



ECHO Program



Supportive Care for Chronic GVHD

Moderator:

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Director of Utah Blood and Marrow Transplantation Program
Professor, University of Utah
Salt Lake City, UT

Presenter:

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Director of Long-Term Follow-Up
Fred Hutchinson Cancer Center
Professor of Pediatrics, University of Washington
Seattle, WA



ECHO Program



Welcome to the Sixth ECHO Program of the GVHD Interactive Provider Network

- The goal of the GVHD Interactive Provider Network ECHO is to connect GVHD specialists with community providers to share expertise, discuss cases, and improve patient care.
- The network is based on the ECHO Model™ (Extension for Community Healthcare Outcomes) which uses proven adult learning techniques and interactive video technology to connect community providers with specialists in collaborative sessions.
- The sessions, designed around case-based learning and mentorship, will help primary care and community-based practitioners gain the practical expertise required to care for GVHD patients. Questions and comments from the learners will be encouraged to facilitate discussion.



ECHO Program



Target Audience

This CE activity is intended for physicians of all specialties, nurse practitioners, physician assistants, and other healthcare professionals who treat patients with chronic GVHD.

Educational Objectives

After completing this CE activity, the participant should be better able to:

- Distinguish chronic GVHD supportive care from long-term follow-up care and the importance of integrating both
- Identify chronic GVHD supportive care options for infection, cardiovascular, metabolic, and bone complications
- Discuss how to provide supportive care for chronic GVHD thereby preventing complications and disabilities



ECHO Program



Program Agenda

- Welcome and Introductions – Daniel Couriel, MD, MS, MBA
- Didactic presentation with cases – Paul Carpenter, MB BS BSc and Daniel Couriel, MD MS, MBA
- Q & A and Discussion
- Closing Announcements

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Nursing Continuing Professional Development

Successful completion of this nursing continuing professional development activity will be awarded 1.0 contact hour and 1.0 contact hour in the area of pharmacology.

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IPCE CREDIT™

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Steve Pavletic, MD, MS, has no relevant financial relationships with ineligible companies to disclose for this educational activity.

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Daniel Couriel, MD, MS, MBA has a financial interest/relationship or affiliation in the form of:

Advisory Board/Consultant: Seagen

Speakers' Bureau: Seagen

The following relationships have ended within the last 24 months:

Advisory Board/Consultant: Incyte, Kite

Faculty Disclosures

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Advisory Board: AbbVie

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ECHO Program



*The GVHD Interactive Provider Network is administered by
the Aplastic Anemia and MDS International Foundation*



Partner Organizations of the GVHD Interactive Provider Network:





ECHO Program



For educational and quality improvement purposes,
we will be recording this video-session

By participating in this program you are consenting to be recorded –
we appreciate and value your participation

If you have questions or concerns, please email gvhdnetwork@aamds.org



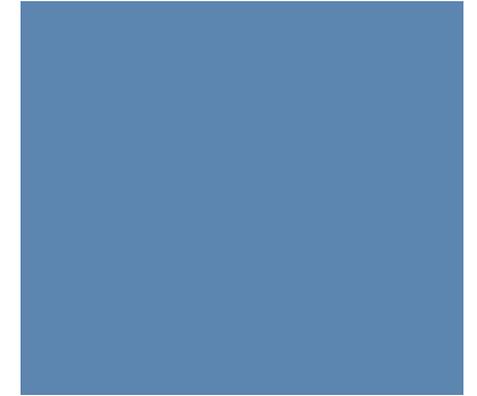
ECHO Program



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- Please mute your microphone when not speaking (left bottom corner of your screen)
- To ask a question or make a comment, raise your hand on camera or use the raised hand icon in the Reaction section at the bottom of your screen
- Speak clearly and state your name and institution or practice before stating your question or comment
- You may also use the chat function to submit comments or questions

Supportive Care for Chronic GVHD



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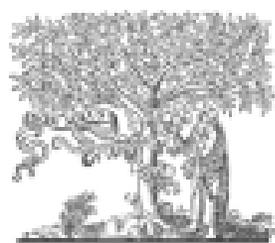
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GVHD
Interactive
PROVIDER
NETWORK

Part 1
Overview



ELSEVIER

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org



Report

National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: V. The 2014 Ancillary Therapy and Supportive Care Working Group Report



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What is Chronic GVHD Supportive Care?

- Defined and discussed by the NIH Consensus efforts of 2005 & 2014
- “Ancillary and supportive care” embraces the most frequent...
 - *Topical immunosuppressive or anti-inflammatory* interventions
 - Any *other interventions directed at organ-specific control of symptoms or complications resulting from GVHD and its therapy*
 - Also included in this definition are *educational, preventive*, and *psychosocial interventions with this same objective*
- Several important aspects of LTFU care such as monitoring and management of certain toxicities (hypertension, hyperlipidemia, renal dysfunction), iron overload, etc, are out of scope.

Ancillary and Supportive Care Interventions

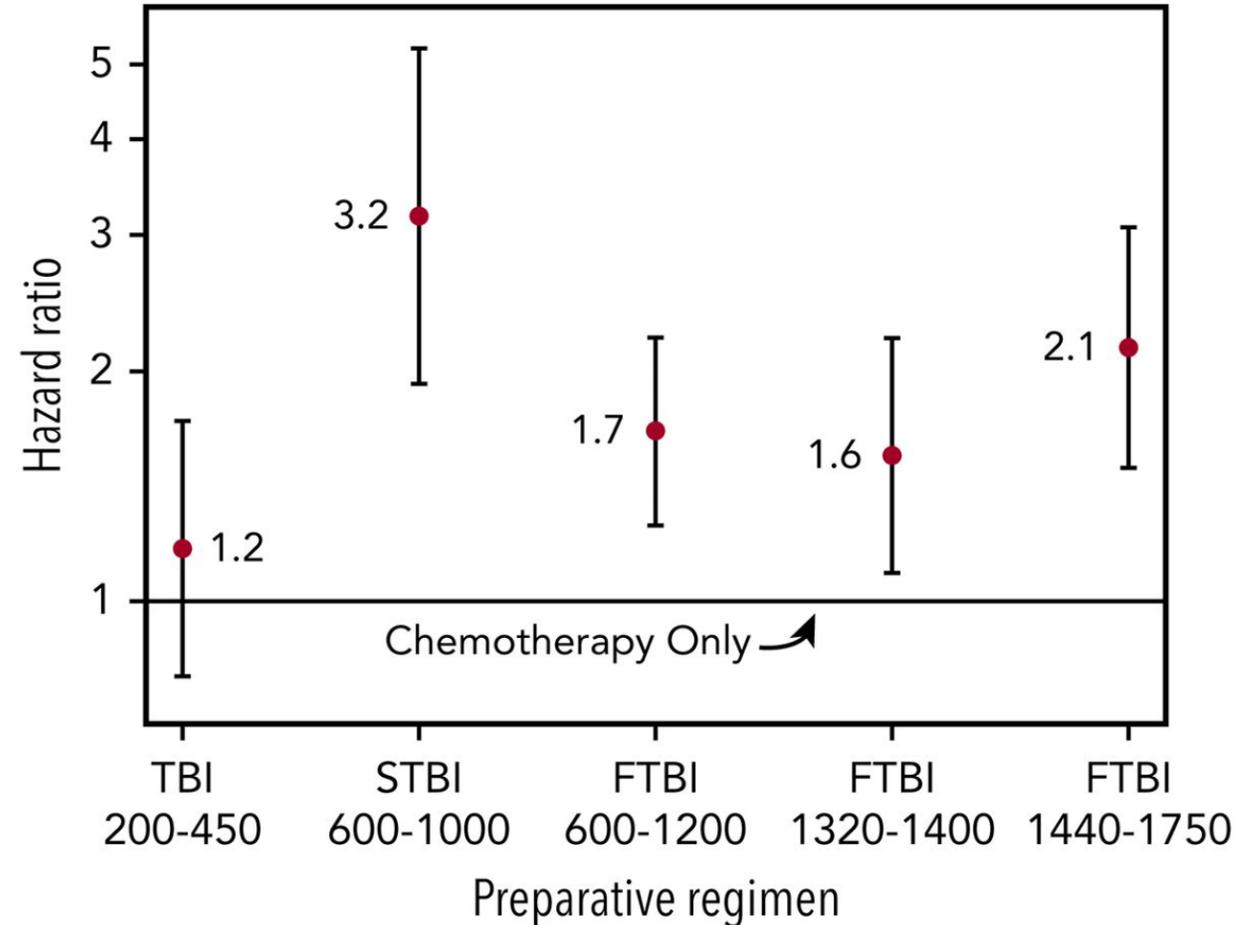
Organ system	Prevention	Treatment
Skin	Photoprotection, surveillance (M, I) M = malignancy, I = infection	Emollients, CNI creams, wound care, cultures, antibiotics, protective films, hyperbaric O2
Oro dental	Hygiene, surveillance (M, I)	Topical steroids, CNIs, analgesics, sialogogues
Eyes	Photoprotection, surveillance (I, cataracts, intraocular pressure)	PFAT or serum tears, topical steroids/CNI, punctal occlusion, sialogogues, doxycycline, scleral lenses
Vulva/Vagina	Surveillance (M, I, atrophy)	Lubricants, topicals (E2, steroids, CNI) dilators, surgery
GI / Liver	Surveillance (I), avoid toxins	Manage GERD or <u>iron overload</u> , ursodeoxycholic acid, topical steroids, esophageal dilatations
Lungs	Surveillance (I)	FAM+LABA, Supp O ₂ , Pulm. Rehab, ?lung transplant
Heme	Surveillance (I)	Growth factors, IVIG
Neuro	Surveillance (I, CNI levels, ± EMG)	OT/PT/PM&R; orthotics/walkers; SSRI/gabapentin
Immune/ID	Surveillance (I), Vaccinations, prophylaxis, ± IVIG	Organism-specific and sometimes empiric antibiotics
Musculoskeletal	Surveillance (PROM, DEXA, Vertebral #, Ca+VitD), PT?	PT/ PMR&R; bisphosphonates, walking program, resistance training, core strengthening

Subsequent Neoplasms

Baker KS et al, Blood 2019 (N=4905)

- Median f/up 12.5 yrs
- Standardized Incidence Ratios: bone > oral > skin > CNS > endo.
- Highest **Excess Absolute Risks**: breast > oral > skin cancers
- 22% CI of SNs at 30 y (= **SIR 2.8x**)
 - 8.1% CI age <20, 24% CI age >50
 - **Age <20 y** at HCT had **SIR ~5-15x** at >30y down to 1-10 y post-HCT
- **Life-time monitoring required**

Adjusted hazard ratios for risk of subsequent malignant neoplasms is dependent upon total body irradiation (TBI) dose (cGy) and fractionation (S=single, F=fractionated).

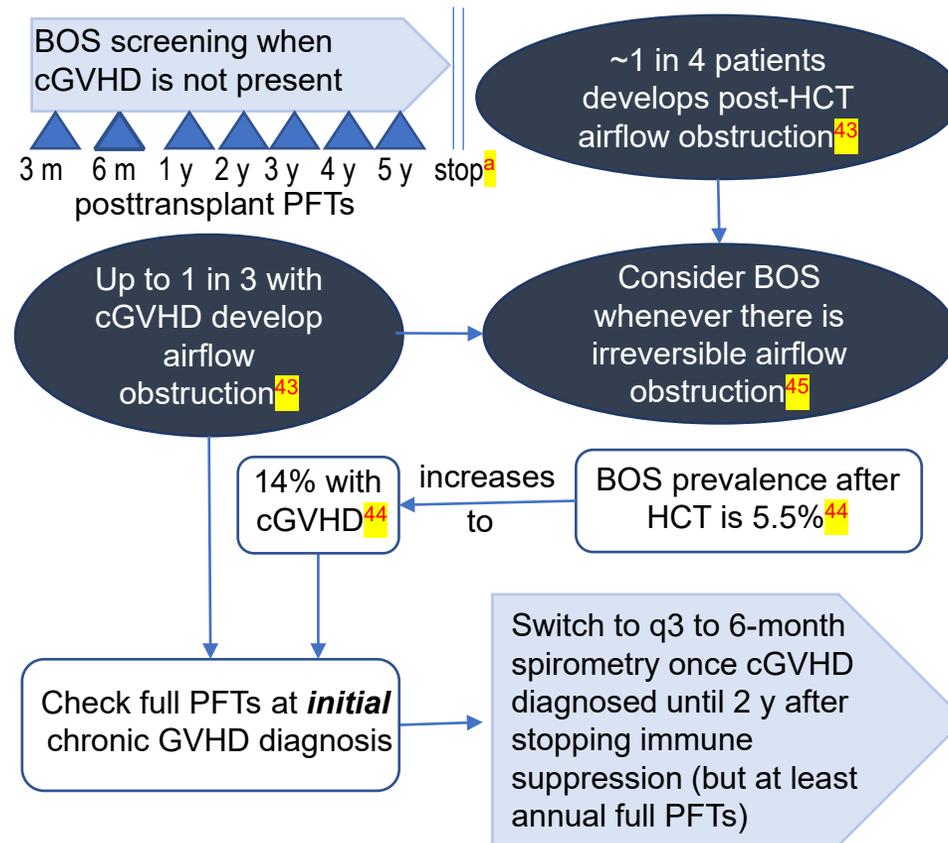


Iron overload

	AUTO-HCT	ALLO-HCT
5-y cumulative incidence	0.7%	25.4%
Prevalence rate liver iron content ≥ 1.8 mg/g	-	32%

- Avoid iron-containing MVI if ferritin not too high with low/normal %TS
 - ⇒ Add phlebotomies if ferritin high, especially if TS>50% (EPO shots might facilitate)
 - ⇒ Manage some Dx more aggressively (eg., hemoglobinopathies) from D180 (may need phlebotomies + iron chelator)
 - ⇒ Consider T2*MRI to follow liver iron content; stop phlebotomies when ferritin/TS% normal.

Approach to screening, diagnosis, and monitoring of bronchiolitis obliterans syndrome

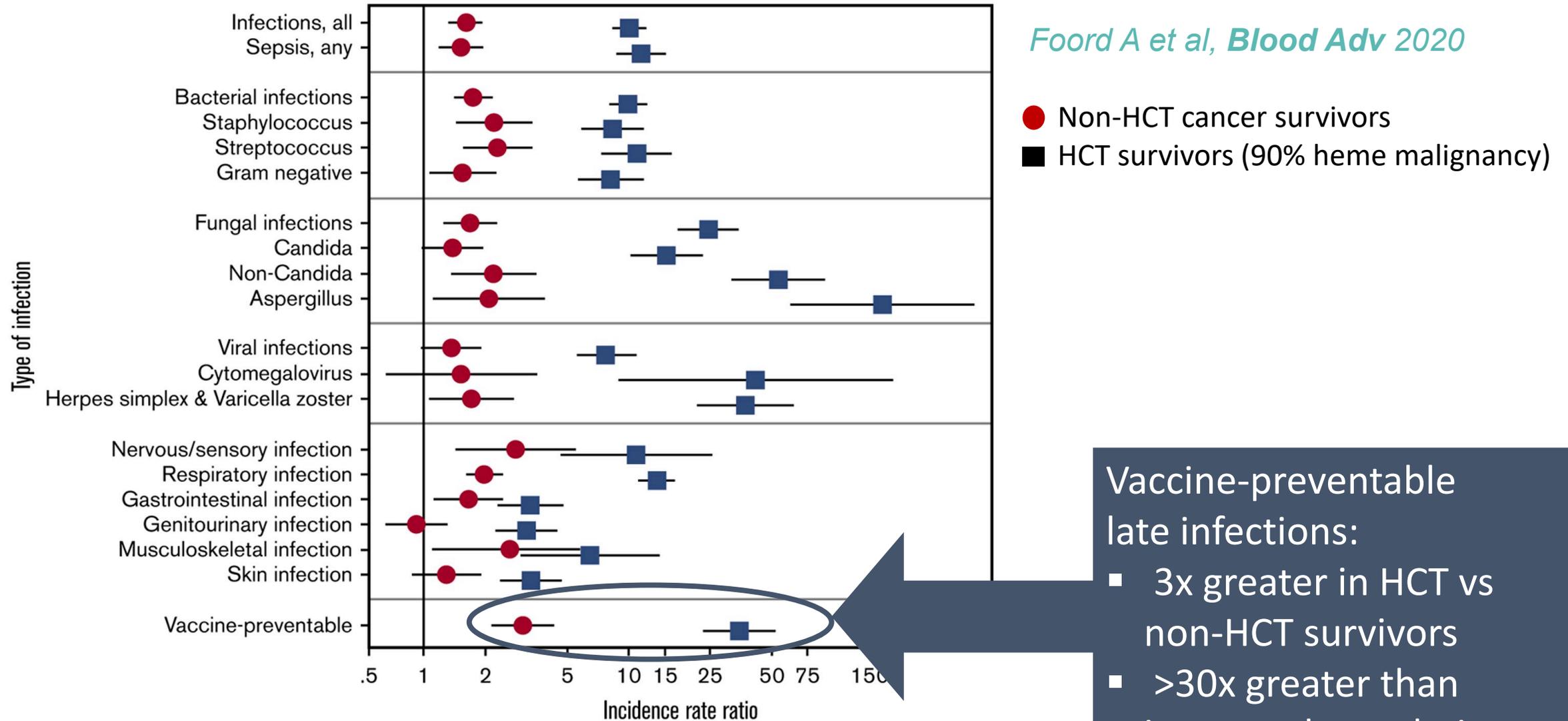


BOS Diagnosis requires 1-4:

1. FEV1/FVC <0.7 **or** FEV1/SVC <0.7
2. FEV1 <75% predicted **or** ≥10% decline over <2 y (albuterol does not correct)
3. Absence of infection
4. CGVHD in another organ **or**
 - Air-trapping by high-resolution CT = small airway thickening, or bronchiectasis
 - Air-trapping by PFT = residual volume >120% predicted

^aIn children PFTs continue annually until they reach final adult height or 5 years post-HCT, whichever later

HCT Survivors (≥ 2 y) have significant, persistent infectious burden vs other cancer survivors and general population



Vaccine-preventable late infections:

- 3x greater in HCT vs non-HCT survivors
- >30x greater than in general population

Infectious and Immunologic Supportive Care

- Functional asplenia in active cGVHD
- Numeric and functional immunity may be delayed

Preventive approaches:

- ***Shingles, PJP and encapsulated organism prophylaxis*** during and for several months after chronic GVHD therapy
- ***SARS-CoV-2 + routine post-HCT vaccinations*** per “national guidelines” or see *Carpenter and Englund Blood 2016 “How I treat”*
- ***Judicious IVIG*** per ASTCT “Choosing Wisely” unless profoundly low IgG (esp. with ↓↓ IgA)

http://www.choosingwisely.org/wp-content/uploads/2018/01/ASTCT-CTTC-Choosing-Wisely-List_2019.pdf

Recommended Vaccinations after Hematopoietic Cell Transplantation

Vaccine	Months from HCT to first vaccine	Total doses in primary series	Comments and qualifiers
Inactivated vaccines PCV13	3-6	3-4	Although single-dose PCV15 and PCV20 were FDA-approved in 2021 for age ≥ 18 y it is unknown if one dose of either will be sufficient post-HCT. Therefore, standard remains 3 doses of PCV13 plus a 4 th dose given if GVHD is active and immune reconstitution is delayed
PCV20 PPSV23	Not applicable	1	If vaccine titers suggest good response to primary series of PCV13, then give PPSV23 6-12 months (minimum 8 weeks) after last dose of PCV13
DTaP	6-12	3	FDA approved for age <7 y but off-label use at all ages preferred by HCT consensus guidelines (higher antigen content, greater immunogenicity than adult options of Tdap or Td)
Hib	6-12	3	
MCV4	6-12	2	For all age > 9 months
MenB (Group B)	6-12	2 or 3 depending on brand	ACIP advises for high-risk age ≥ 10 y in addition to MCV4. Also offered on an individual basis to any adolescent or young adult (ideally age 16-18 y). Consider off-label use for >25-year-olds with anatomic asplenia or cGVHD, or workplace risks
IPV (polio)	6-12	3	
HBV	6-12	3	Double dose (40 micrograms) advised in HCT.
HAV	6-12	2	Can be given separately or as combination (HAV + HBV) with dose 1 and dose 3 of HBV vaccination
HPV9	6-12	3	Recommended for all age 9-26 years. ACIP advises shared clinical decision-making for age 27-45 years.
IIV (flu)	4-6	1-2	Second dose 1 month after first dose for age <9 y if was first ever IIV. Also consider second dose for any age if dose 1 given <4 months post-HCT during influenza epidemic.
SARS-CoV-2	3	3	3-doses of mRNA vaccines preferred each 28 days apart with a bivalent dose (4 th dose) given at least 2 months after 3 rd dose of primary series.
Zoster (recombinant)	24	2	Although SHINGRIX has been given safely between 9-24 months after HCT, lack of efficacy data means vaccination does not mitigate the need to continue zoster prophylaxis while still on immunosuppressive therapy for cGVHD
Live vaccines MMR	24	2	Generally, should not be given <1y after stopping immunosuppression and >8 months after IVIG therapy. Recent local epidemics measles outbreaks due to falling herd immunity have led ASTCT to relax this rule to 12 months post-HCT if on no or low-dose immunosuppression.
MMRV	24	2	Varicella seronegative patients get MMRV but seropositive patients get MMR plus SHINGRIX if age ≥ 50 y (FDA approved for age ≥ 18 y if immune compromised but see SHINGRIX comment above)

Abbreviations: ACIP, Advisory Committee on Immunization Practices; FDA, Food and Drug Administration.

Screen joints with **P**hotographic **R**ange **O**f **M**otion Scale

Fasciitis/sclerosis

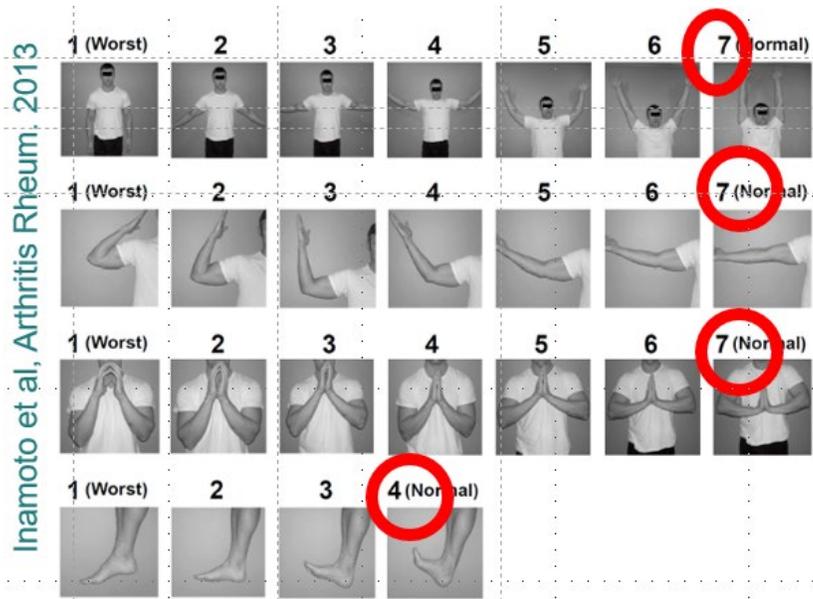
Usually chronic GVHD-related

Full range (score) = $7 + 7 + 7 + 4 = 25/25$

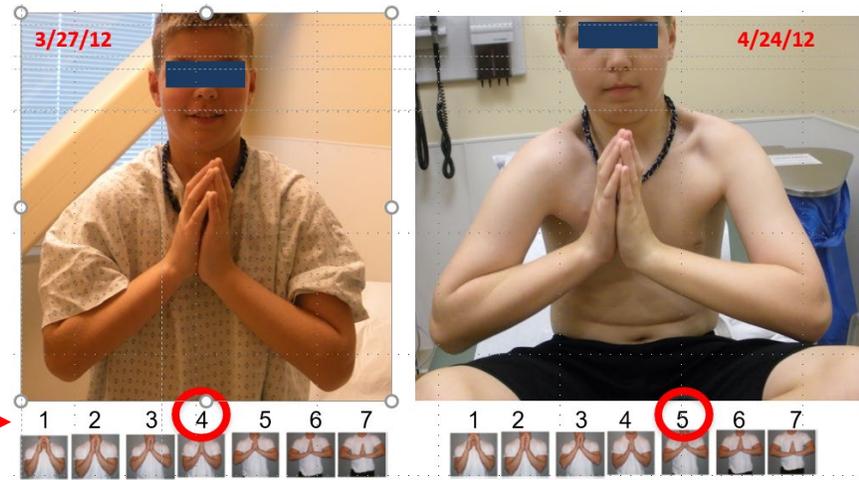
Refined NIH response algorithm for **GVHD in joints and fascia**

2-point total change clinically meaningful

Inamoto et al, Blood Advances 2020



versus
abnormal



Musculoskeletal Health

■ Low bone mineral density

Parameter	Age (yrs)	Std Deviation
Z-score	< 20	>2 below mean

- ❖ Allo-HCT > auto-HCT recipients
- ❖ CGVHD (glucocorticoid use)
- ❖ Low body weight / low BMI
- ❖ Inadequate calcium / vitamin D
- ❖ Physical inactivity
- ❖ Hypogonadism / delayed puberty

Approach: - Vit D, estradiol, testosterone level
- Optimize Ca/D intake
- DEXA scan at least at 1 year
- gonadal hormones vs
bisphosphonates vs newer agents

■ Avascular necrosis

- ❖ Less common than ↓BMD
- ❖ Glucocorticoid-related
- ❖ Increased in sickle cell disease

Approach: - Symptom screen
- Plain x-rays vs MRI
- Referral to Orthopedics
- ?bisphosphonates or newer agents for pre-collapse AVN

*Bar M et al, BBMT 2020
ASCTC Expert Panel Opinion*

Sequential “head-to-toe” LTFU

ORGAN-based	SYSTEMS-based	PROBLEM-based
1. Ocular ●●	10. Graft + chimerism ●	15. Chronic GVHD ●
2. Ear ●	11. Immunity ●	16. Infection ●
3. Oral ●	12. Endocrine + metabolic ●●	17. Infertility ●●
4. Lung ●	13. Neurocognitive ●	18. Iron Overload ●●
5. Cardiac ●	14. Psychological ●	19. Quality of life ●●
6. GI / hepatic		20. Subsequent Neoplasms ●●
7. Musculoskeletal ●	DISEASE-based overlay	
8. Renal / GU ●	<i>Always view 1-20 through the lens of underlying disease indication for HCT</i>	
9. Skin ●		

Example: LTFU individualized After HCT for Fanconi anemia

1. Graft/chimerism
2. Chronic GVHD
3. Infection
4. Immunity
5. Lung
6. Musculoskeletal
7. Subsequent Neoplasms
 - skin, anal
 - breast
 - oral, ENT
 - genitourinary
8. Congenital issues
 - cardiac, eye, ear, genitourinary, renal
9. Thyroid, infertility
10. Neuropsychological, quality-of-life

- Most relevant core elements of LTFU after allogeneic HCT
- Other late effects essentials for underlying diagnosis of Fanconi Anemia

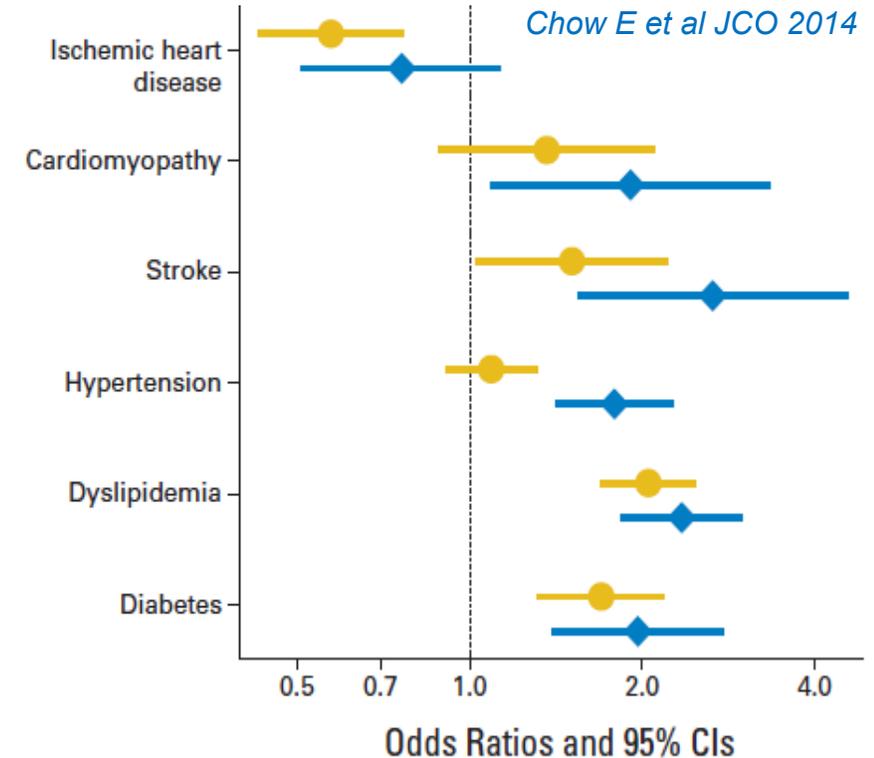
Cardiovascular Disease and Metabolic Syndrome

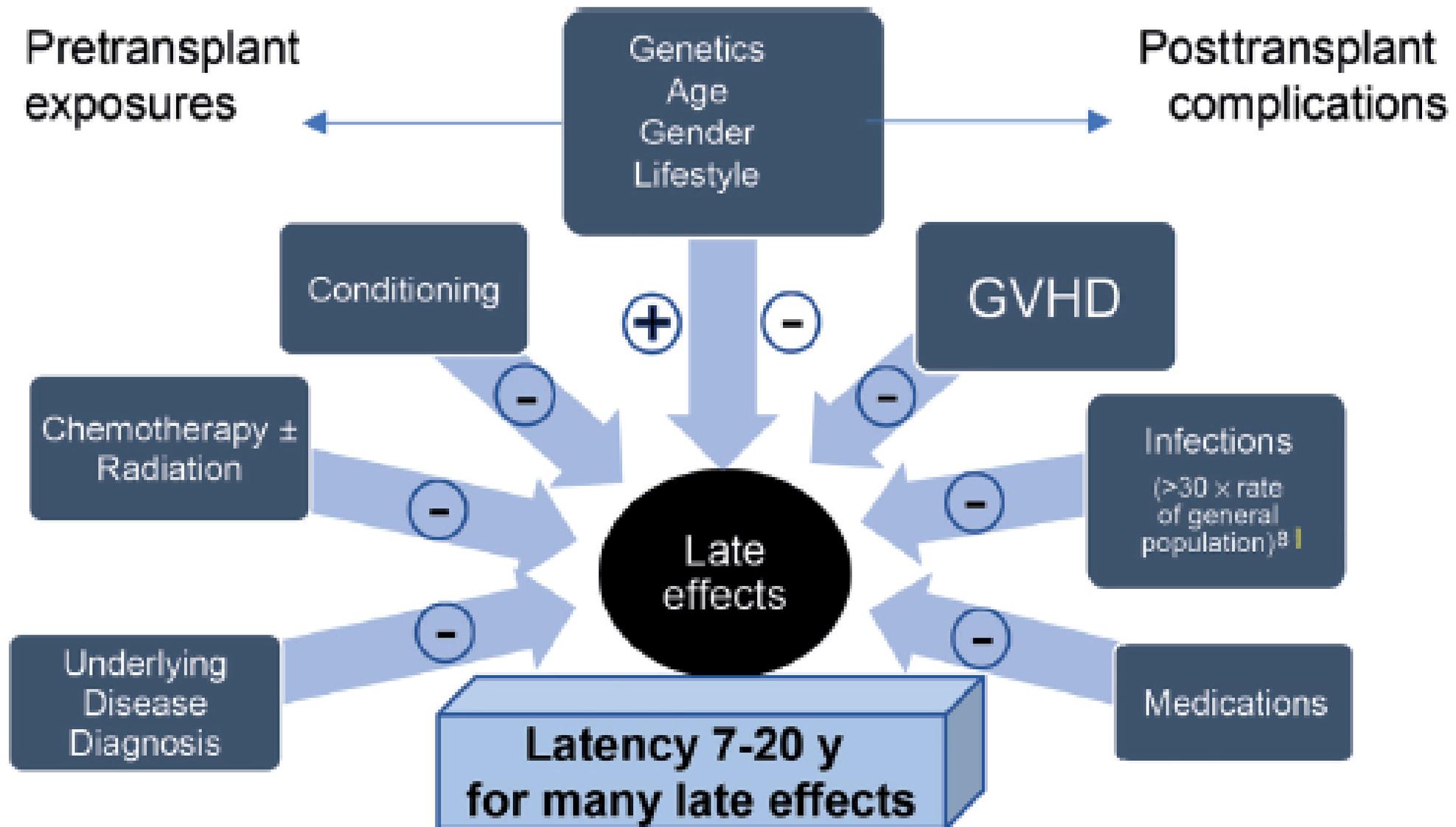
Cardiovascular disease	10-y CI
Deaths due to CVD: 10-y CI, 30-y CI	3.7% ^A , 4.1%
Congestive cardiac failure: 10-y CI, 15-y CI	6.6%, 9.1% ^B
Coronary artery disease: 10-y CI	3.8% ^A
Stroke: 10-y CI	3.5%
Metabolic syndrome: 1-y prevalence	37.5% ^A
Hypertension: 1-y period prevalence, 10-y CI	61%, 38%
Fasting hyperglycemia: 1-y period prevalence	47%
Dyslipidemia: 1-y period prevalence, 10-y CI	51%, 47%
Elevated waist circumference, 1-y period prevalence	67%

^A Auto-HCT similar as allo-HCT

^B Increases in higher-risk groups (age, anthracycline dose, chest radiation, hypertension, diabetes, smoking)

Bhatia et al, Blood 2007; Armenian et al, Blood 2011; Chow et al, BBMT 2014; Greenfield et al, BMT 2021; Armenian et al, Blood 2012







GVHD
Interactive
**PROVIDER
NETWORK**

**Part 2
Cases**

Case 1 – 29M - MUD PBSCT for T-cell ALL

- 8m: Late AGVHD GI/Skin – began budesonide + TACRO increased (on VORI for fungal pneumonia)
- 19m: CGVHD mouth + late AGVHD liver after stopping TACRO. Starts DEX rinses and oral beclomethasone.
- 21m: Cushingoid. PROM 22/25 (shoulders 5-6/7). Starts PRED 20 mg/day
- 22m: ↑LFTs, joint pain improved. PRED ↑ 40 mg. Restarts TACRO. Starts Ursodiol.
- 23m: FEV1 49%, FEV1/FVC 0.61, RV 114%. ?New bilateral shoulder sclerosis, stable oral and resolved liver GVHD. Starts FAM+LABA for new BOS Dx. Still on voriconazole.
- 28m: sees me for LTFU/ GVHD consultation:
 - Chief complaint: tight shoulders + left hip pain
 - Outside PT diagnoses possible frozen shoulder
 - Cushingoid, buffalo hump, striae, ruddy face, acne. PROM 22/25; no groove signs or dimpling or dyspigmentation. No sclerosis detected anywhere. FEV1 47%, FEV1/FVC 0.60, RV 111%. Normal LFTs
 - GVHD mostly stable on PRED 30 mg per day, budesonide 3 mg per day, TACRO.
 - What did I advise?

Table 12**Ancillary Therapy and Supportive Care Recommendations for Fasciitis, Contractures, Steroid Myopathy, and Avascular Necrosis**

Type of Intervention	Rating
Fasciitis/Contractures	
Refer to PT for quantitative ROM measurements, to provide the patient with stretching exercises and to monitor progress.	AIII
Evaluation of ROM at each clinic visit.	AIII
Daily stretching exercises at home	AIII
PT stretching 2-3 times a wk (severe impairment)	AIII
Surgical release	DIII
Steroid myopathy and deconditioning	
Strengthening: isometric, isotonic, isokinetic exercise	AII
Decreased stamina: aerobic exercise should be progressive with increase in duration and resistance to achieve elevated heart rate	AIII
Avascular necrosis	
Nonoperative management in more advanced cases (bracing, crutches, intra-articular steroids, oral medications)	DIIb
Surgical management, including joint replacement	BIIB

PEDIATRIC CONSIDERATIONS

In children, a major goal is to avoid early replacement with artificial joints that have a finite lifespan. Therefore, therapy for moderate to severe AVN in children involves appropriate chronic analgesia and a variety of temporizing surgical interventions including core decompression, partial or total hip resurfacing at centers specializing in these approaches.

Case 2 – 66M - MUD HCT for MDS

- H/o hypertension
- D0 to D100: moderate tremors, mild renal dysfunction on TAC; no longer on his prior two antihypertensive meds
- D270: dry mouth, dysgeusia, sensitive to spice. Started PRED 1 mg/kg + SIRO – good response
- Tapered off PRED 2 mo later, continued SIRO (7-10 ng/mL); no other lab monitoring
- Presents to ED, 14 mo post-HCT:
 - Severe headaches
 - Acute chest pain radiating to LUE
 - BP 190/115
 - EKG/troponin suggest MI
 - Triglycerides 800 mg/dL, TC 320, LDL 200

Cardiac Effects

BMT survivors have 1.4 - 3.5 X higher risk of heart disease compared to general population

Complications: Coronary Artery Disease, Cardiomyopathy

Risk Factors: Chemotherapy (Anthracyclines), chest radiation, total body irradiation, GVHD, steroids, high blood pressure, dyslipidemia, diabetes, obesity, alcohol, smoking, inactive lifestyle

Interventions: Optimize blood pressure, cholesterol, and diabetes; weight control/diet; exercise; smoking & alcohol cessation; health & wellness coach; support groups

Screening tests: EKG, Echocardiogram, cardiac stress test?

Case 3 – 41F - MRD PBSCT for Ph-ALL

- Acute grade 2 skin GVHD
- 9 m post-HCT off immune suppression (IS)
- 11 m: worsening dry eyes, very mild oral dryness. Started herself on PFAT 20-30 x per day.
 - Ophthalmology Dx'd eye GVHD
 - Prescribed CSP eye drops and plugged her lacrimal ducts
- 14 m Ophtho follow-up:
 - Eyes worse
 - Starts prednisolone eye drops
- 16 m Ophtho follow-up:
 - Severe bilateral ocular pain affecting vision; dryness and redness.
 - Dx: punctate keratopathy and cicatricial conjunctivitis

Table 5
Ancillary Therapy and Supportive Care Recommendations for Eye GVHD

Therapy	Indication	Rating
Topical	Mild*	
	AT, preservative free	A1b
	Viscous ointment at bedtime/viscous tears during the day	B1b
	Moderate/severe*	
	Cyclosporine eye drops	C1b
	Topical steroid drops	B1IIa
Oral	Lacriserts (Valeant Pharmaceuticals) for patients that use AT more frequently than hourly	C1b
	Autologous serum eye drops (limited availability)	C1b/CIIa
	Moderate/severe*	
	Cevimeline	C1b
	Pilocarpine	C1b
Surgical	Moderate/severe*	
	Punctal occlusion (temporary or permanent occlusion, using silicone plugs or thermal cautery)	B1b/IIa
	Superficial debridement of filamentary keratitis	CIII
	Partial tarsorrhaphy	CIIb
Eye wear/environmental strategy	Moderate/severe*	
	Occlusive eye wear (www.dryeyepain.com ; www.panoptx.com)	BIII
	Lid care/warm compress/humidified environment	CIII
	Bandage contact lens (used with caution)	CIII
	Gas-permeable scleral lens	CIIa

PEDIATRIC CONSIDERATIONS

Although severe ocular sicca is uncommon in children with chronic GVHD, measured tear production is reduced, and surveillance for keratoconjunctivitis sicca is necessary.

Ocular sicca generally responds to ancillary measures in conjunction with systemic immunosuppression.

Experience is limited and dosing is not established for many of the topical and oral medications for ocular GVHD.

AT indicates artificial tears.

* Definitions of severity follow the Diagnosis and Scoring report [47].

EYES

The clinical spectrum of chronic ocular GVHD includes acute conjunctival inflammation, pseudomembranous and cicatricial conjunctivitis, and, most frequently, keratoconjunctivitis sicca (or KCS). KCS often accompanies chronic GVHD activity in other organs and may be a prominent disease manifestation. Conversely, dry eyes may occasionally be the only manifestation of chronic GVHD [31]. The diagnosis of KCS is made by the presence of appropriate symptoms, tear production averaging ≤ 5 mm (Schirmer's test), and clinical signs of keratitis. Although ocular symptoms and external examination can be ascertained from a clinic visit, a slit lamp examination by an ophthalmologist is generally required to make the diagnosis of KCS. In all cases, infectious keratitis must be ruled out. Most ancillary treatment for ocular chronic GVHD is aimed at relief of dry eyes (Table 5). When the sole manifestations of chronic GVHD are ocular, systemic immunosuppressive therapy may need to be initiated (or resumed) when topical and other local measures are insufficient to control inflammation and symptoms.

Case 4 – 49M - MUD BMT for AML

- H/o long-standing oral CGVHD
- Oral symptoms stable on low dose PRED + dexamethasone oral rinses as needed, but unable to taper PRED below 5 mg every-other-day
- Today, 3 weeks after his 2nd dose SARS-CoV-2 mRNA vaccine he presents with worse oral symptoms:
 - Marked buccal oral erythema
 - Bilateral oral ulcers
 - Lichenoid changes >50% (vs <25% last month)

SARS-CoV-2 Vaccination and CGVHD flares?

- Literature raises some concerns:
 - Reporting bias of small case series
 - Two retrospective reports:

Ali et al, TCT 2021 (N = 113)	Pabst et al, Vaccine 2022 (N = 167)
40% CGVHD when vaccinated	41 (25%) CGVHD when vaccinated
4 (3.5%) worsened	10/167 (6%) worse ^B CGVHD within 80 days
11 (9.7%) new or worse within 60 days	9 ^A /41 (22%)

^Aneeding increased IS or restarting IS

^B9 of 10 on IS for smoldering CGVHD, or tapering IS for controlled CGVHD

- What to do with these data?
 - Counsel patients but mostly proceed without mods.
 - ?Avoid tapering IS around time of vaccination
 - Prioritize risk: benefit and need to begin primary series
 - As pandemic potentially wanes risk:benefit may change
 - Need larger more detailed studies including IS details



Moderator Wrap-up



Announcements

All Previous GVHD Interactive Provider Network ECHO Programs Are Available On-Demand

- Treatment Decisions in Chronic GVHD – July 2022
- Mucocutaneous GVHD – August 2022
- Sclerotic GVHD – September 2022
- Bronchiolitis Obliterans – October 2022
- Challenges of Atypical Manifestations of Chronic GVHD – November 2022

Visit www.gvhdnetwork.org to access all on-demand programs



Announcements

ON-DEMAND WEBINAR

AFTER THE RESULTS:
Quality of Life Pre- and Post-Transplant:
The Role of Transplant for Treating MDS in Older Patients

[ACCESS NOW](#)





Announcements



Meredith A. Cowden Foundation GvHD 2022-23 National Symposium Series

Friday, January 27 – 10:00 am to 12:00 pm EST

“How to Choose Drugs for cGvHD” – Dr. Joseph Pidala, MD, PhD, Moffitt Cancer Center

Spring 2023 – Patient Advocacy

For more information, contact lynhaselton@cowdenfoundation.org

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