SCID compass

An educational program of the Immune Deficiency Foundation

Organ Function and Long-term Outcomes following HSCT

November 16th, 2022

IDF MISSION

Improving the diagnosis, treatment, and quality of life of people affected by primary immunodeficiency through fostering a community empowered by advocacy, education and research.

Immune Deficiency Foundation

HOUSEKEEPING

- Attendees will not have access to their microphone or webcam throughout the event.
- To see the full slides, you can adjust the settings on the speaker view panel on the top of the Zoom screen and select "side-by-side" in the dropdown option.
- Please submit all questions for the presenter via the Q&A box

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SCID Compass
An educational program of the Immune Deficiency Foundation

Immune Deficiency Foundation

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To view all SCID Compass Resources ,Materials, and Events visit: www.SCIDCompass.org

WELCOME

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Immune Deficiency Foundation

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Late Effects and Survivorship

FOLLOWING
PEDIATRIC HEMATOPOIETIC STEM CELL TRANSPLANTATION

Ami J. Shah, MD
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Potential Late Effects

Chronic GVHD

Infection

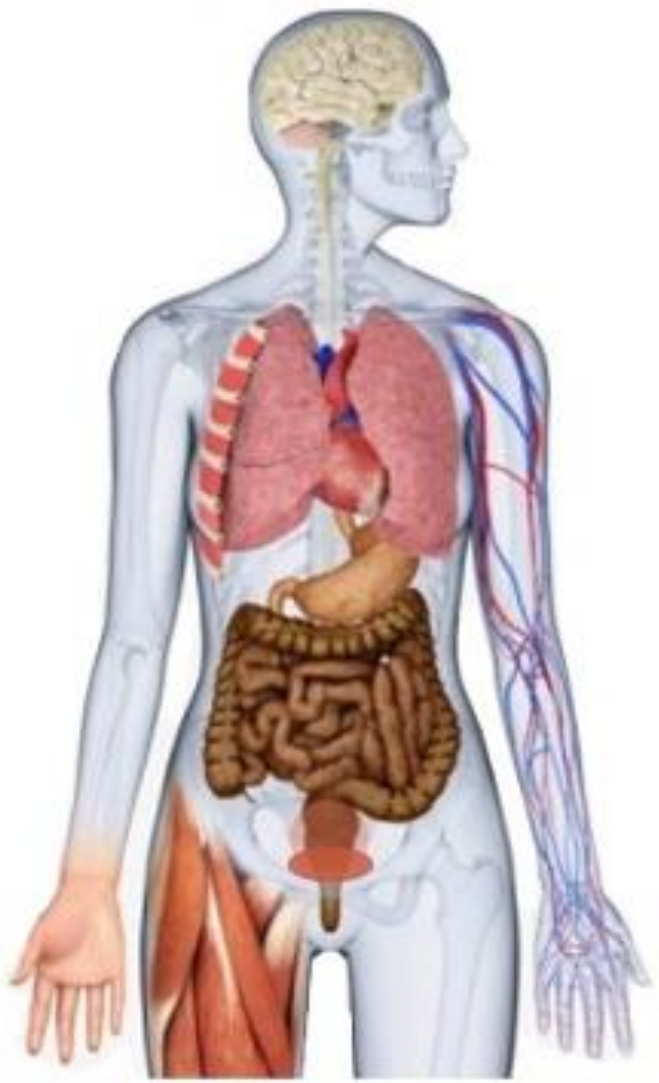
Pulmonary dysfunction

Cardiovascular disease

Hypogonadism

Growth hormone deficiency

Renal insufficiency



Iron overload

Osteoporosis/AVN

Cataracts

Dental anomalies

Neurocognitive dysfunction

Psychological

Secondary Malignancy

Etiology of Late Effects

- Primary disease
- Previous treatment for primary disease
- Pre-transplant co-morbidities
- Type of transplant (source, match, manipulation)
- Conditioning regimen
- Patient age at transplant
- Acute transplant complications
- GVHD

Case Study

Case Study:

R.E. is an **11-year-old female** with history of SCID (Omenn's)

-10 years status post **a 9/10 HLA matched unrelated donor BMT.**

-Her conditioning regimen was busulfan, cytoxan and ATG.

-**Severe GVHD** of the GI tract and skin., treated with **steroids**.

-Infectious complications including disseminated aspergillosis, due to immunosuppression. Treated with prolonged amphotericin

Late Effects:

- Chronic GVHD
- Delayed immune reconstitution/multiple infections
- Endocrine dysfunction: growth disturbance, adrenal insufficiency (steroids)
- Chronic kidney disease
- Pulmonary fibrosis (mild)
- Osteoporosis
- Neurocognitive Dysfunction
- Cataracts

Chronic Graft-versus-Host Disease

Incidence

- varies greatly, from 20 to 85%

Risk varies based on:

- Transplant source
- Donor characteristics
- Patient characteristics
- History of acute GVHD

Surveillance: Screening consists of thorough clinical examination, laboratory data (CBC, CMP), Pulmonary function testing, assess joints

Treatment: First line for moderate to severe cGVHD usually consists of steroids ± calcineurin inhibitor

Infection

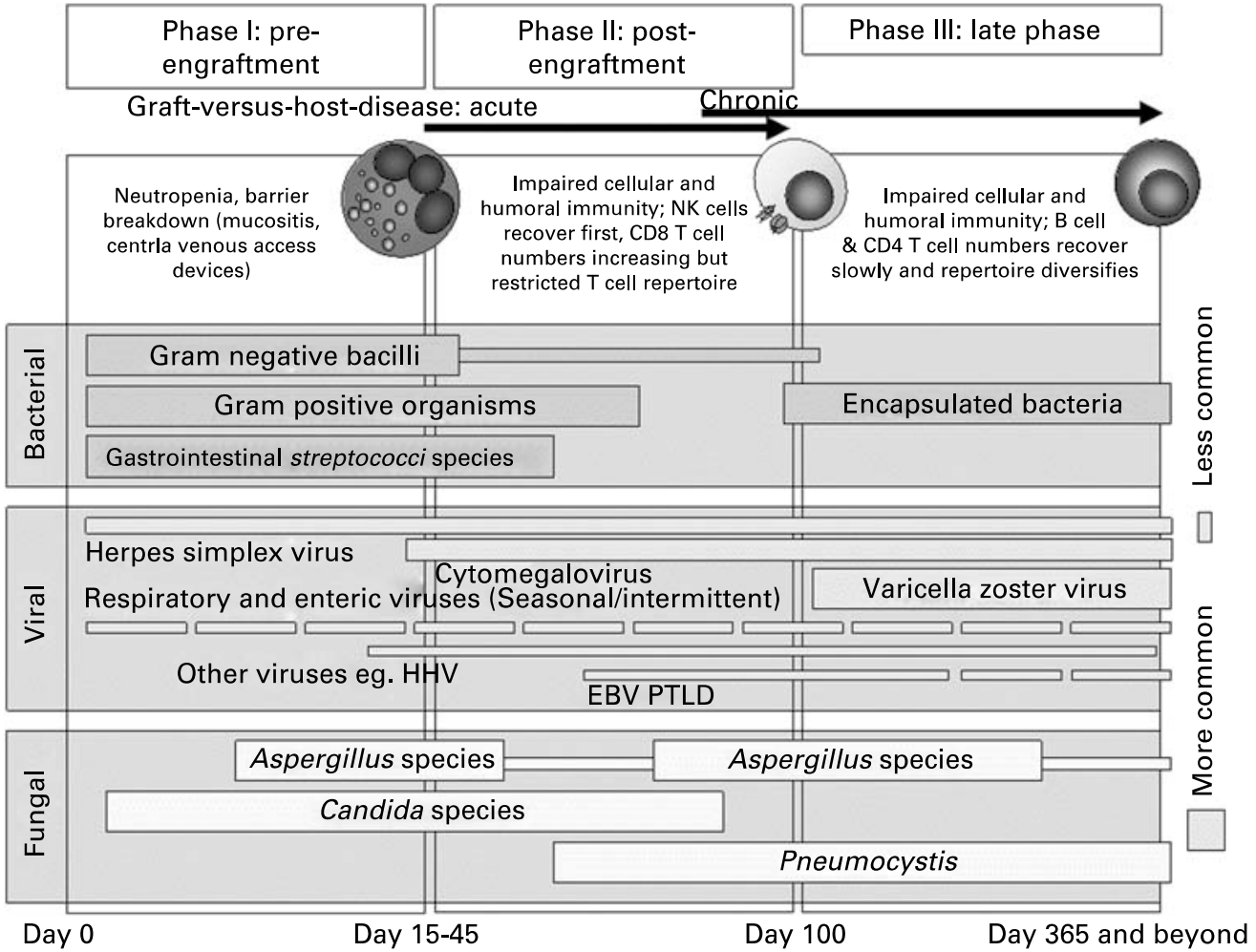


Figure 2 Phases of opportunistic infections among allogeneic HCT recipients. HHV6, human herpesvirus 6; NK, natural killer; PTLD, post transplant lymphoproliferative disease.

Mackall et al. (2009) *Bone Marrow Transplant*, 44, 457-462.

Endocrinopathies

Risk factors:

- Age at transplant
- Previous therapy
- Conditioning regimen
- Prolonged treatment with steroids

Late effects:

- Hypothyroidism
- Hypoadrenalism
- Growth hormone deficiency
- Linear growth disturbance
- Gonadal failure

Endocrine Dysfunction: **Adrenal Insufficiency**

Risk Factors

- Prolonged steroid use
- Radiation

Prevention

- Slow wean of steroids

Surveillance:

- Clinical symptoms
- AM cortisol levels and ACTH stimulation testing, if indicated

Treatment

- Stress doses of steroids for illness and procedures

Endocrine: **Growth Disturbance**

Definition: decrease in growth velocity that is inappropriate for age

Incidence: occurs in up to 1/3 of patients post-HSCT

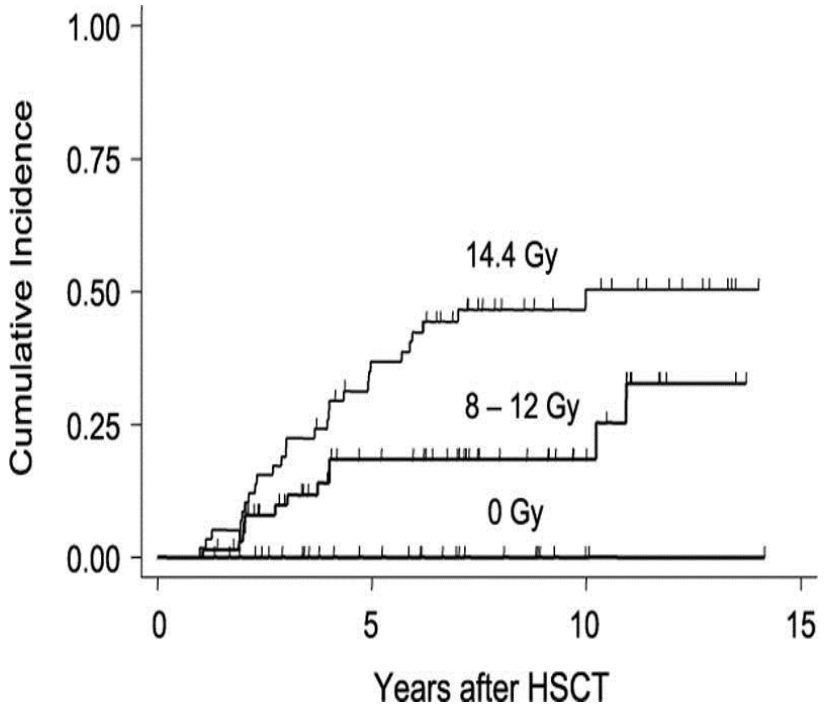
Risk factors: TBI and cranial radiation, steroids, age at transplant, previous primary disease treatment history

Surveillance:

- Height/weight
- Tanner Staging

Treatment:

- Referral to endocrinology for possible growth hormone therapy (patient must be over a year off of therapy)



Leung Medicine 2007

Case Study 2 : Renal Dysfunction

R.E. is an **11-year-old female** with history of SCID (Omenn's)

-10 years status post **a 9/10 HLA matched unrelated donor BMT.**

-Her conditioning regimen was busulfan, cytoxan and ATG.

-**Severe GVHD** of the GI tract and skin., treated with **steroids**.

-Infectious complications including disseminated aspergillosis, due to immunosuppression. Treated with prolonged amphotericin

Late Effects:

- Chronic GVHD
- Delayed immune reconstitution/multiple infections
- Endocrine dysfunction
- **Chronic kidney disease**
- Osteoporosis
- Cataracts

Chronic Kidney Disease

Definition: irreversible kidney function and/or reduction of kidney function, with at least one of the following

- GFR <60 mL/min per 1.73 m2 for greater than 3 months
- GFR >60 mL/min per 1.73 m2 that is accompanied by structural damage or other markers of function kidney abnormalities (proteinuria, albuminuria, renal tubular disorders, pathologic abnormalities by histology or imaging)

Incidence: estimated at 20%

Risk factors: acute renal failure, h/o antihypertensive treatment, GVHD, nephrotoxic agents

Surveillance: BP monitoring, annual metabolic panel and UA

Treatment: BP control, dialysis

Pulmonary Complications

Late effects

- Restrictive disease: total lung capacity (TLC) < 80% predicted
- Obstructive disease: forced expiratory volume-1/forced vital capacity (FEV1/FVC) ratio of less than 70%. (ex. Bronchiolitis obliterans)

Risk factors:

- GVHD
- Age
- Infection
- Conditioning regimen

Assessment

- Clinical presentation variable
- Pulmonary Function Tests
- High-resolution chest CT

Treatment

- Supportive (not GVHD-related)
- Immunosuppression (bronchiolitis obliterans/GVHD)

Skeletal:
Osteopenia and Osteoporosis

Osteoporosis definition (pediatrics): bone mineral density Z score below -2.0 in combination with a fracture

Risk Factors:

- TBI
- steroids
- ovarian failure

Surveillance:

- Bone density via DEXA scans, annual vitamin D-25(OH) levels

Prevention/Treatment:

- Weight-bearing exercise
- calcium and vitamin D supplements
- hormone replacement therapy (if indicated)

Endocrine Dysfunction: **Gonadal Failure**

Definition:

- Female: irregular or absent menses and FSH in postmenopausal range
- Male: elevated FSH and low testosterone levels causing primary testicular failure and impaired spermatogenesis

Clinical presentation: delayed pubertal development based on Tanner staging, amenorrhea, early menopausal symptoms

Risk factors: Busulfan, TBI

Monitoring: Annual LH, FSH, and testosterone level (males)/estradiol level (females)

Surveillance: Annual gynecologic exams and annual mammograms after the age of 35 (or earlier depending upon family history)

Treatment:

- Sperm banking and freezing eggs when possible prior to therapy
- Hormone replacement therapy
- Management of menopausal symptoms

Skeletal: **Avascular Necrosis**

Definition: necrosis of bone tissue due to lack of blood supply often leading to destruction of joint articular surfaces

- Hip joint is most often affected
- Can be seen as late as 10 years post-transplant

Incidence: 4-10% at one year post-transplant

Risk factors: Steroids, gender (male), age > 16 years old

Treatment: Joint replacement surgery

Dental

Risk factors:

- Conditioning regimen
- Chronic GVHD
- Age at transplant

Late effects

- Poor root development
- Premature apical closure
- Dental caries
- Enamel dysplasia
- Abnormal eruption
- Periodontal disease

Surveillance: Twice yearly dental examination, radiographic studies

Liver Dysfunction

Risk factors: PRBC transfusions, TPN, and medication toxicities

Late effects:

- Iron overload
- Fatty liver disease
- chronic GVHD
- Hepatitis

Surveillance: Annual LFTs; hepatitis screening at 1,2 and 5 years post-transplant; and ferritin levels, T2* MRI

Treatment:

- Iron overload: oral iron chelation or monthly therapeutic phlebotomy

Neurocognitive Dysfunction

Neurocognitive disabilities are significant and common late effects of HSCT, including difficulty with:

- Reading,
- Verbal and nonverbal memory,
- Defects in verbal fluency,
- Impaired memory,
- Shortened attention span,
- Poor school performance

Surveillance: neuropsychological testing, esp prior to school starting.

Management:

- IEP, 504 plan
- Strong communication with the school

Psychological Dysfunction

- Depression
- Anxiety
- Adjustment disorder
- Post-traumatic stress disorder (PTSD)

PIDTC Data:
Retrospective Data for patients> 2 years post HSCT

-Manuscript in preparation (being submitted soon, Eissa et al)

-Retrospective data from 662 patients on SCID patients treated with one transplant between 1982 and 2012.

-Of the 662 patients: exclusion of 263 patients:

- 150 expired prior to 2 years
- 64 received a second transplant
- 49 were lost to follow up and did not have any data available

-Total used in this study was 399 patients.

- 76% male/ 24% female
- median age at dx: 131 days (0 to 6781 days)
- median follow up: 8.2 years (2-32.2 years)
- median age at tx: 178 days (7 – 7067 days)

Patient Transplant Characteristics

Infection Status at time of transplant

no infection:	28.1%
active infection:	**40.1%**
resolved infection:	28.1%
unknown data:	3.8%

Conditioning

No Conditioning:	**69.6%**
Reduced intensity:	9%
Myeloablative:	20.6%
unknown dose:	0.8%

Donor Source

Matched sibling:	18.3%
Other donor:	5.3%
MMRD:	**58.1%**
URD:	18.3%

Product type

Cord Blood:	11.3%
BM	75.4%
PBSC:	13.3%

Prevalence of Chronic Late Effects

# of individuals experiencing ≥ 1 CLE (N= 399)		2 years	5 years	10 years	15 years
		Cumulative Incidence			
1 organ system	100 (25%)	24.8	30.66	35.13	41.46
2 organ system	26 (6.5%)				
3 organ system	10 (2.5%)				
4 organ system	4 (1%)				
5 organ system	1 (0.3%)				
6 organ systems	1 (0.3%)				

Organ System Prevalence

	Prevalence	2 year	5 year	10 year	15 year
Neuro	34 (8.5%)	5.51	6.89	8.73	8.73
Development	31 (7.8%)	6.02	7.7	7.7	8.37
Dental	30 (7.5%)	0.25	4.12	8.47	10.52
Pulmonary	26 (6.5%)	5.26	6.41	6.88	6.88
MSK	24 (6%)	3.26	4.14	6.21	6.83
Hepatic	18 (4.5%)	2.26	2.51	3.91	5.9
Autoimmune	15 (3.8%)	1	2.32	3.62	5.87
Endocrine	15 (3.8%)	0.75	1.6	2.93	4.67
GI	5 (1.3%)	0.25	0.52	0.52	1.07
Cardiac	2	0.25	0.25	0.25	0.25
Malignancy	9	0.5	1.41	1.41	2.84

Neuro Complications

-Motor Disturbances (2.8%)

-Hearing/ Speech/ and or visual Disturbances (2.3%)

-Seizures (2%)

-Other Complications (<1% each)

- Cerebral palsy
- Headache
- Neuropathy
- TIA

Developmental Complications

-Global developmental delays

-Behaviorial Delays

-6 patients reported depression

-6 patients reported ADD/ ADHD

-3 patients reported autism disorders

-1 patient reported severe anxiety

Some patients reported depression in addition to anxiety/ ADHD.

Dental Complications

-caries/ decay

-mal-development

-missing permanent teeth

-poor dentition

** many of the children have not had all of their teeth in place

Growth

-2-5 years post HSCT

- 44% had a Z score < 25%ile
- 23% had a Z score < 5%

-6-10 years post HSCT

- 46.4% had a Z score < 25%
- 21.5% had a Z scre <5%

Malignancies

2.3% of patients developed a malignancy

-lymphoma/ lymphoproliferative disease (0.9%)

-non-melanoma skin malignancy (0.6%)

Reproduction

-97 females*

-33 females > 14 yrs

-80% achieved menarche

(11NC, 5 IS, 3RIC, 5MAC)

-3 of those who received an unconditioned transplant had a child

-302 males*

-3 reported fathering a child, none of the 3 received conditioning

FACTORS for Chronic Late Effects

-Pre-transplant infections (esp neurologic complications)

-RIC/ MAC conditioning regimens (growth, dental and endocrine abnormalities)

-cGVHD (autoimmune, hepatic and GI CLE)

-Artemis patients (DCLRE1C) had the greatest numbers of CLE

Take Aways

- Patients who undergo HSCT are at high risk of chronic health conditions
- Consistent long-term follow up is key to identifying and treating late effects of therapy
- **More research is needed**

Concerns for this retrospective data

1. Most centers did not collect the same data and we had to rely on what the center had available. Data managers extracted what was written in the notes, which may not have captured all information

2. Although many patients were in follow up at the same center, many patients stopped going to their doctor when they felt well. Therefore information regarding reproduction is only descriptive

QUESTIONS???

Q&A SESSION:
YOUR QUESTIONS ANSWERED

Have more Questions?

primaryimmune.org/ask-idf

800-296-4433

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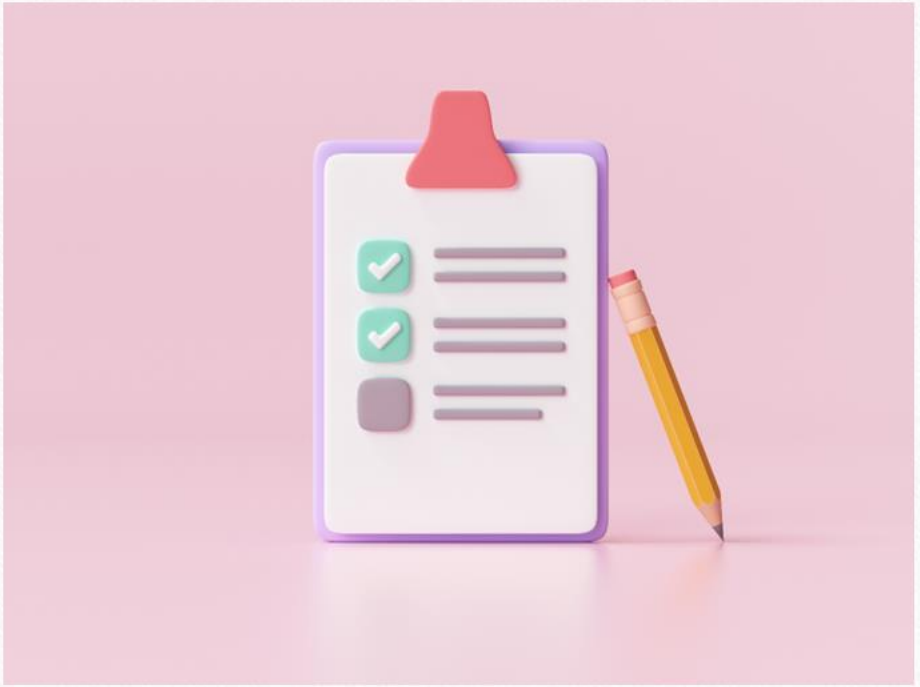
WE VALUE YOUR FEEDBACK!

Please take our poll to let us know your level of comfort level with indoor and in-person events…



NEXT PROGRAM

SCID Compass Lunch & Learn: Pain Management & Coping for Kids in a Medical Setting

Samantha Childs, CCLS
November 30th, 2022
1:00-2:00 PM ET

www.scidcompass.org/events

THANK YOU!

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