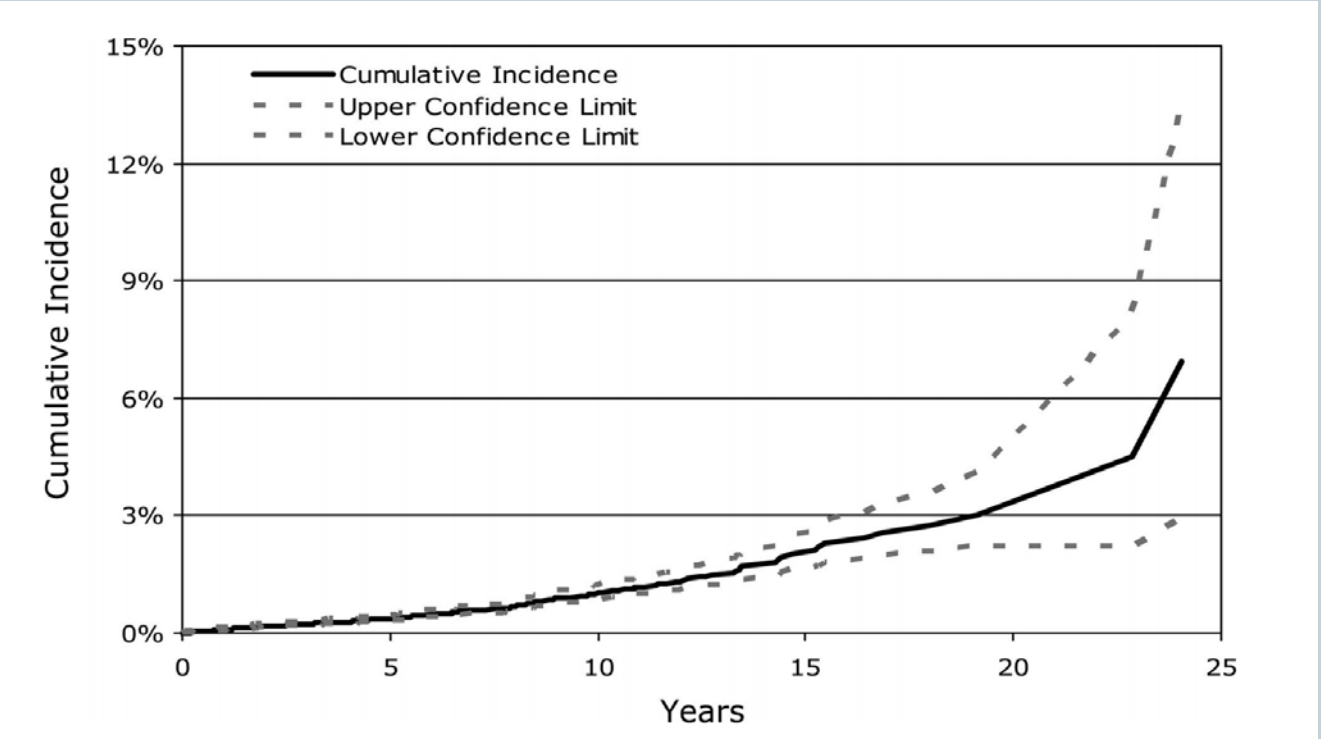
- Osteopenia / osteoporosis
  - 50% prevalence
  - Risk factors: **steroids**, chemo, radiation, CNI, Vit D deficiency, gonadal failure
  - Action: 25(OH) vit D level and DEXA scan at D100, Y1, Y2 +/- later years if indicated
  - Preventative recommendations:
    - Calcium 1200 mg/d total, Vit D 2000 units/d, weight bearing exercise, avoid smoking and excess alcohol
  - Consider bisphosphonate if:
    - Osteopenia/osteoporosis w/ high fracture risk
    - Osteopenia w/ concomitant steroids (until off steroid or for up to 5 y)
    - Denosumab if renal dysfunction

Bone Diseases

- Avascular necrosis
  - Cumulative incidence 3-10% at 5 years
  - Severe bone pain/destruction, significant QoL impact
  - Risk factors: steroids, CNI, older age, TBI
  - Low threshold for MRI and early involvement of orthopedic surgery

Secondary Malignancies

- Increased risk after HSCT c/w gen pop'n
  - Overall 2x (3x by 15 y)
  - Continues to rise without plateau



Rizzo et al. Blood 2009; 113(5)

Secondary Malignancies

- Risk factors
  - **Myeloablative TBI**
  - Young age at HCT
  - Chronic GVHD
  - Prolonged I/S >2 y
- Most common:
  - Skin, oral, breast, thyroid

Secondary Malignancies

- Recommended screening:
  - Skin: annual skin surveillance (+ sun protection)
  - Oral: dental visits 2x/y
  - Breast: mammogram q1-2 y (annual if TBI)
  - Thyroid: annual neck palpation, low threshold U/S / bx
  - Colon: pop'n guidelines (age 50)
  - Prostate: annual prostate exam +/- PSA (age 50)
  - Cervix: annual Pap x 2y or until off I/S (whichever later), then pop'n guidelines

- Variation among centers
- Consider individual risks (eg. TBI, family history)

Neuropsychological Effects

- Under-recognized
- Depression
  - 12-30% survivors
  - Risk factors: female, younger, poor social supports, disease recurrence, chronic pain, cGVHD
- PTSD
  - 28% at 6 mo; persists in 5-13%
  - Risk factors unclear

Neuropsychological Effects

- "Chemo brain"
  - Short term memory
  - Processing time
  - Multi-tasking
  - Coordination
  - Potential mechanisms: cytokine and immune dysregulation, DNA and telomere length damage, oxidative stress, hormonal changes, CNS infections, calcineurin inhibitor toxicity (TMA, PRES)

Neuropsychological Effects

- "Chemo brain"
  - Syrjala et al, 2011 prospective observational study
  - 92 survivors, 66 case-matched controls
  - Standardized neuropsychological tests for info processing speed, verbal memory, executive function, and motor dexterity/speed
  - Results: neurocog fxn declines substantially at 80 days post-HCT, returns to pre-HCT levels at 1y, continues to improve 1 to 5 years post-HCT,
    - **but deficits remain in 40% survivors (mostly mild)

Neuropsychological Effects

- Action: screening on history

- Interventions:
  - L/BMT psychiatrist
  - Patient and Family Counseling via BC Cancer
  - Inspire Health
  - Community counselors / psychologists
  - Neuropsychology

Conclusions

- Progress in HCT → increasing numbers of long-term survivors
- Awareness and screening for late complications is key starting early after the transplant
  - Early detection
  - Prevention
  - Treatment

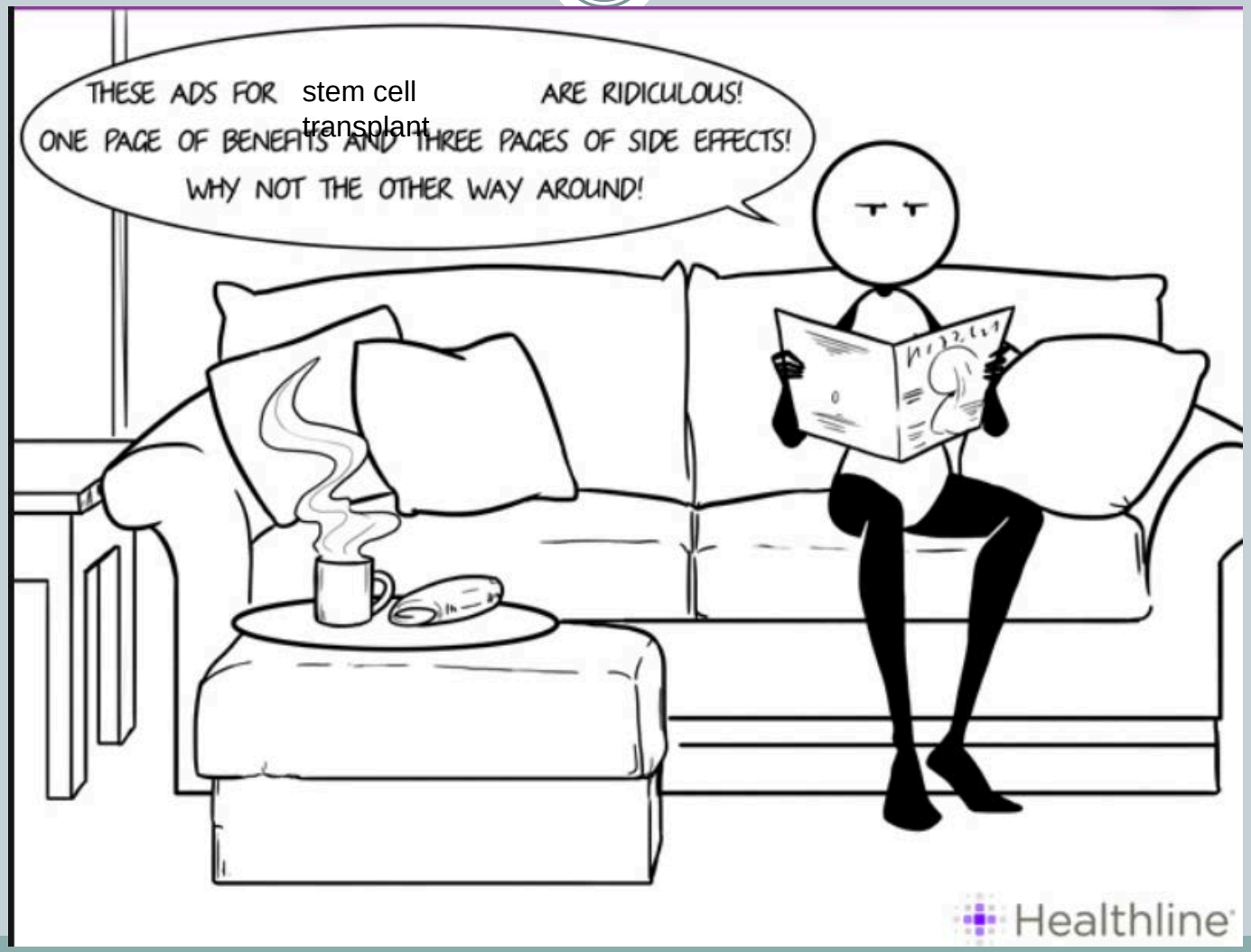
Guidelines / Resources

- Recommended Screening and Preventive Practices for Long-Term Survivors after Hematopoietic Cell Transplantation
  - 2012 ASBMT publication
    - Consensus recommendations
    - CIBMTR, EBMT, ASBMT 2006
      - Updated 2012 with Asia-Pacific, East Mediterranean, Australia, New Zealand, and Brazil
- Fred Hutch (Seattle) guidelines
- National Marrow Donor Program (NDMP)
  - Clinician and patient versions of guidelines
  - Easy-to-use app (Be The Match)

References

- Flowers M et al. How we treat chronic graft-versus-host-disease. Blood. 2015;125(4):606-15.
- Inamoto Y et al. Late effects of blood and marrow transplantation. Haematologica. 2017;102(4):614-25.
- Khera N et al. Nonmalignant late effects and compromised functional status in survivors of hematopoietic cell transplantation. J Clin Oncol. 2012;30(1):71-77.
- Martin P et al. Life expectancy in patients surviving more than 5 years after hematopoietic cell transplantation. J Clin Oncol. 2010;28(6):1011-16.
- Pulsipher et al. National Cancer Institute, National Heart, Lung and Blood Institute / Pediatric Blood and Marrow Transplantation Consortium First International Consensus Conference on Late Effects and Pediatric Hematopoietic Cell Transplantation: The Need for Pediatric-Specific Long-Term Follow Up Guidelines. BBMT 2012;18:334-47.
- Rizzo JD et al. Solid cancers after allogeneic hematopoietic cell transplantation. Blood. 2009;113(5):1175-83.
- Salooja N, et al. Pregnancy outcomes after peripheral blood or bone marrow transplantation: a retrospective survey. Lancet. 2001;358(9278):271-276
- Syrjala KL, et al. Prospective neurocognitive function over years after allogeneic hematopoietic cell transplantation for cancer survivors compared with matched controls at 5 years. J Clin Oncol. 2011;29(17):2397-2404.
- Tichelli et al. Late complications after hematopoietic stem cell transplantation. Expert Rev Hematol. 2009;2(5):583-601.

Questions?


THESE ADS FOR stem cell transplant ARE RIDICULOUS!
ONE PAGE OF BENEFITS AND THREE PAGES OF SIDE EFFECTS!
WHY NOT THE OTHER WAY AROUND!
Healthline