Aplastic Anemia & MDS INTERNATIONAL FOUNDATION

Hematopoietic Cell Transplantation

Managing Post-transplant

July 18, 2015

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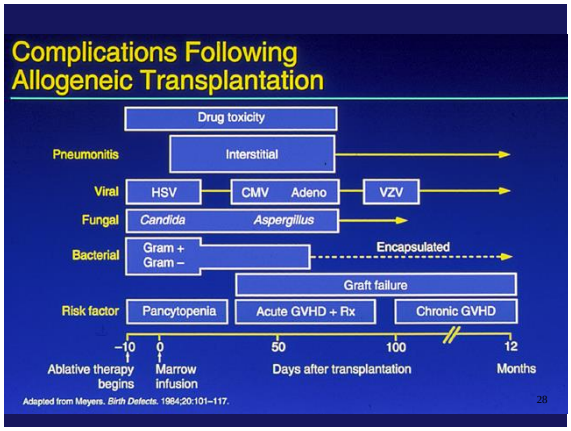
Topics

1. Early and late complications
2. Treatments
3. Follow-up
4. Supportive services

Most Common Early-complications After Allogeneic Transplant

- Infection
- Acute graft-versus-host disease



Infection- early (first 100 days)

- **Neutropenic sepsis-** fever, often with positive blood cultures, will develop in nearly all patients within 7 days of becoming neutropenic. Sepsis usually caused by enteric bacteria or bacteria found on the skin. Antibiotics are continued until neutrophil count begins to rise (>500/ul)
- **Prevention of fungal infections-** for patients who are expected to have prolonged neutropenia, antifungal prophylaxis is used, including oral fluconazole (Diflucan 200 mg bid) or voriconazole (Vfend 200 mg bid). Liposomal amphotercin B or caspofungin/micafungin are other formulations used.
- **Oral herpes simplex reactivation-** nearly all patients who are seropositive for herpes simplex virus (HSV) will have a reactivation of the virus. To prevent this problem, most transplant programs use acyclovir during the neutropenic phase.

Infection- early (first 100 days)

- **Cytomegalovirus viremia/infection-** preemptive strategies have dramatically reduced morbidity and mortality.
- Pretransplant recipient CMV seropositivity most important risk factor for reactivation (Transplant Infect Dis 2010;12:322)

Multivariate analysis of risk factors for cytomegalovirus (CMV) reactivation

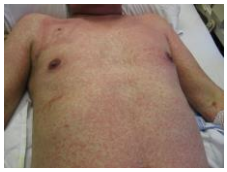
Variable	Relative risk	95% CI	P value
High-risk CMV serostatus (R + /D + / –)	27.84	985–80.33	< 0.0001
Presence of acute GVHD	3.8	2.13–6.94	< 0.0001
Use of alemtuzumab	2.43	0.71–8.31	0.1559
RIC	1.98	1.07–3.64	0027

CI, confidence interval; R, recipient; D, donor; GVHD, graft-versus-host disease; RIC, reduced intensity conditioning.

- Most effective strategy to prevention reactivation of CMV infection is preemptive use of ganciclovir at the first sign of CMV after transplant. Duration somewhat controversial but usually for at least 2 weeks after CMV PCR assay becomes negative.
- Monitoring for CMV infection after therapy needed, esp pts with GVHD, cord blood recipients, T cell depleted transplant recipients

Acute graft-versus-host disease

- **Clinical syndrome that results from infusion of immunocompetent lymphocytes in the stem cell graft that recognize minor HLA-related antigens in the host and initiate an immunologic reaction.**
- **Primary organs affected by acute GVHD are the skin, liver, and gastrointestinal tract.**
- **Occurs within 15-60 days after transplant and can vary in severity.**



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Acute graft-versus-host disease

- **Prophylaxis: all patients who undergo non T cell depleted transplant require some form of GVHD prophylaxis**
- **Most common regimens involve a combination of methotrexate and cyclosporine or tacrolimus (Prograf).**
- **The combination of tacrolimus and sirolimus (Rapamune) appears to be an effective preventive approach without methotrexate.**
- **These medications, in the absence of GHVD, are tapered over 6 to 12 months after HCT**

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Acute graft-versus-host disease

- Despite prophylaxis, many patients still develop some degree of GVHD and require increasing doses of prednisone (1 to 2 mg/kg/d).
- Unfortunately only about half of patients respond to steroids alone. There is no clear second line agent for steroid refractory acute GVHD.

Table 1. Treatment of steroid-refractory acute GVHD

Organ with predominant GVHD manifestation	Secondary therapy
Skin	ATG (thymoglobulin, ATGAM); denileukin diftitox; monoclonal antibodies (anti-CD25, anti-CD3, anti-CD52); phototherapy (PUVA, ECP); chemotherapy (MMF, calcineurin inhibitors, pentostatin, sirolimus)
Liver	ATG; denileukin diftitox; monoclonal antibodies; chemotherapy (sirolimus, pentostatin, calcineurin inhibitors); phototherapy
Intestinal tract	"Nonabsorbable" steroids (beclomethasone, budesonide); ATG; TNFα blockade (infliximab, etanercept); chemotherapy (sirolimus, pentostatin, calcineurin inhibitors); mesenchymal "stem" cells; octreotide

Blood 2007;109:4119

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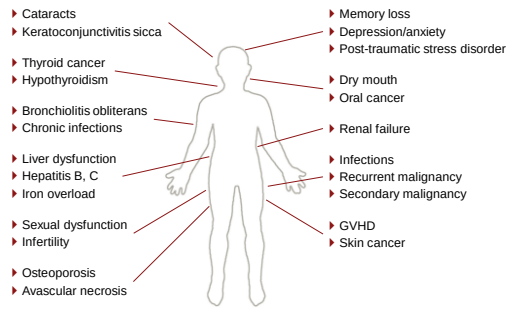
Late Effects After Allogeneic Transplant



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Most Common Late-complications After Allogeneic Transplant (>100days)

- Recurrent disease
- Secondary malignancy
- Chronic graft-versus-host disease
- Infection
- Cardiovascular and pulmonary complications
- Significant stressors:
  - Chronic pain
  - Fatigue
  - Insomnia
  - Sexual dysfunction
  - Memory loss
  - Mood changes
  - Vision and dental complications
  - Financial stressors

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Relapse After Transplant Is Still The Primary Cause of Transplant Failure

CIBMTR Time Trends Study 2014

26,563 patients with acute leukemia, chronic myeloid leukemia and myelodysplastic syndrome.

	No. of patients at risk		No. of patients at risk		No. of patients at risk		
Outcome events		1995-1999 Prob (95% CI)		2000-2003 Prob (95% CI)		2004-2007 Prob (95% CI)	P-value
Relapse							
@ 1 year	4908	20 (19-21)	3258	27 (26-28)	3947	27 (26-28)	<0.001
@ 3 years	3742	26 (25-26)	2337	33 (32-34)	2430	34 (33-35)	<0.001
@ 5 years	3114	27 (26-28)	1714	34 (33-35)	977	37 (35-38)	<0.001

Arai, Pavletic, in submission

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Secondary Cancers

- AlloHCT survivors are at high risk for secondary leukemia, PTLD, new solid tumor at 2-4 times increased incidence compared to age-matched controls
- Particular high incidence exists for secondary oral cancers and thyroid cancers, especially in pts with chronic GVHD or prior irradiation

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Late Effects Guidelines 2012 by CIBMTR

- Emphasis on regular age-appropriate cancer screening
- Earlier mammography recommended for women with h/o TBI, starting at age 25 years or 8 years after radiation
- Regular exam of the oral cavity and thyroid
- Increased risk of skin cancers – educate on importance of sunscreen protection and regular skin examination

Majhail, BMT 2012

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cGVHD

- cGVHD inicidence increasing despite advances in transplant practice
- Causes significant morbidity
- Skin involvement – sclerotic changes, fasciitis or myositis complicated by joint contractures, visual issues, GYN complications, hepatitis, oral and intestinal involvement (diarrhea, anorexia), obstructive or restrictive lung disease
- Pathogenesis: highly complex immune pathology involving both donor B cells and T cells as well as other cells

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cGVHD

- Occurs in:
  - 30% (young, with sibling donors) to
  - 70% (older, unrelated donors)
- Median time to development is 4-6 months after transplant
- 50% have 3 or more involved organs/tissues
- Risk factors: expansion of the donor population beyond HLA-identical siblings, older age patients, use of peripheral blood cells as graft source, donor and recipient gender disparity (female donor to male recipient), prior acute GVHD

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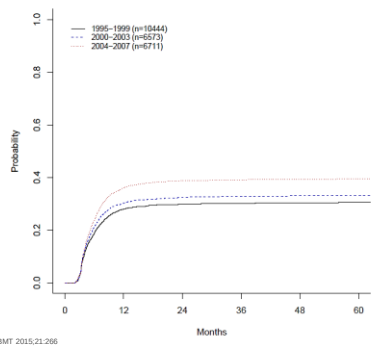
Figure 1. **Cumulative incidence of cGVHD over years of tx**



Arai, Pavletic, BBMT 2015;21:266

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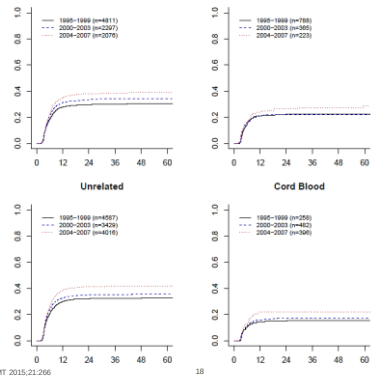
Figure 2a. **HLA identical sibling** **Other relatives** **Unrelated** **Cord Blood**



Arai, Pavletic, BBMT 2015;21:266

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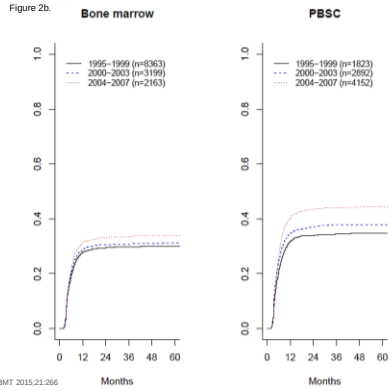
Figure 2b.



Arai, Pavletic, BBMT 2015;21:266

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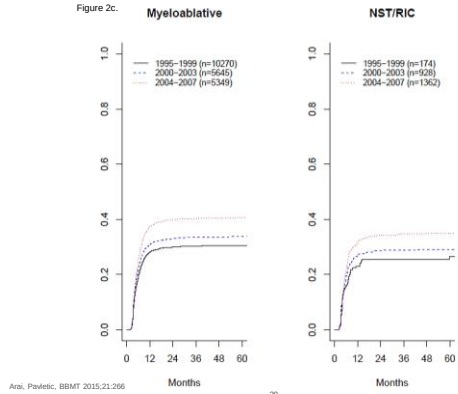
Figure 2c.



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cGVHD- what is new in diagnosis?

- cGVHD is primarily a clinical diagnosis- In 2005, new National Institutes of Health (NIH) Consensus Criteria were published (Filipovich BBMT 2005), designed to provide more detailed information about the individual organ involvement. A global score of severity (mild, moderate, severe) can be generated that is predictive of NRM and OS.
- 8 major organs involved; 6 are diagnostic- **skin**, **mouth**, eyes, **genitalia**, **GI tract**, liver, **lung**, **muscles/fascia/joints.**

Table 3. Chronic GVHD review of systems

No.	System/others	Inquire/description
1	Skin	Skin feels tight or hard, increased dryness, pruritus, or looks different (ie, new rash, papules, discoloration, shining scar-like, scaly)?
2	Sweat glands	Inability to sweat or to keep body warm?
3	Skin appendages	Loss of hair (scalp or body including brows or lashes), or nail changes (ridges or brittle, loss)?
4	Fascia/joints	Stiffness or pain in the wrists, fingers, or other joints?
5	Eyes	Eye dryness, sensitivity to wind or dry environments (air conditioning), pain?
6	Mouth	Oral dryness, taste alterations, sensitivities (spicy/carbonate drinks, toothpaste), ulcers/sores, pain?
7	Esophagus	Foods or pills gets stuck upon swallowing?
8	Lungs	Cough, dyspnea (on exertion or rest) or wheezes?
9	Genital tract	Vaginal dryness, pain, dyspareunia (female); pain or dysuria due to stenosis of urethra (male)?
10	Weight loss	Unexplained weight loss or inability to gain weight (pancreatic insufficiency or hypercatabolism)?

Blood 2015;125:606

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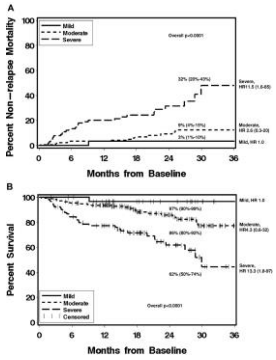

Arai S et al. Blood 2011;118:4242-4249

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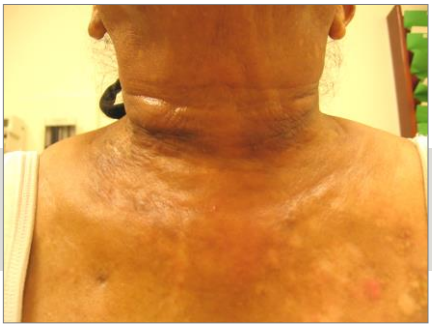
Sclerotic skin changes



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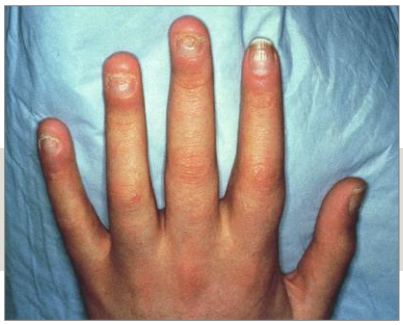
Nails



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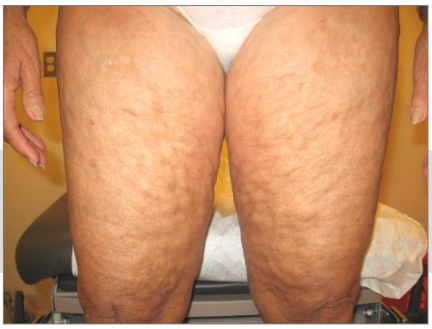
Fasciitis



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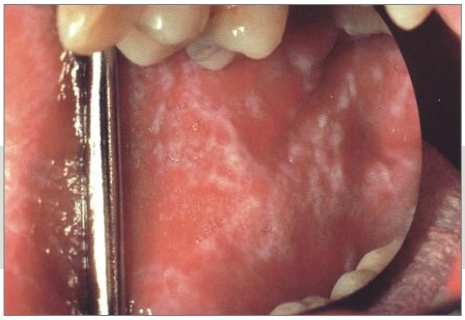
Oral Mucosal Lichenoid Changes



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cGVHD Treatment

- There is no FDA-approved treatment for aGVHD or cGVHD. The frontline treatment of choice for both in patients needing systemic therapy is steroids.
- For patients with cGVHD, the NIH Consensus Conference recommends systemic treatment with corticosteroids for those with moderate or severe disease.
- One mg/kg prednisone or equivalent is standard, but no randomized studies comparing this with an alternate dose exist.
- There are no consistent guidelines for tapering steroids for patients who have achieved a response.
- The median duration of therapy is 2–3 years.
- 15% still require therapy 7+ years after diagnosis.
- Attempts to improve on initial response rates have proven frustrating.
- Half of the patients require second-line treatment.

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Table 6. Agents used for secondary treatment of chronic GVHD*

Treatment	% Overall response*	Survival
ECP	65-70	70%-78% at 1 y
Rituximab	66-86	72% at 1 y
Imatinib	22-79	75%-84% at 1.5 y
Pentostatin	53-56	34%-60% at 1-3 y
Mesenchymal stem cells	50-74	78% at 2 y
Mycophenolate mofetil	26-64	67%-96% at 1 y
mTOR inhibitor	76	72% at 3 y
Interleukin-2	52	Not reported
Other therapies summarized in other reviews**		
Calcineurin inhibitor		
High-dose methylprednisolone		
Methotrexate		
Thalidomide		
Hydroxychloroquine		
Clofazimine		
Thoracoabdominal irradiation		
Alefacept		
Infliximab		
Etanercept[70]		

mTOR, mammalian target of rapamycin.
*Simplified from Inamoto and Flowers[36]; see Flowers et al,[36] Wolff et al,[63] and Flowers and Deeg[64] for other reviews.
**20%-82% overall response rates reported.

Blood 2015;125:606

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Chronic GVHD Consortium

Clinical Sites:

Fred Hutchinson
Stanford University
University of Minnesota
Dana-Farber Cancer Institute
Vanderbilt University
Medical College of Wisconsin
H. Lee Moffitt Cancer Center
Washington University
National Cancer Institute
University of North Carolina
Weill Cornell Medical College
Mayo Clinics
Roswell Park Cancer Institute
Cleveland Clinic
Ohio State University

CA118953, CA163438

CHRONIC GRAFT VERSUS HOST DISEASE CONSORTIUM

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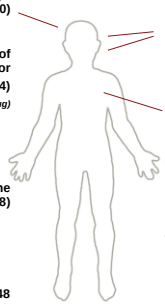
Consortium Clinical Trials

Bandage Lenses for eye chronic GVHD (N=20)

Randomized Phase II of imatinib vs. rituximab for cutaneous sclerosis (N=74)
(Novartis, Genentech providing drug)

Longitudinal study of Immune Mediated Disorders (N=1,118)



Randomized Phase III of Restasis vs. Placebo for Prevention of ocular GVHD (N=254)
(Allergan providing drug and support)

Phase II of FAM for BOS (N=40)
(GSK, Merck providing drug)

Steroid-refractory chronic GVHD
Tocilizumab (N=42) – *Genentech*
Carfilzomib (N=20) – *Onyx*

ORD
CA1643348

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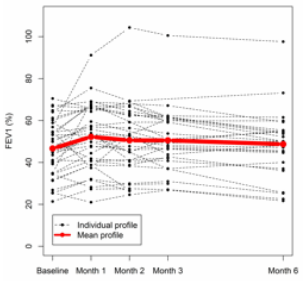
Phase II Trial of Inhaled Fluticasone Propionate, Azithromycin, and Montleukast (FAM) for BOS

Change in individual and mean percentage FEV1% over time



FAM (**Fl**uticasone proprionate (440 mcg inhaled bid), **A**zithromycin (250 mg 3x/week), and **M**ontelukast (10mg QD)

Primary endpoint was treatment success, defined as < 10% FEV1 decline at 3 months

Eighty-three percent (n=30/36) had treatment success at 3 months.

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Long Term Infectious Disease Concerns

- Risk highest in immediate post-transplant period up to 2years
- However, susceptibility often persists long term due to delays in immune reconstitution, impaired cellular and humoral immunity, esp in those with cGVHD on chronic IS therapy
- Lifelong complication- encourage pt to seek prompt medical attention if signs of infection even if WBC normal

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Long Term Infectious Disease Concerns

- Pts with cGVHD have impaired opsonization, should be treated with abx prophylaxis against encapsulated organisms in addition to viral and PJP prophylaxis
- All transplant pts should be given inactivated vaccines appropriate to their age, whereas live vaccines should be withheld in pts with cGVHD and impaired immunity
- Live vaccines may be administered at 2 years post-HCT if it has been more than 1 year since receiving IS therapy and at least 5 mos since the last IVIG
- The zoster vaccine (Zostavax) has higher viral titers and remains contraindicated.

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Long Term Infectious Disease Concerns - Vaccinations

- Pneumococcal conjugate (PCV)- may be given 3-6 mos
- Tetanus, Diphtheria, Acellular Pertussis- may be given 3-6 mos
- Inactivated influenza- yearly, may be given 4-6 mos
- Recombinant Hepatitis B- may give 6-12 mos
- Inactivated Polio- may give 6-12 mos
- MMR (live)- all children and seronegative adults, may be given 2 years. Not recommended for patients with active GVHD and patients on immune suppression.

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General Medical Care

- Pts with predisposing risk factors are at high risk for metabolic syndrome and CV disease- recommend heart-healthy lifestyle

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Prevalence of metabolic syndrome 49%; a 2.2 fold increase over controls.

Table 2 Prevalence of metabolic syndrome and its individual components among allogeneic HCT and NHANES controls

Component	*HCT recipients*		*NHANES controls*		*Odds ratio (95% CI)*
	N	*Prevalence, % (95% CI)*	N	*Prevalence, % (95% CI)*	
Total subjects	86		258		
Metabolic syndrome	42	49 (38–60)	78	30 (25–36)	2.2 (1.3–3.6)
Individual components of metabolic syndrome[a]					
Elevated triglycerides (≥ 150 mg per 100 ml or on drug treatment for elevated triglycerides)	50	58 (48–68)	90	35 (29–41)	2.6 (1.6–4.3)
Elevated blood pressure (≥ 130 mm Hg SBP or ≥ 85 mm Hg DBP or on drug treatment for hypertension)	48	56 (45–66)	101	39 (33–45)	2.0 (1.2–3.2)
Elevated waist circumference (≥ 102 cm in men or ≥ 88 cm in women)	38	44 (34–55)	96	37 (31–43)	1.3 (0.8–2.2)
Elevated fasting glucose (≥ 100 mg per 100 ml or on drug treatment for elevated glucose)	35	41 (31–51)	110	43 (37–49)	0.9 (0.6–1.5)
Reduced HDL-C (< 40 mg per 100 ml in men or < 50 mg per 100 ml in women or on drug treatment for reduced HDL-C)	35	41 (31–51)	125	48 (42–55)	0.7 (0.4–1.2)

Majhail, BMT 2009

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General Medical Care

- **Pulmonary** complications - chronic infections to small airway destruction d/t cGVHD
- Initial post-transplant f/u includes PFT, low threshold for chest imaging in pts with respiratory complaints
- Abstain from smoking
- **Liver**: cGVHD is a major complication of liver dysfunction. In pts surviving beyond 3 years, at least yearly LFTs
- **Kidney**: Routine screening for renal failure d/t calcineurin inhibitors
- **Skeletal** complications- high risk for osteoporosis- routine dexa scan, vit D-calcium. Routine use of bisphosphonates in pts with osteopenia
- **Eye**: Risk for cataracts, keratoconjunctivitis, sicca syndrome, retinopathy – annual eye exam
- **Oral**: Increased oral cancers and dental issues- annual oral and dental evaluations recommended
- **Endocrine**: Prevalence of hypothyroidism 20-40%- annual TFT

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Additional Medical Conditions

Chronic Pain

Emotional Distress

Financial Hardship

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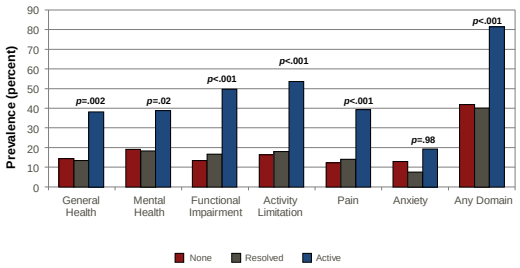
Prevalence of HCT Survivors with Adverse Health Outcomes by cGVHD Status



Fraser C J et al. Blood 2006;108:2867-2873

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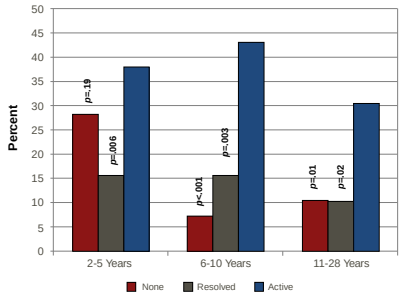
Percentage of Subjects with Poor or Fair General Health According to Time Since HCT and cGVHD Status



Fraser C J et al. Blood 2006;108:2867-2873

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Psychosocial and Psychological Issues

- Survivors likely to be burdened financially
- More likely to be unemployed than their peers
- Sexual dysfunction, infertility
- Shortage of transplant physicians to survivors
- Survivor clinics

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Clinics

- Levels of service
  - Transition to survivorship
  - Manage long and late effects of cancer and its treatment

Supportive Care

- Survivorship Lecture Series
  cancer.stanford.edu/survivorship
- Contact Kelly Bugos
  - kbugos@stanfordhealthcare.org

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Final message

- The care of HCT survivors requires a multidisciplinary approach that incorporates the expertise and resources of transplant centers, referring hematologists–oncologists, primary care physicians and other health care providers.
- Providers should integrate and involve their patients in this process, and ensure that they understand their risks and the surveillance required to prevent late complications.

BetheMatch.org

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Stanford BMT Reunion

Last Saturday of Each July

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