Long term follow up post-transplant

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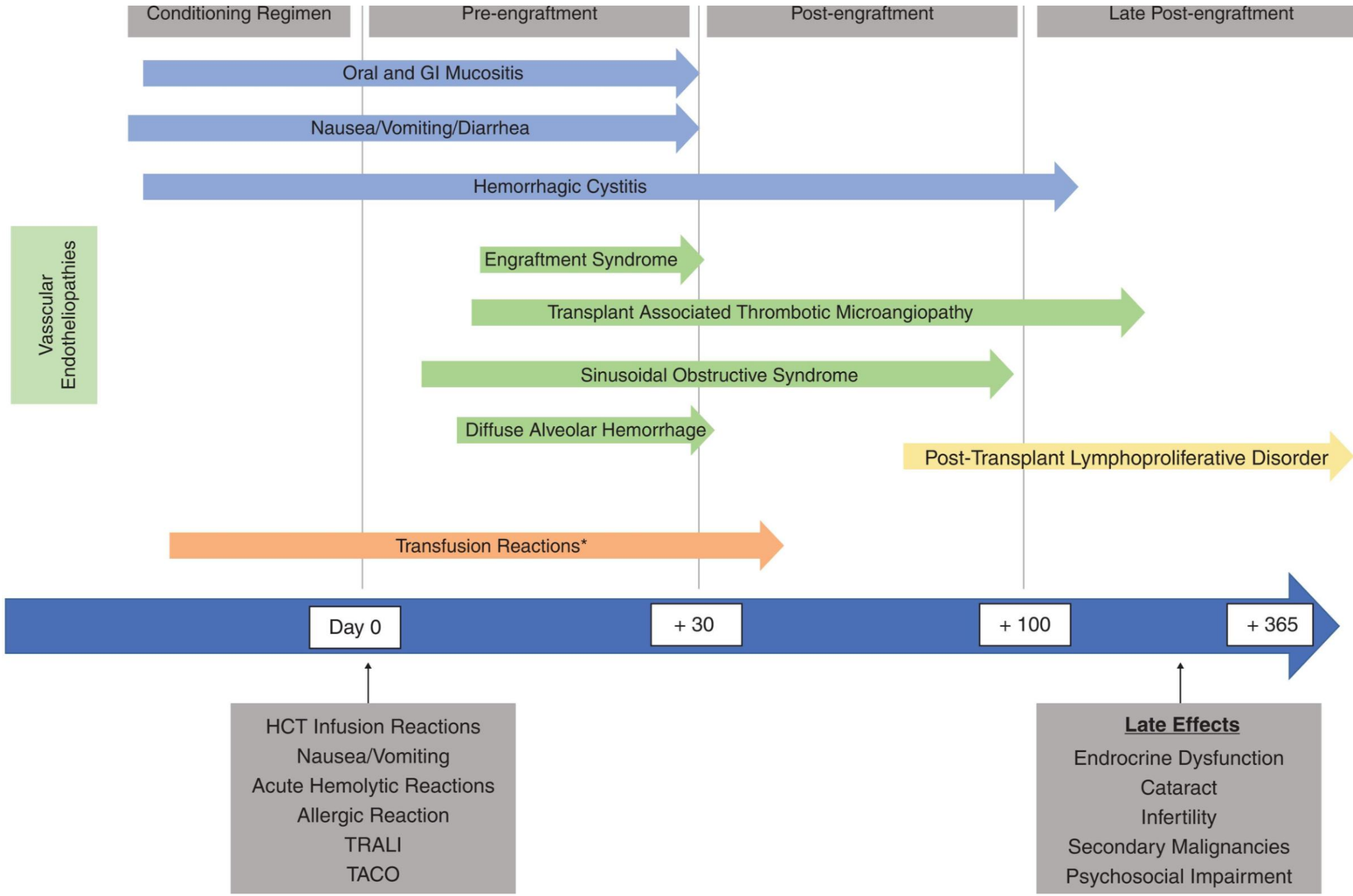
Objectives

To understand

- Need to monitor HSCT patients
- Case based learning
- Risk-adapted/ exposure related screening
- Limitations in setting up clinics

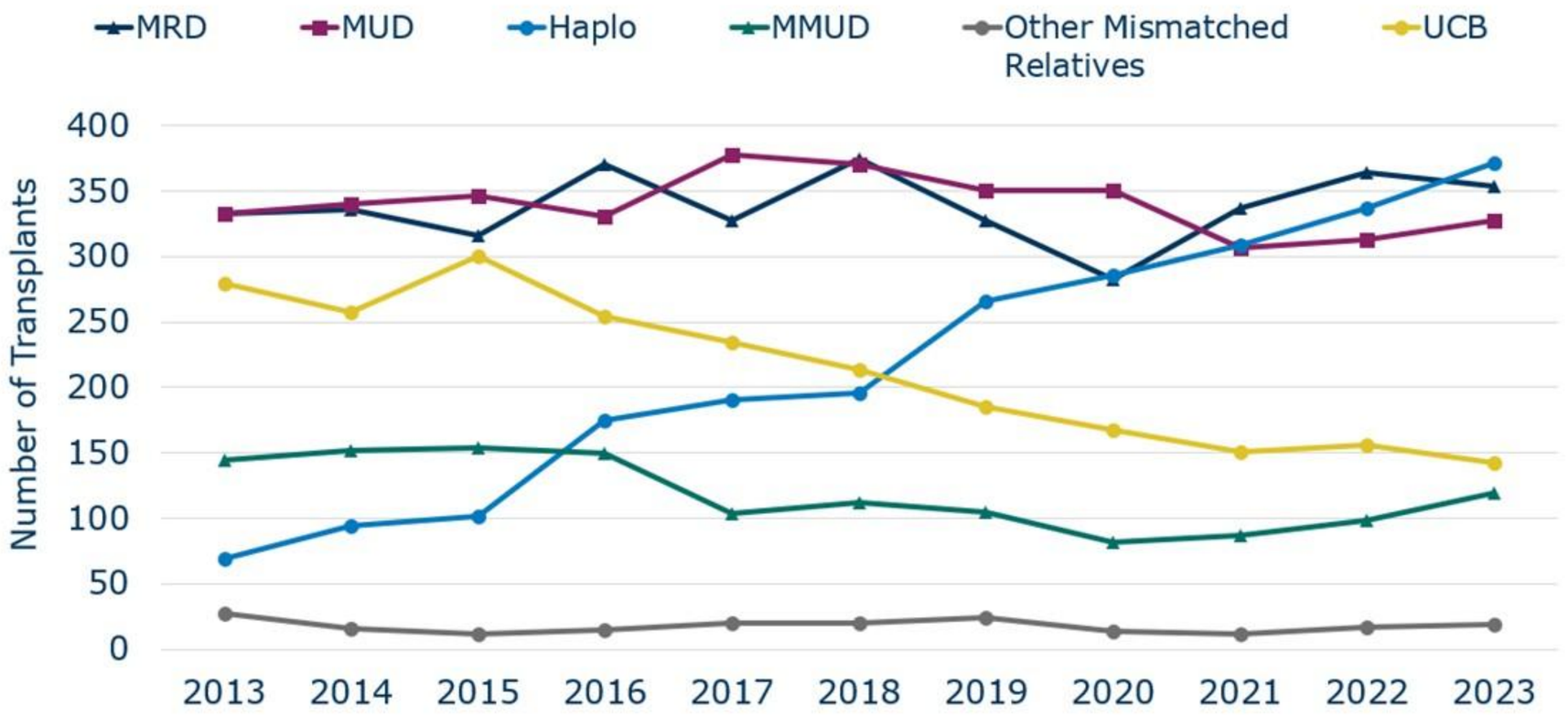
Introduction

- HSCT =curative intent
- Increasing number of survivors
- Cumulative exposure (compared to non-HSCT gp)
  - Increasing morbidity
  - Wide range of adverse effects
  - Poor QoL
  - Premature mortality
  - Long latency between HSCT and morbidities



Chow EJ, Anderson L, Baker KS, Bhatia S, Guilcher GM, Huang JT, Pelletier W, Perkins JL, Rivard LS, Schechter T, Shah AJ, Wilson KD, Wong K, Grewal SS, Armenian SH, Meacham LR, Mulrooney DA, Castellino SM. Late Effects Surveillance Recommendations among Survivors of Childhood Hematopoietic Cell Transplantation: A Children's Oncology Group Report. Biol Blood Marrow Transplant. 2016 May;22(5):782-95. doi: 10.1016/j.bbmt.2016.01.023. Epub 2016 Jan 21. PMID: 26802323; PMCID: PMC4826622.

Number of Allogeneic HCTs in the US by Donor Type, Pediatrics



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Abbreviations: MRD, matched related donor; MUD, matched unrelated donor; Haplo, ≥ 2 HLA antigen mismatch; MMUD, mismatched unrelated donor ≤ 7/8 HLA allele match; UCB, umbilical cord blood

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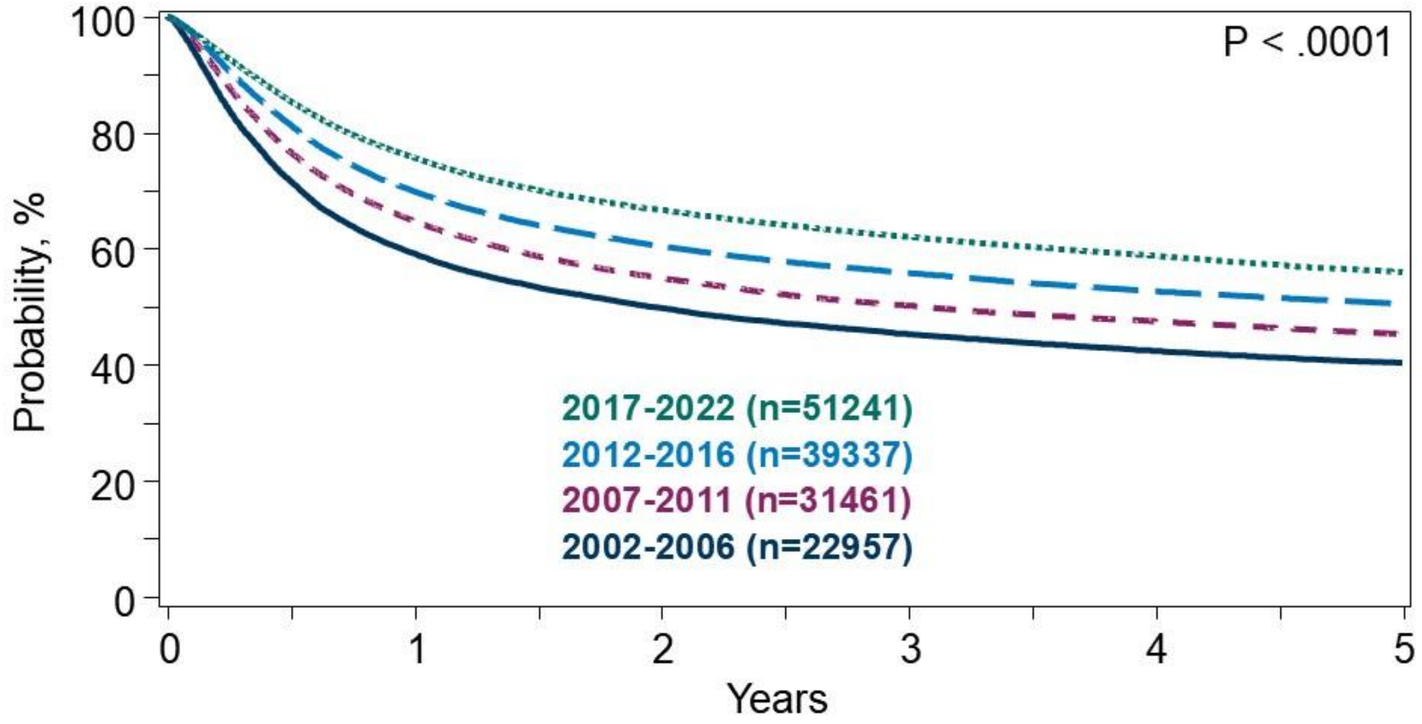
Trends in Survival after Allogeneic HCTs, in the US, 2002-2022



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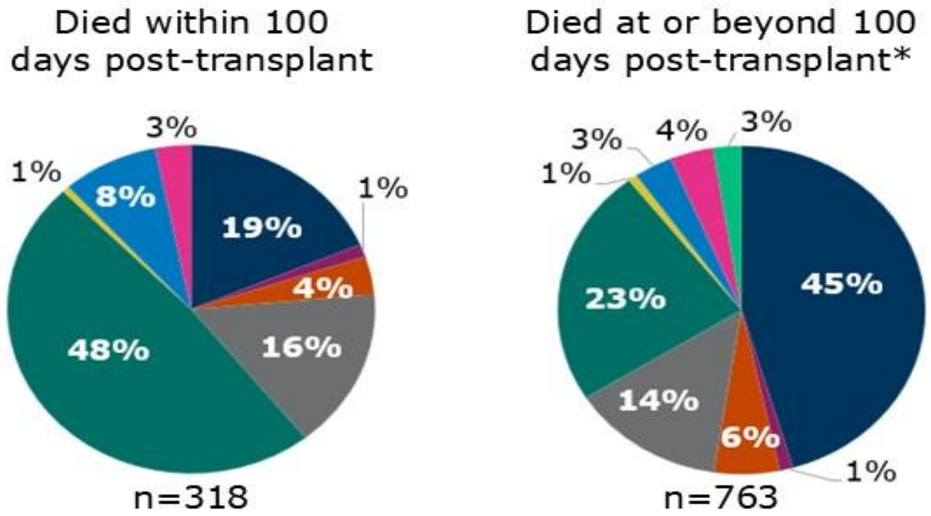
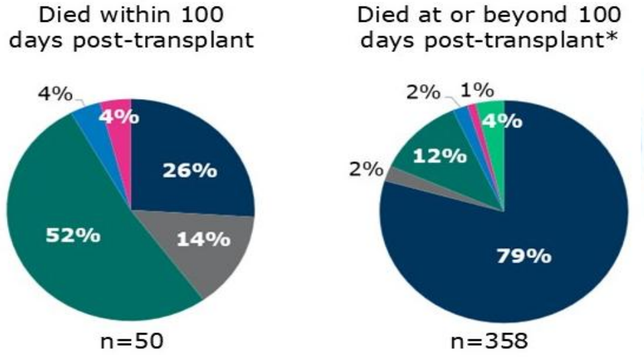
Causes of Death after Allogeneic HCTs in the US, 2019-2023

Age <18 years
Total transplants = 6264



Causes of Death after Autologous HCTs in the US,

Age <18 years
Total transplants = 2545



- Primary disease
- Organ failure
- Hemorrhage
- Graft rejection
- GVHD
- Infection
- Malignancy subsequent to HCT
- Other
- Not reported

*Data reflects 10-year mortality.

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Styczyński, J., Tridello, G., Koster, L. et al. Death after hematopoietic stem cell transplantation: changes over calendar year time, infections and associated factors. Bone Marrow Transplant 55, 126–136 (2020).

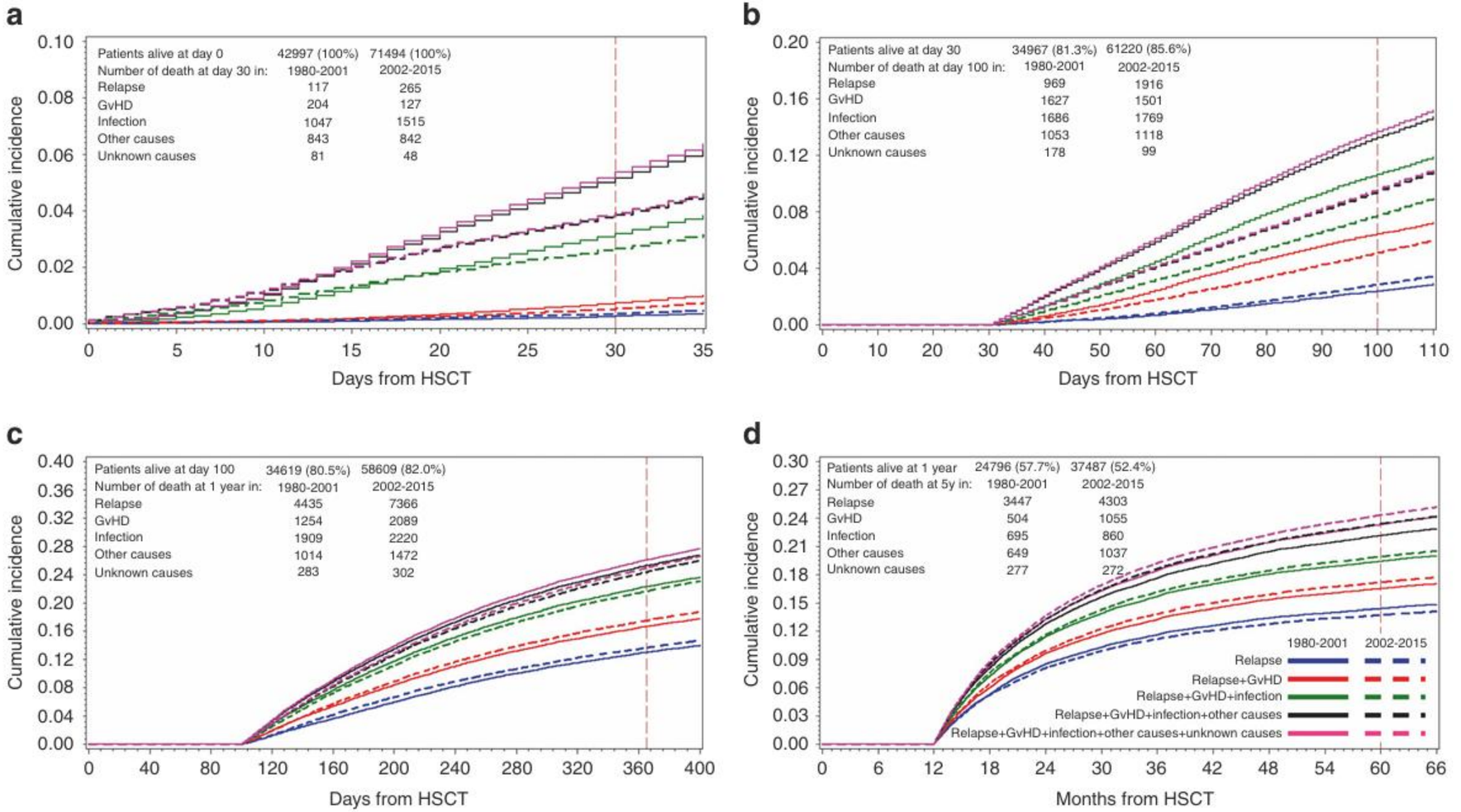


Fig. 1 Cumulative incidences of mortality after HSCT over four post-transplant phases and from cohort 1 to cohort 2. The stacked curves for the four post-transplant phases for the two cohorts combined in landmark analysis are presented: **a** 30-day mortality; **b** 100-day mortality (for patients alive at day 30); **c** 1-year mortality (for patients alive at day 100); **d** 5-year mortality (for patients alive at 1 year)

Introduction

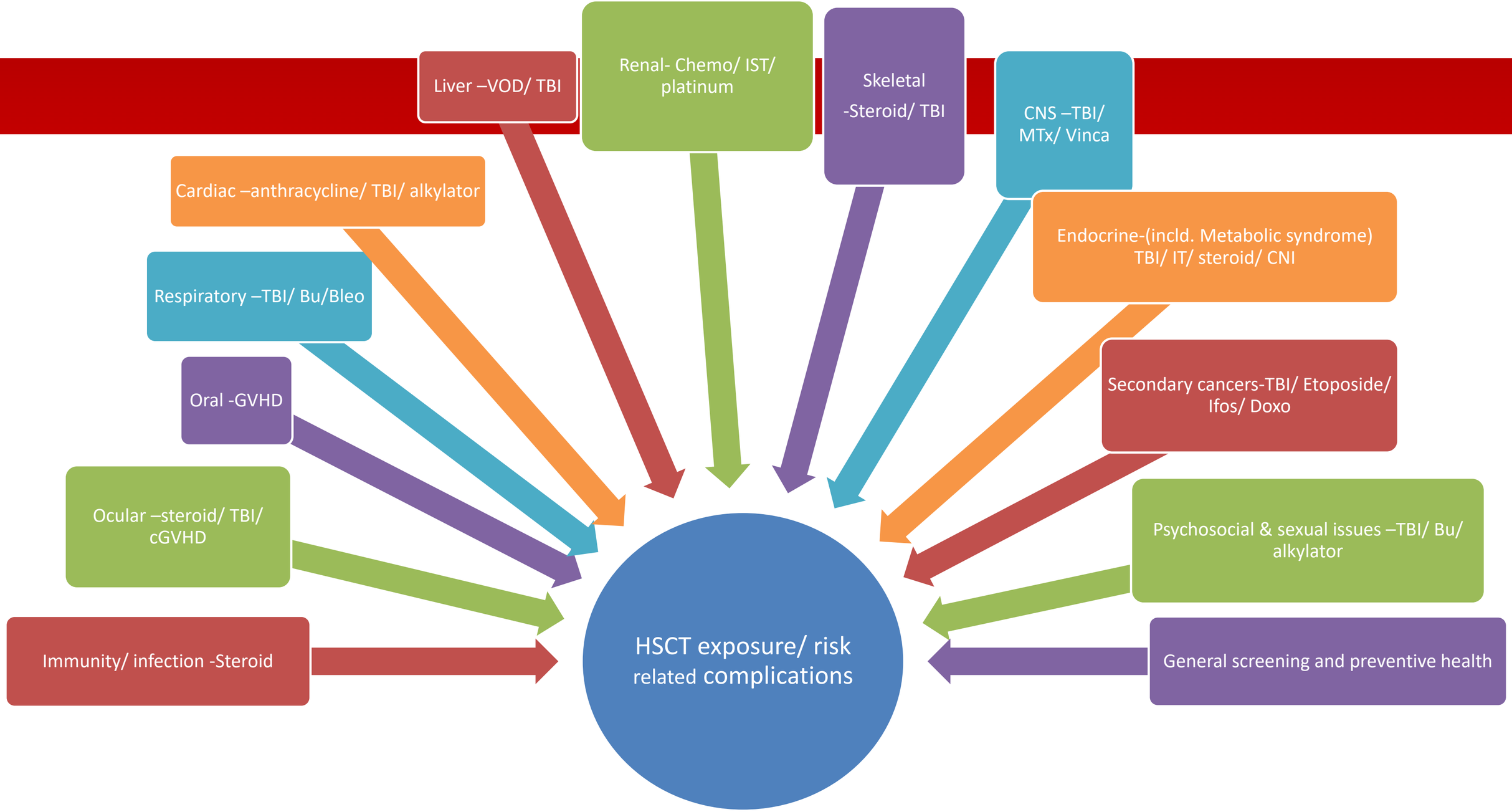
- 15-year cumulative incidence of severe or life-threatening chronic health conditions ~40%
- Need for longitudinal monitoring: recommendations for LTFU
  - Based on childhood cancer survivors
- Definition:
  - ≥ 2 years off therapy in childhood cancer
  - ≥1 yr post HSCT
- Risk-based and exposure-related screening recommended
- Early identification and appropriate intervention –reduces burden of morbidity

Overview of existing long-term follow-up guidelines with relevance to survivors of pediatric hematopoietic cell transplantation.

Sponsor	Perceived strengths	Perceived limitations	Other comments
Children's Oncology Group (COG) [8] Children's Cancer Study Group (UK) [9]	Comprehensive, pediatric- focused with a HCT- specific section.	May be overly complex, not exclusive to HCT patients; primarily focused on patients treated for underlying malignancy (vs. non- malignant processes)	Exposure- based
CIBMTR, ASBMT, EBMT, APBMT, BMTSANZ, EMBMT, SBTMO [10]	HCT-focused, relatively concise	Not pediatric focused, less comprehensive compared with pediatric-specific guidelines; does not always fully account for pre-HCT exposures	Systems- based

Chow EJ, Anderson L, Baker KS, Bhatia S, Guilcher GM, Huang JT, Pelletier W, Perkins JL, Rivard LS, Schechter T, Shah AJ, Wilson KD, Wong K, Grewal SS, Armenian SH, Meacham LR, Mulrooney DA, Castellino SM. Late Effects Surveillance Recommendations among Survivors of Childhood Hematopoietic Cell Transplantation: A Children's Oncology Group Report. Biol Blood Marrow Transplant. 2016 May;22(5):782-95. doi: 10.1016/j.bbmt.2016.01.023. Epub 2016 Jan 21. PMID: 26802323; PMCID: PMC4826622.

https://www.survivorshipguidelines.org



Bhatia S, Davies SM, Scott Baker K, Pulsipher MA, Hansen JA. NCI, NHLBI first international consensus conference on late effects after pediatric hematopoietic cell transplantation: etiology and pathogenesis of late effects after HCT performed in childhood--methodologic challenges. Biol Blood Marrow Transplant. 2011 Oct;17(10):1428-35. doi: 10.1016/j.bbmt.2011.07.005. Epub 2011 Jul 18. PMID: 21763253; PMCID: PMC3177028.

Immunity/ Infection

- Assessment: T cell recovery
- Risk: cGVHD, TCD
- Anti-infective prophylaxis and Vaccination –including splenic prophylaxis

Ocular

- cGVHD/ TBI/ infection –including posterior chamber vasculopathy
- At risk: routine ophthal -yearly

Oral

- cGVHD/ Fanconi/ radiation to H&N region
- Xerostomia/ peri-oral fasciitis/ oral cancers/ dental issues
- Regular –yearly dental examination/ smoking and sugary beverages -AVOID

Respiratory

- TBI/ GVHD/ Bu/ BCNU/ IPS/ BOS/ BOOP
- Regular screening/ PFTs
- Health education –avoid risk

Cardiac

- TBI/ alkylators/ Anthracyclines/ iron overload
- Pre HCT assessment or risk and selection of conditioning
- Routine Echo -1 yr post and then risk based 2-5 yearly
- Healthy lifestyle and early aggressive treatment

Liver

- VOD/ radiation/ Hepatitis/Iron overload/ cGVHD
- Urso/ IST
- Liver transplant

Renal

- Platinum/ CNI/ Methotrexate/ TBI/ Hemorrhagic cystitis
- HTN screening/ urine routine-yearly for proteinuria
- Radiology screening as indicated
- 6 -12 monthly long term assessment for “at risk”

Skeletal and Musculo skeletal

- TBI/ Steroid/ GVHD/hypogonadism secondary to conditioning
- Myopathy/ contractures/ osteopenia/ osteoporosis
- Physical activity/ Vit D and Calcium supplements, hormone replacement
- Screening of patients with no skeletal maturity–Ht, weight, BMI, tanner staging -6 monthly
- If abnormal growth –early endocrine referral for ? GH replacement

CNS

- Drug-related/ infection/ TBI/ IT therapy
- Cognitive issues –maybe subclinical
- Assessment for all at 1 yr and then at risk population

Endocrine & metabolic syndrome

- TBI/ Head and neck radiation –annual T4. TSH, pubertal development, Fasting glucose, lipid profile
- Hypopituitarism/ hypothyroidism, GH deficiency
- Yearly growth and development assessment
- Replacement therapy as indicated

Psychosocial & Sexual issues

- TBI/ pelvic radiation/ alkylators/ Busulfan
- Chronic fatigue/ low mood/ loss of libido/ infertility/ premature ovarian failure
- Replacement therapy/ Fertility specialist referral

Second cancers

- 2-3 fold increase of developing solid cancer
- RT/ IS/ cGVHD/ Fanconi anaemia/ cranial radiation/ alkylators/ topoisomerase II inhibitor therapy
- Avoidance of risk –UV rays, screening programs, smoking and tobacco avoidance

General screening & preventative health

- Recommended screening for general population
- PAP smear, Breast Ca risk assessment and screening, Prostate for males
- Healthy lifestyle/ screening & treatment of metabolic syndrome

Case scenario

- 26 year old young man presented to ER with h/o severe pain in right hip.
- PMH:
  - **Diagnosed and treated for Burkitt lymphoma at 15 years of age. Treated according to LMB protocol.**
  - **Relapsed; ICE salvage chemotherapy: (<12 months post EoT)**
  - **Allogenenic HSCT –MSD:**
    - Cy/TBI conditioning
    - ***Chronic GVHD: treated with Sirolimus and Steroids for upto 24 months.***
    - In remission now
- Lost to follow up –due to logistics and financial constraints
- Xray : partial collapse of right head of femur and sclerosis

Case scenario

Agent	Cumulative Dose
Cyclophosphamide	8.5 g/sq.m (LMB Protocol) + 3.2 g/sq.m (HSCT conditioning) = 11.7 g/sq.m
Methotrexate	32 g/sq.m
Etoposide	2.1 g/sq.m (LMB Protocol) + 1 g/sq.m (ICE salvage) = 3.1 g/sq.m
Cytarabine	17.5 g/sq.m
Doxorubicin	240 mg/sq.m
Prednisone	780 mg/ sq.m
Vincristine	8 mg/ sq.m
Ifosfamide	18 g/sq.m
Carboplatin	1.6 g/sq.m
Total Body Irradiation (TBI)	13.2 Gy (8 fractions)

Primary Concern

- Osteonecrosis of right femoral hip
- Allogeneic HSCT: 15% at 10 years; low risk –auto
- Femur> knee/ shoulder
- Risk factors:
  - Male
  - GVHD
  - TBI
- Management:
  - Clinical anticipation of risk/ supplements
  - Prompt radiology (Dexa scan for at RISK with Z-scores for paediatric patients)
  - Early intervention
  - Reduce burden of morbidity
  - Surgery!

Risk-adapted approach

- Identify potential risk
  - Cardiac toxicity (anthracycline/ TBI/ Cyclophosphamide)
  - Pulmonary toxicity
  - Renal (Calcineurin/ Methotrexate/ Ifosfamide/ Carboplatin/ TBI)
  - Peripheral neuropathy (Vincristine/ Carboplatin)
  - Hypothyroidism (TBI)
  - Neurocognitive effects (Intrathecal/ Methotrexate/ TBI/ Cytarabine)
  - Early cataracts (TBI/ steroids)
  - Secondary AML (alkylators, topoisomerase II inhibitors)
  - Radiation related solid tumors
  - Gonadal dysfunction (Cyclophosphamide/ Ifosfamide/ TBI)

Care plan for the patient

Care Aspect	Details/Actions
Initial Assessment	- Complete treatment summary - Baseline organ function tests (cardiac, pulmonary, renal, endocrine)
Monitoring Schedule	- 1st year: Frequent multidisciplinary assessments (3-6 monthly) - Years 2-5: Annual specialized screening - Beyond 5 years: Tailored screening based on risk and symptoms
Organ-Specific Surveillance	- Cardiac: Echo, ECG for anthracycline & TBI exposure - Pulmonary: PFTs for chemo/TBI exposure - Endocrine: Thyroid function, growth, gonadal status - Bone health: DEXA scan for osteonecrosis risk
Immunosuppression & GVHD	- Monitor and adjust immunosuppressants - Early intervention for chronic GVHD symptoms
Psychosocial Support	- Counseling for mental health and cognitive effects - Lifestyle modifications (nutrition, exercise, smoking cessation)
Patient Education	- Importance of adherence to follow-up - Signs/symptoms of late effects to report
Coordination of Care	- Transition plan to primary/community care - Shared survivorship care plan with all providers

survivorship PASSPORT

GASLINI

encca

SIOPE

PanCareSurFup

SUMMARY OF CANCER TREATMENT

This Survivorship Passport is a short summary extracted from the information reported in the medical record. It describes the disease and its clinical course as well the treatments you received.This document does not replace the medical record that is always available at our center.

*****

Passport Number: IT12509**85**

PERSONAL DATA

Date of birth	**/**/2002	**Sex**	Female

FIRST TUMOR

DIAGNOSIS

Date of diagnosis	20/09/2005
Institution	Istituto "Giannina Gaslini", Genova
Diagnosis	Nephroblastoma, NOS
Diagnosis description	Wilms' Tumor
Site	Kidney, NOS
Laterality	Left
Metastatic	No

OTHER DISEASES

Hereditary Cancer Predisposition Syndrome or medical condition cancer associated	No
Other medical conditions, not cancer associated	No

FRONT LINE TREATMENT

The treatment has been executed following	Trial/Protocol: AIEOP TW 2003	
Group/Arm/Randomization	1A	
Summary of major treatments	Chemotherapy	Yes
	Stem Cell transplantation	No
	Radiotherapy	No
	Major Surgery	Yes
Progression/relapse during frontline treatment	No	
Date of first elective end of treatment	04/11/2005	

RELAPSE AFTER FIRST ELECTIVE END OF TREATMENT

N. 1

Type of event	Relapse	
Date	08/02/2006	
Type	Local	
The salvage treatment has been executed following	Trial/Protocol: AIEOP TW 2003	
Summary of major treatments	Chemotherapy	Yes
	Stem Cell transplantation	Yes
	Radiotherapy	Yes
	Major Surgery	No
Date of end of treatment	13/06/2006	

CHEMOTHERAPY

CLINICAL COURSE

Start date	20/09/2005	**End date**	04/11/2005
	CLASSIC/TRADITIONAL ANTINEOPLASTIC AGENTS		
Drug name		**Total cumulative dose**	**Measure unit**
Vincristine		8.64 (Dose given)	mg/m2
Dactinomycin		3.9 (Dose given)	mg/m2
Intrathecal injections		No	
	OTHER ANTINEOPLASTIC AGENTS		
Hormones		No	
Immunotherapy		No	
	OTHER TREATMENTS		
Other treatments		No	

RELAPSE AFTER FIRST ELECTIVE END OF TREATMENT N. 1

N. 1

Start date	08/02/2006	**End date**	13/06/2006
	CLASSIC/TRADITIONAL ANTINEOPLASTIC AGENTS		
Drug name		**Total cumulative dose**	**Measure unit**
Etoposide		1161.29 (Dose given)	mg/m2
Ifosfamide		11.61 (Dose given)	gr/m2
Cyclophosphamide		1.29 (Dose given)	gr/m2
Melphalan		129.03 (Dose given)	mg/m2
Carboplatin		1725.81 (Dose given)	mg/m2
Doxorubicin		111.29 (Dose given)	mg/m2
Intrathecal injections		No	
	OTHER ANTINEOPLASTIC AGENTS		
Hormones		No	
Immunotherapy		No	
	OTHER TREATMENTS		
Other treatments		No	

STEM CELL TRANSPLANTATION

RELAPSE AFTER FIRST ELECTIVE END OF TREATMENT N. 1

N. 1

Date of transplant	27/04/2006
Type of donor	Autologous

RADIATION THERAPY EPISODE

RELAPSE AFTER FIRST ELECTIVE END OF TREATMENT N. 1

N. 1

Type of radiotherapy		External beam: Linac (Linear Accelerator) electrons			
Start date	29/05/2006	**End date**	13/06/2006		
Site (1)		Flank / hemiabdomen (top of diaphragm to iliac crest) (left)		**Dose**	20 Gy

MAJOR SURGERY

CLINICAL COURSE

N. 1

Date of surgery	20/09/2005
Surgery description	Left Nephrectomy

OTHER INFORMATION AND RELEVANT CLINICAL EVENTS DURING TREATMENT

RELAPSE AFTER FIRST ELECTIVE END OF TREATMENT N. 1

N. 1

CVC positioning	Yes
If yes, specify the site	Right jugular vein
Last transfusion date	05/05/2006

RECOMMENDATIONS FOR FOLLOW-UP

Because of the treatment you have had we have listed the tests recommended for you. This advice is because a few people who had the same treatment as you have developed problems which we hope can be picked up at an early and treatable stage.

Cardiomyopathy Screening

We think that you need regular checks on how your heart is working.

Premature Ovarian Insufficiency Surveillance

We think that you need regular checks to monitor your ovarian function.

Although the risk is greater with higher doses of treatment, it is still possible for lower doses to cause premature ovarian insufficiency in a few females.

Data are updated to the date of issue of the passport or the date of the last clinical examination certified by the physician.

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Passport issued by ***Davide Saraceno***

Institution ***Istituto "Giannina Gaslini", Genova***

Date of issue ***28/02/2018***

Signature of the doctor in charge:

Ifosfamide	11.61 (Dose given)	gr/m2
Cyclophosphamide	1.29 (Dose given)	gr/m2
Melphalan	129.03 (Dose given)	mg/m2
Carboplatin	1725.81 (Dose given)	mg/m2

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Institution	***Istituto "Giannina Gaslini", Genova***
Date of issue	***28/02/2018***

Signature of the doctor in charge:

Challenges to monitoring late effects

- Applicable to ALL SURVIVORS OF CANCER & HSCT
- “Moving” population
- Resource availability
  - –Specialists
  - –Procedures
  - –Funding
  - –Access to healthcare

Take home message

- HSCT survivors - significant long term risks due to cumulative chemo and RT exposure

- **Risk-adapted**, **exposure-focused**, **lifelong** monitoring helps detect and manage late effects early.

- **MDT** approach optimises survivor outcomes

- Comprehensive care plans /survivorship passports enhance **continuity** and quality of care for **transitions**

- Patient **education** to encourage adherence to follow up & promote healthy lifestyles

References

Core Review Articles & Overviews

- **Chow EJ**, Anderson L, Baker KS, Bhatia S, et al. Late Effects Surveillance Recommendations among Survivors of Childhood Hematopoietic Cell Transplantation. Biol Blood Marrow Transplant. 2016;22(3):578-595.
- **Bhatia S**, Davies SM, Scott Baker K, Pulsipher MA, Hansen JA. NCI, NHLBI First International Consensus Conference on Late Effects After Pediatric HCT. Biol Blood Marrow Transplant. 2011;17(10):1428-1435.
- **Majhail NS**, et al. Recommended screening and preventive practices for long-term survivors after HSCT. Hematol Oncol Stem Cell Ther. 2022;15(3):152-159.
- National Comprehensive Cancer Network (NCCN) Guidelines on Survivorship. Version 2.2025.
- **Majhail NS.** *Long-Term Complications After Hematopoietic Cell Transplantation.* **Hematology Am Soc Hematol Educ Program.** 2017:220–227.
- **Armenian SH, et al.** *Late Effects in Hematopoietic Cell Transplant Survivors.* **Clin Rev Allergy Immunol.** 2017;52:137–154.

Survivorship Guidelines (Must-Read)

- National Marrow Donor Program (NMDP) / CIBMTR Survivorship Guidelines.
- Children’s Oncology Group (COG) Long-Term Follow-Up Guidelines, HSCT sections.

Quiz

- Which of the following is a leading cause of non-relapse mortality among long term BMT survivors
  - Second malignancies
  - Cardiovascular disease
  - Endocrine dysfunction
  - Chronic kidney disease

- Which conditioning regimen/ drug component is a major risk factor for several late effects including second malignancies, thyroid dysfunction and AVN?
  - Steroids
  - Alkylators
  - TBI
  - Etoposide