

7-23-2021

Standardizing Definitions of Hematopoietic Recovery, Graft Rejection, Graft Failure, Poor Graft Function, and Donor Chimerism in Allogeneic Hematopoietic Cell Transplantation: A Report on Behalf of the American Society for Transplantation and Cellular Therapy.

Mohamed A. Kharfan-Dabaja

Ambuj Kumar

Ernesto Ayala

Mahmoud Aljurf

Taiga Nishihori

See next page for additional authors

Follow this and additional works at: <https://jdc.jefferson.edu/medoncfp>



Part of the [Oncology Commons](#)

[Let us know how access to this document benefits you](#)

This Article is brought to you for free and open access by the Jefferson Digital Commons. The Jefferson Digital Commons is a service of Thomas Jefferson University's [Center for Teaching and Learning \(CTL\)](#). The Commons is a showcase for Jefferson books and journals, peer-reviewed scholarly publications, unique historical collections from the University archives, and teaching tools. The Jefferson Digital Commons allows researchers and interested readers anywhere in the world to learn about and keep up to date with Jefferson scholarship. This article has been accepted for inclusion in Department of Medical Oncology Faculty Papers by an authorized administrator of the Jefferson Digital Commons. For more information, please contact: JeffersonDigitalCommons@jefferson.edu.

Authors

Mohamed A. Kharfan-Dabaja, Ambuj Kumar, Ernesto Ayala, Mahmoud Aljurf, Taiga Nishihori, Rebecca Marsh, Lauri M. Burroughs, Navneet Majhail, A. Samer Al-Homsi, Zaid S. Al-Kadhimi, Merav Bar, Alice Bertaina, Jaap J. Boelens, Richard Champlin, Sonali Chaudhury, Zachariah DeFilipp, Bhagirathbhai Dholaria, Areej El-Jawahri, Suzanne Fanning, Ellen Frint, Usama Gergis, Sergio Giral, Betty K. Hamilton, Shahrukh K. Hashmi, Biljana Horn, Yoshihiro Inamoto, David A. Jacobsohn, Tania Jain, Laura Johnston, Abraham S. Kanate, Ankit Kansagra, Adetola Kassim, Leslie S. Kean, Carrie L. Kitko, Jessica Knight-Perry, Joanne Kurtzberg, Hien Liu, Margaret L. MacMillan, Zahra Mahmoudjafari, Marco Mielcarek, Mohamad Mohty, Arnon Nagler, Eneida Nemecek, Timothy S. Olson, Betul Oran, Miguel-Angel Perales, Susan E. Prockop, Michael A. Pulsipher, Iskra Pusic, Marcie L. Riches, Cesar Rodriguez, Rizwan Romee, Gabriela Rondon, Ayman Saad, Nina Shah, Peter J. Shaw, Shalini Shenoy, Jorge Sierra, Julie Talano, Michael R. Verneris, Paul Veys, John E. Wagner, Bipin N. Savani, Mehdi Hamadani, and Paul A. Carpenter



Guideline

Standardizing Definitions of Hematopoietic Recovery, Graft Rejection, Graft Failure, Poor Graft Function, and Donor Chimerism in Allogeneic Hematopoietic Cell Transplantation: A Report on Behalf of the American Society for Transplantation and Cellular Therapy



Mohamed A. Kharfan-Dabaja^{1,*}, Ambuj Kumar², Ernesto Ayala¹, Mahmoud Aljurf³, Taiga Nishihori⁴, Rebecca Marsh⁵, Lauri M. Burroughs⁶, Navneet Majhail⁷, A. Samer Al-Homsi⁸, Zaid S. Al-Kadhimi⁹, Merav Bar⁶, Alice Bertaina¹⁰, Jaap J. Boelens¹¹, Richard Champlin¹², Sonali Chaudhury¹³, Zachariah DeFilipp¹⁴, Bhagirathbhai Dholaria¹⁵, Areej El-Jawahri¹⁴, Suzanne Fanning¹⁶, Ellen Fraint¹¹, Usama Gergis¹⁷, Sergio Giral¹⁸, Betty K. Hamilton⁷, Shahrukh K. Hashmi^{19,20}, Biljana Horn²¹, Yoshihiro Inamoto²², David A Jacobsohn²³, Tania Jain²⁴, Laura Johnston²⁵, Abraham S. Kanate²⁶, Ankit Kansagra²⁷, Adetola Kassim¹⁵, Leslie S. Kean²⁸, Carrie L. Kitko²⁹, Jessica Knight-Perry³⁰, Joanne Kurtzberg³¹, Hien Liu⁴, Margaret L. MacMillan³², Zahra Mahmoudjafari³³, Marco Mielcarek⁶, Mohamad Mohty³⁴, Arnon Nagler³⁵, Eneida Nemecek³⁶, Timothy S. Olson³⁷, Betul Oran¹², Miguel-Angel Perales¹⁸, Susan E. Prockop¹¹, Michael A. Pulsipher³⁸, Iskra Pusic³⁹, Marcie L. Riches⁴⁰, Cesar Rodriguez⁴¹, Rizwan Romee⁴², Gabriela Rondon¹², Ayman Saad⁴³, Nina Shah⁴⁴, Peter J. Shaw⁴⁵, Shalini Shenoy⁴⁶, Jorge Sierra⁴⁷, Julie Talano⁴⁸, Michael R. Verneris³⁰, Paul Veys⁴⁹, John E. Wagner³², Bipin N. Savani¹⁵, Mehdi Hamadani⁵⁰, Paul A. Carpenter⁶

¹ Division of Hematology-Oncology and Blood and Marrow Transplantation and Cellular Therapies Program, Mayo Clinic, Jacksonville, Florida

² Program for Comparative Effectiveness Research, Morsani College of Medicine, University of South Florida, Tampa, Florida

³ Department of Adult Hematology and Stem Cell Transplantation, King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia

⁴ Department of Blood and Marrow Transplantation and Cellular Immunotherapy, Moffitt Cancer Center, Tampa, Florida

⁵ Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio

⁶ Fred Hutchinson Cancer Research Center, Seattle, Washington

⁷ Blood and Marrow Transplant Program, Taussig Cancer Institute, Cleveland Clinic, Cleveland, Ohio

⁸ NYU Langone Health, New York, New York

⁹ Division of Oncology and Hematology, Department of Internal Medicine, University of Nebraska Medical Center, Omaha, Nebraska

¹⁰ Division of Stem Cell Transplant and Regenerative Medicine, Department of Pediatrics, Stanford University, Stanford, California

¹¹ Stem Cell Transplantation and Cellular Therapies Program, Department Pediatrics, Memorial Sloan Kettering Cancer Center, New York, New York

¹² Department of Stem Cell Transplantation and Cellular Therapy, The University of Texas MD Anderson Cancer Center, Houston, Texas

¹³ Ann and Robert H. Lurie Children's Hospital of Chicago, Chicago, Illinois

¹⁴ Department of Hematology-Oncology and Hematopoietic Cell Transplant and Cellular Therapy Program, Massachusetts General Hospital, Boston, Massachusetts

¹⁵ Department of Hematology-Oncology, Vanderbilt University Medical Center, Nashville, Tennessee

¹⁶ Blood and Marrow Transplant Program, University of South Carolina School of Medicine, Greenville, South Carolina

¹⁷ Bone Marrow Transplant and Immune Cellular Therapy, Thomas Jefferson University Hospital, Philadelphia, Pennsylvania

¹⁸ Department of Medicine, Division of Hematologic Malignancies, Memorial Sloan Kettering Cancer Center Weill Cornell Medical College, New York, New York

¹⁹ Division of Hematology, Department of Internal Medicine, Mayo Clinic, Rochester, Minnesota

²⁰ Department of Medicine, Sheikh Shakhboub Medical City, Abu Dhabi, United Arab Emirates

²¹ Department of Pediatrics, Division of Hematology/Oncology, University of Florida, UF Health Shands Children's Hospital, Gainesville, Florida

²² Department of Hematopoietic Stem Cell Transplantation, National Cancer Center Hospital, Tokyo, Japan

²³ Division of Blood and Marrow Transplantation Center for Cancer and Blood Disorders, Children's National Medical Center, Washington, DC

²⁴ Hematologic Malignancies and Bone Marrow Transplantation Program, Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University School of Medicine, Baltimore, Maryland

²⁵ Division of Blood and Marrow Transplantation, Department of Medicine, Stanford University School of Medicine, Stanford, California

²⁶ West Virginia University, Morgantown, West Virginia

²⁷ UT Southwestern Medical Center, Dallas, Texas

Financial disclosure: See Acknowledgments on page 648.

*Correspondence and reprint requests: Mohamed A. Kharfan-Dabaja, MD, MBA, FACP, Mayo Clinic Florida, 4500 San Pablo Road, Jacksonville, FL 32224.

E-mail address: KharfanDabaja.Mohamed@mayo.edu (M.A. Kharfan-Dabaja).

<https://doi.org/10.1016/j.tct.2021.04.007>

2666-6367/© 2021 The American Society for Transplantation and Cellular Therapy. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>)

²⁸ Boston Children's Hospital, Dana-Farber Cancer Institute, Boston, Massachusetts

²⁹ Division of Pediatric Hematology/Oncology, Department of Pediatrics, Vanderbilt University Medical Center, Nashville, Tennessee

³⁰ Department of Pediatrics, Division of Hematology/Oncology/BMT, University of Colorado School of Medicine, Aurora, Colorado

³¹ Pediatric Blood and Marrow Transplant Program, Duke University School of Medicine, Durham, North Carolina

³² Blood and Marrow Transplant Program, Masonic Cancer Center, University of Minnesota Medical School, Minneapolis, Minnesota

³³ Division of Pharmacy, University of Kansas Cancer Center, University of Kansas Health System, Lawrence, Kansas

³⁴ Sorbonne Université, INSERM, Centre de Recherche Saint-Antoine and Hôpital Saint-Antoine, Service d'Hématologie Clinique et Thérapie Cellulaire, Paris, France

³⁵ Chaim Sheba Medical Center, Tel Hashomer, Israel

³⁶ Knight Cancer Institute, Oregon Health & Science University, Portland, Oregon

³⁷ Blood and Marrow Transplant Section, Division of Oncology, Department of Pediatrics, Children's Hospital of Philadelphia, Pennsylvania

³⁸ Children's Hospital Los Angeles Cancer and Blood Disease Institute, USC Keck School of Medicine, Los Angeles, California

³⁹ Division of Oncology, Department of Medicine, Washington University School of Medicine, St Louis, Missouri

⁴⁰ Division of Hematology, University of North Carolina at Chapel Hill, North Carolina

⁴¹ Department of Hematology and Oncology, Wake Forest University School of Medicine, Winston-Salem, North Carolina

⁴² Cellular Therapy and Stem Cell Transplant Program, Dana Farber Cancer Institute, Harvard Medical School, Boston, Massachusetts

⁴³ Division of Hematology, The Ohio State University, Columbus, Ohio

⁴⁴ Division of Hematology-Oncology, Department of Medicine, University of California San Francisco, San Francisco, California

⁴⁵ The Children's Hospital at Westmead, Sydney, Australia

⁴⁶ Department of Pediatrics, Washington University School of Medicine, St. Louis, Missouri

⁴⁷ Department of Hematology, Hospital de la Santa Creu i Sant Pau, Josep Carreras Leukemia Research Institute, Barcelona, Spain

⁴⁸ Department of Pediatric Hematology/Oncology, Children's Hospital of Wisconsin, Medical College of Wisconsin, Milwaukee, Wisconsin

⁴⁹ Blood & Marrow Transplant Unit, Great Ormond Street Hospital, University College London, London, United Kingdom

⁵⁰ Division of Hematology and Oncology, Department of Medicine, Medical College of Wisconsin, Milwaukee, Wisconsin

Article history:

Received 11 April 2021

Accepted 11 April 2021

Key Words:

Allogeneic hematopoietic cell

transplantation

Hematopoietic recovery

Graft rejection

Graft failure

Donor chimerism

A B S T R A C T

Allogeneic hematopoietic cell transplantation (allo-HCT) is potentially curative for certain hematologic malignancies and nonmalignant diseases. The field of allo-HCT has witnessed significant advances, including broadening indications for transplantation, availability of alternative donor sources, less toxic preparative regimens, new cell manipulation techniques, and novel GVHD prevention methods, all of which have expanded the applicability of the procedure. These advances have led to clinical practice conundrums when applying traditional definitions of hematopoietic recovery, graft rejection, graft failure, poor graft function, and donor chimerism, because these may vary based on donor type, cell source, cell dose, primary disease, graft-versus-host disease (GVHD) prophylaxis, and conditioning intensity, among other variables. To address these contemporary challenges, we surveyed a panel of allo-HCT experts in an attempt to standardize these definitions. We analyzed survey responses from adult and pediatric transplantation physicians separately. Consensus was achieved for definitions of neutrophil and platelet recovery, graft rejection, graft failure, poor graft function, and donor chimerism, but not for delayed engraftment. Here we highlight the complexities associated with the management of mixed donor chimerism in malignant and nonmalignant hematologic diseases, which remains an area for future research. We recognize that there are multiple other specific, and at times complex, clinical scenarios for which clinical management must be individualized.

© 2021 The American Society for Transplantation and Cellular Therapy. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>)

INTRODUCTION

Allogeneic hematopoietic cell transplantation (allo-HCT) is potentially curative for certain hematologic malignancies and nonmalignant diseases [1,2] and is now more broadly applicable owing to improved outcomes using not just HLA-matched sibling or unrelated donors, but also umbilical cord blood and haploidentical related donors. Increased options of reduced-intensity (RIC) or nonmyeloablative (NMA) conditioning can mitigate transplantation-related mortality in high-risk allo-HCT and further expand feasibility [3–7]. More than 95% of patients needing an allo-HCT now have access to a suitable donor. These advances have led to clinical practice conundrums when applying traditional definitions of hematopoietic recovery, graft rejection, and graft failure, because hematopoietic recovery and engraftment kinetics may vary based on donor type, cell source, cell manipulation and dose, primary disease, graft-versus-host disease (GVHD) prophylaxis, and conditioning intensity, among other factors [8–12]. In daily clinical practice definitions have been used interchangeably, albeit inconsistently or incorrectly. For instance, recovery of neutrophils, operationally defined as achievement of an absolute neutrophil count (ANC) of ≥ 500 cells/ μL , is at times also used to define hematopoietic engraftment. The latter implies that donor neutrophils have reached 500 cells/ μL , which might

not be true in the case of primary graft failure with autologous neutrophil recovery. Moreover, in NMA conditioning, especially for nonmalignant diseases, engraftment definitions based only on neutrophil recovery but agnostic of chimerism are insufficient to address late graft failure, because neutrophil recovery might occur with complete loss of donor chimerism.

Contemporary allo-HCT practice measures the level of donor chimerism by quantifying the percentage of unsorted marrow and/or microfluorimetrically sorted peripheral blood leukocytes. Leukocyte compartments most commonly evaluated include granulocytes (via CD33 surface expression) and T cells (CD3), sometimes extending to B cells (CD19) and natural killer cells (CD56), depending on the disease indication for allo-HCT. Full donor chimerism is most commonly defined empirically using a cutoff of $>90\%$, $>95\%$, or $>97.5\%$. Partial, more commonly known as mixed, donor chimerism has been defined empirically using lower-end cutoffs such as $>2.5\%$ up to $>10\%$ and upper-end cutoffs such as 90% up to 97.5% . Absence of donor chimerism has been empirically defined by cutoffs of $<2.5\%$, $<5\%$, and $<10\%$ [13]. RIC or NMA conditioning regimens are more likely to result in mixed donor chimerism compared with myeloablative conditioning (MAC) regimens [14]. In the 2001 workshop, the authors recommended avoiding using a specific threshold to define mixed chimerism,

owing to multiple factors that may potentially affect results, including assay sensitivity, underlying disease, and cellular compartment(s) involved; accordingly, mixed chimerism was simply defined as any reliable detection of host hematopoietic cells, hence the wide range still used in current practice [15]. Although this is conceptually factual, certain levels of mixed chimerism within this wide range might be considered clinically acceptable or not, depending on the underlying allo-HCT indication. For instance, in patients who undergo allo-HCT for sickle cell disease, a certain level of stable mixed donor myeloid chimerism is considered an acceptable endpoint for disease correction because it tracks with donor erythrocyte chimerism. Similarly, marrow failure syndromes, like Fanconi anemia or Diamond Blackfan anemia, are correctable with stable mixed chimerism, but anything less than full donor myeloid chimerism does not erase concerns about future (host) myelodysplasia or acute myelogenous leukemia. After allo-HCT for hematologic malignancies, it is intuitive that early, durable full donor chimerism is desirable, because a low level of donor chimerism is associated with an elevated risk for disease relapse [16,17].

To address these contemporary challenges, we organized a panel of pediatric and adult allo-HCT experts to attempt to standardize definitions of hematopoietic (neutrophil and platelet) recovery, graft rejection, primary and secondary graft failure, poor graft function, and donor chimerism. We conducted a survey of adult and pediatric transplantation physicians separately. Whenever applicable, we provide clinical scenarios to highlight the application of these consensus definitions in clinical practice.

METHODS

Panel Composition

We assembled a steering committee of 14 physicians with expertise in allo-HCT and 1 independent methodology expert with expertise in evidence synthesis and the RAND-modified Delphi methods to develop the survey questions. The steering committee drafted the protocol and consensus statements based on systematic review of the literature and clinical practice considerations, and set up the expert panel. The first round of the survey comprised 3 questions on panel demographics, 4 questions on practice setting, and 26 questions on definitions and clinical management. Considering the differences in transplantation practices across age groups, we assembled separate final panels for adult (n = 25) and pediatric (n = 23) HCT physicians with steering committee representative(s) from either panel. Panel physicians included diverse geographical representation and expertise in the field, as demonstrated by a track record of peer-reviewed publications, leadership of clinical trials, and involvement in national and international transplantation societies. The methodology expert assisted with designing, developing, and administering the surveys along with data collection and analysis, but did not participate in the voting process at any stage.

Methodology

Before voting on recommendations, a formal guidance document on the RAND-modified Delphi method was shared with all participants; a statement with $\geq 70\%$ vote in favor/against was considered a consensus. A formal evaluation of patient values and preferences and cost was not conducted; however, an overall assumption was made that recommendations would be feasible in the setting across panel member practices and would not add any additional burden on existing resources. The questions covered the broad domains of definitions and clinical practice recommendations. Consistent with the RAND-modified Delphi methodology, participants rated all statements anonymously for all rounds of voting. Furthermore, all but one rounds of voting were administered online via Qualtrics survey management software (Qualtrics, Provo, UT). One round of the survey was administered anonymously online via Poll Everywhere (polllev.com) during the virtual meeting aimed at reaching consensus, in lieu of an in-person meeting, owing to the COVID-19 pandemic. Descriptive statistics was used to analyze the results of the survey, which are summarized as proportions.

Table 1
Panel Member Demographics

Characteristic	Adult Transplantation Physicians (n = 20)	Pediatric Transplantation Physicians (n = 19)
Age, yr, n (%)		
5-45	6 (30)	4 (21)
46-55	10 (50)	8 (42)
56-65	3 (15)	6 (32)
>65	1 (5)	1 (5)
Sex, n (%)		
Female	3 (15)	10 (53)
Male	17 (85)	9 (47)
Years in practice, n (%)		
<5	1 (5)	1 (5)
5-10	3 (15)	2 (11)
11-15	7 (35)	2 (11)
16-20	5 (25)	6 (32)
>20	4 (20)	8 (42)

RESULTS

Demographics

During the initial round, 20 of the 25 invited identified themselves as adult-treating and 19 of 23 invited identified themselves as pediatric-treating transplantation physicians. In the adult-treating group, the majority were male (85%), and 80% of participants had more than 10 years of experience. In the pediatric-treating group, female physicians composed 53% of the total participants, and 85% had more than 10 years of experience (Table 1).

Practice Characteristics

The majority (55%) in the adult-treating group reported practicing in transplant centers that perform >100 allo-HCT procedures annually, mostly from HLA-matched unrelated donors (MUDs) using peripheral blood stem cells as the preferred cell source. On the other hand, the majority in the pediatric-treating group (63%) reported practicing in centers that perform >50 allo-HCT procedures annually, mostly from HLA-MUDs using bone marrow (BM) as the preferred cell source (Table 2).

Definitions and Management Recommendations

Neutrophil and Platelet Recovery

As summarized in Table 3, both the adult and pediatric transplantation panels endorsed existing working definitions of neutrophil and platelet recovery set forth by the Center for International Blood and Marrow Transplant Research (CIBMTR).

Delayed Engraftment, Graft Rejection, Graft Failure, Poor Graft Function, and Secondary Graft Failure

Neither panel could reach consensus on the definition of delayed engraftment (Table 3). However, there was consensus on differentiating graft rejection from graft failure, defining poor graft function, and secondary graft failure. Both panels defined graft rejection as an immune-mediated process, whereas graft failure was considered to represent a wider array of possibilities, including cell dosing, disease, infections, drugs, and an immune-mediated event.

There was consensus on defining primary graft failure based on different cell sources. For instance, both panels defined graft failure when using peripheral blood stem cells or unstimulated BM as lack of achievement of an ANC $\geq 500/\mu\text{L}$

Table 2
Transplant Center and Practice Characteristics

Center Characteristics	Adult Transplantation Physicians	Pediatric Transplantation Physicians
Number of allo-HCTs/yr, n (%)		
<50	2 (10)	7 (37)
51–100	7 (35)	9 (47)
101–200	6 (30)	1 (5)
>200	5 (25)	2 (11)
Cell source, n (%)[*]		
PBSCs	20 (74)	5 (21)
Unstimulated BM	6 (22)	13 (54)
G-CSF-stimulated BM	1 (4)	0
UCB	0	4 (17)
Other	0	2 (8) [†]
Donor type, n (%)[*]		
MRD	10 (29)	7 (17)
MUD	16 (47)	15 (36)
MMRD/haploidentical	7 (21)	7 (17)
MMUD	0	6 (14)
UCB	1 (3)	7 (17)

PBSCs indicates peripheral blood stem cells; UCB, umbilical cord blood; MRD, HLA-matched related donor; MUD, HLA-matched unrelated donor; MMRD: HLA-mismatched related donor; MMUD: HLA-mismatched unrelated donor.

^{*} More than one option may apply/the number of responses may exceed the number of participants.

[†] Alpha-beta-depleted haploidentical transplantation (n = 1), ex vivo T cell-depleted PBSCs (n = 1).

by day +30 with associated pancytopenia. When using cord blood, both panels defined graft failure as lack of achievement of an ANC $\geq 500/\mu\text{L}$ by day +42 with associated pancytopenia. This assumes that donor chimerism testing is also done to confirm the suspicion of graft failure. There was no consensus by either panel to define graft failure when using G-CSF-stimulated BM (Table 3).

Poor graft function was defined as frequent dependence on blood and/or platelet transfusions and/or growth factor support in the absence of other explanations, such as disease relapse, drugs, or infection (Table 3).

Secondary graft failure was defined as a decline in hematopoietic function (possibly involving hemoglobin and/or platelets and/or neutrophils) necessitating blood products or growth factor support, after having met the standard definition of hematopoietic (neutrophil and platelet) recovery (Table 3). Both panels recommended assessing secondary graft failure by evaluating hematopoietic function (based on peripheral blood counts), BM cellularity, and donor chimerism (Table 4).

Donor Chimerism

Both panels endorsed current definitions of full donor chimerism as >95%, mixed donor chimerism as 5% to 95%, and absent donor chimerism as <5%, for both myeloid and lymphoid lineages (Table 3).

Measuring Donor Chimerism

Both panels recommended routine measurement of donor chimerism using CD3 or similar for lymphoid cells and CD33 or similar for myeloid cells. During the first year after allo-HCT, both panels recommended routine measurement of donor chimerism on approximately days +30, +90, and +180 and at 1 year regardless of the intensity of the preparative

regimen or whether T cell-replete or T cell-depleted grafts were prescribed (Table 4).

Managing Mixed Donor Chimerism in Allo-HCT

Although both panels endorsed the current definition of mixed donor chimerism as 5% to 95% for both myeloid and lymphoid lineages, they also recognized the practical importance of using the actual percentage of donor cells for clinical management. In this case, the panels recommended that individual patient management be based on a consideration of the actual (downward or upward) trajectories of percent donor myeloid and lymphoid chimerism, together with complete blood counts and clinical status. Because trajectories can help inform medical decision making, the panel recommends measuring donor chimerism at specific time points during the first year post-allo-HCT (eg, days +30, +90, +180, and +365).

Pertaining to specific management of downward trajectories in donor CD3 and CD33 chimerism in the malignant disease setting, Figure 1 highlights the complex decision-making in real-world clinical practice. Although withdrawal (or tapering) of immune suppression appeared to be the most frequently chosen approach for declining donor chimerism, the median response was to select 2 possible therapeutic options (range, 1 to 5). Decision making is further complicated by other variables, for example, did the downward donor chimerism trajectory occur in the setting of disease relapse/progression or during a continuous remission? Was GVHD present or not? What was the ablative intensity of the conditioning regimen? Was T cell depletion part of conditioning? These are just a few examples.

Figure 2 also highlights the complex clinical decision process associated with managing similar downtrends in donor chimerism in the context of nonmalignant disease. Interestingly, fewer adult transplantation physicians responded to this question relative to pediatric transplantation physicians (n = 15 versus n = 17; Figure 2) compared with responses to the same questions for malignant disease context (n = 19 versus n = 16; Figure 1). This may highlight the broader experience with allo-HCT for nonmalignant diseases in the pediatric transplantation group. Both panels recognized that the level of donor chimerism required for nonmalignant disease correction depends on the specific underlying disease indication for transplantation; however, specific levels of donor chimerism were not discussed for particular disease indications.

Finally, the panel could not identify a single best approach to the management of down-trending donor chimerism in either the malignant or the nonmalignant disease setting.

DISCUSSION

This work represents an effort to standardize definitions of hematopoietic recovery, graft rejection, primary and secondary graft failure, poor graft function, and donor chimerism in the setting of allo-HCT, and also to provide broad guidance on the clinical management of mixed donor chimerism. We recognize that there are multiple other specific and at times complex clinical scenarios for which clinical management must be individualized.

Pertaining to neutrophil and platelet recovery, both adult and pediatric transplantation physician panels endorsed the existing CIBMTR working definitions. Here, using the word “recovery” instead of “engraftment” is more appropriate, because confirmation of donor source ideally requires also proof of at least mixed/partial donor chimerism, which generally occurs later in the course of transplantation. Neither panel reached a consensus in defining a specific time point for

Table 3
Consensus Definitions from the Adult and Pediatric Transplantation Physician Panels

Term	Definition
Neutrophil recovery	Both panels endorsed the existing definition of neutrophil recovery as the first of 3 successive days with an absolute neutrophil count of $\geq 500/\mu\text{L}$ after post-transplantation nadir.
Platelet recovery	Both panels endorsed the definition of platelet recovery as the first of 3 consecutive days with a platelet count of 20,000/ μL or higher in the absence of platelet transfusion for 7 consecutive days.
Delayed engraftment	No consensus was reached by either panel.
Graft rejection versus graft failure	Both panels defined graft rejection as an immune-mediated process, whereas graft failure represents a wider array of possibilities, including cell dosing, disease, infection, drugs, and an immune-mediated event.
Graft failure (primary)* (according to cell source)	PBSCs: Both panels defined graft failure as lack of achievement of an ANC $\geq 500/\mu\text{L}$ by day +30 with associated pancytopenia.
	Unstimulated BM: Both panels defined graft failure as lack of achievement of an ANC $\geq 500/\mu\text{L}$ by day +30 with associated pancytopenia.
	G-CSF-stimulated BM: No consensus was reached by either panel.
	UCB: Both panels defined graft failure as lack of achievement of an ANC $\geq 500/\mu\text{L}$ by day +42 with associated pancytopenia.
Poor graft function**	Both panels defined poor graft function as frequent dependence on blood and/or platelet transfusions and/or growth factor support in the absence of other explanations, such as disease relapse, drugs, or infections.
Secondary graft failure*	Both panels defined secondary graft failure as a decline in hematopoietic function (may involve hemoglobin and/or platelets and/or neutrophils) necessitating blood products or growth factor support, after having met the standard definition of hematopoietic (neutrophils and platelets) recovery.
Donor chimerism	Full: Both panels endorsed the existing definition of full donor chimerism as >95% for both myeloid and lymphoid lineages.
	Mixed or partial: Both panels endorsed the existing definition of mixed donor chimerism as 5% to 95% for both myeloid and lymphoid lineages.
	Absent: Both panels endorsed the existing definition of absent donor chimerism as <5% for both myeloid and lymphoid lineages.

PBSC, peripheral blood stem cells; ANC, absolute neutrophil count; BM, bone marrow cells; G-CSF, granulocyte colony stimulating factor.

* Donor chimerism testing is also done to confirm the suspicion of graft failure.

** Assumes that donor myeloid and lymphoid chimerism are within a desirable target level.

Table 4
Recommendations of the Adult and Pediatric Transplantation Physician Panels

Category	Recommendations
Assessment of secondary graft failure	Evaluating hematopoietic function (based on peripheral blood counts), bone marrow cellularity, and donor chimerism(s) when assessing secondary graft failure
Measuring donor chimerism	Routine practice includes measurement of donor chimerism using CD3 or similar for lymphoid cells and CD33 or similar for myeloid cells.
	During the first year after allo-HCT, measure donor chimerism routinely on days +30, +90, and +180 and at 1 year during the first year post- allo-HCT.
	Measure sorted (CD3 and/or CD33) donor chimerism routinely in patients receiving MAC, RIC, or NMA conditioning.
	Measure sorted (CD3 and/or CD33) donor chimerism routinely when using T cell-depleted grafts (in vivo or ex vivo).
Managing mixed donor chimerism (malignant diseases)	The panel recognizes the impact of the actual percentage of donor cells for clinical management.
	Consider using the actual percentages of donor myeloid cells and lymphoid cells, blood counts and the clinical status of the patient for a change in management.
	Use the actual percentage of mixed donor chimerism at specific time points post-allografting (ie, days +30, +90, +180, and +365) for a change in management.
	Consider the decline from a prior chimerism level to inform clinical management.
Managing mixed donor chimerism (nonmalignant diseases/bone marrow failure syndromes)	The panel recognizes that the level of donor chimerism required for disease correction depends on the disease.
	Consider the decline from a prior chimerism level to inform clinical management.

delayed engraftment. This is not surprising, because in theory, delayed engraftment represents a continuum from the time of absence of hematopoietic recovery until objective confirmation of graft failure. Moreover, from a treatment standpoint, these patients generally continue to receive supportive interventions while cytopenic, such as antimicrobial prophylaxis, blood products, and growth factors, among others.

Guidelines differentiate between graft rejection and graft failure because they have different therapeutic implications. For graft rejection, interventions concentrate primarily on overcoming the HLA disparity barrier. However, interventions for graft failure are more varied based on specific situations and might include

administering a CD34-selected cell boost to address poor graft function with or without mixed/absent chimerism in the myeloid compartment and prescribing donor lymphocyte infusion(s) to treat low mixed chimerism, but do require at least 5% donor lymphoid chimerism. Other interventions to treat graft failure include considering a second allo-HCT, treatment of infections, and withholding suspected myelotoxic drugs, among others, as clinically indicated.

Different from graft failure, poor graft function assumes that donor myeloid and lymphoid chimerism are within a desirable target level and that there are other causes that explain the continuous need for blood products or growth

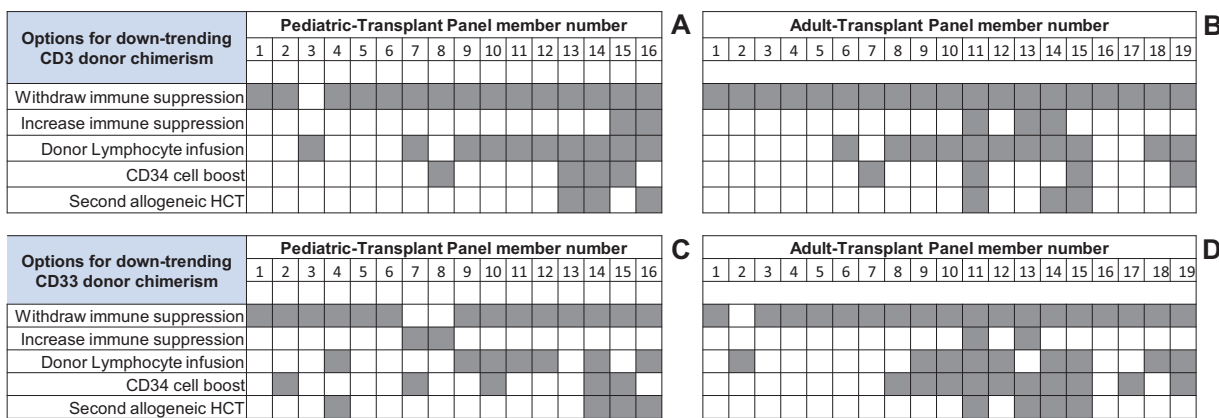


Figure 1. Transplantation physician responses to options for managing down-trending chimerism in malignant diseases. Management responses are shown for pediatric transplantation panel members to declines in CD3 (A) and CD33 donor chimerism (C). Similar responses are shown for adult transplant panel members in (B) and (D), respectively.

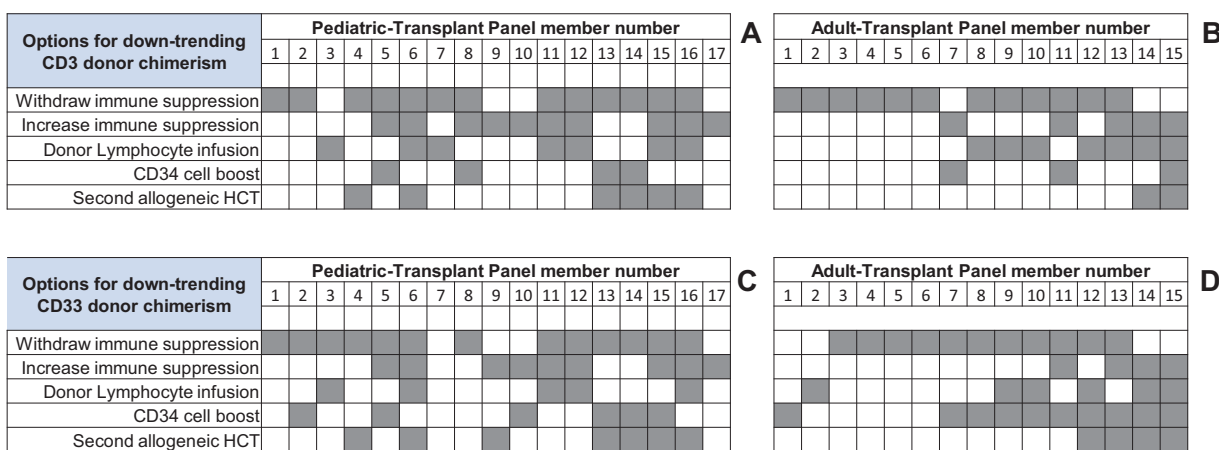


Figure 2. Transplantation physician responses to options for managing down-trending chimerism in nonmalignant diseases. Management responses are shown for pediatric transplantation panel members to declines in CD3 (A) and CD33 donor chimerism (C). Similar responses are shown for adult transplantation panel members in (B) and (D), respectively.

factor support. For instance, diseases such as myelofibrosis could cause poor graft function post-transplantation, requiring frequent transfusion of blood products during the first few months, even in the presence of full donor myeloid chimerism.

For primary graft failure, both panels endorsed using a practical definition based on lack of recovery of ANC to $\geq 500/\mu\text{L}$ in the presence of associated cytopenias at a particular time point based on the prescribed stem cell source (Table 3). We acknowledge that additional workup is certainly required, which should include assessing marrow cellularity and quantifying donor chimerism levels to confirm graft failure (Table 3), and that future interventions could vary depending on several factors, such as patient functional status and disease-specific reasons, among others. In cases of secondary graft failure, patients have a decline in hematopoietic function and confirmation of absent donor chimerism levels after previously documented full or mixed donor chimerism levels.

Notwithstanding the different sensitivities of donor chimerism methodologies, both panels endorsed current working definitions of full donor chimerism in myeloid and lymphoid lineages as $>95\%$, mixed or partial donor chimerism as 5% to 95%, and absence of donor chimerism as $<5\%$ (Table 3). Although both panels endorsed the definition of mixed donor chimerism as 5% to 95%, they acknowledged several clinical

practice limitations related to this definition. Intuitively, patients with lower levels of mixed donor chimerism are likely to be treated differently than those with higher levels. Moreover, mixed chimerism is a dynamic state in which a progressive decline in donor chimerism might portend or confirm graft loss or disease recurrence, depending on the cell compartment analyzed. For instance, a 10% level of CD3 donor chimerism might prompt consideration for donor lymphocyte infusion or even prescription of antineoplastic therapy in the case of a T cell malignancy. On the other hand, an 80% donor CD3 level, which still meets the definition of mixed donor chimerism, is more likely to be followed closely until a clearer trend is established. Furthermore, management could be different if mixed donor chimerism is observed in only one lineage versus both lineages. We acknowledge that in the setting of T cell depletion, ex vivo or in vivo, CD3 chimerism might be low or absent for many months after transplantation.

When managing declining donor chimerism levels, approaches tend to consider not only the specific lineage(s) involved, but also the percentage decline (trajectory) over time from a known peak level. Repeating donor chimerism levels should be considered to confirm the results. When both panels were asked about the immediate next step in managing declines in donor CD3 and CD33 chimerism in the setting of

allo-HCT for malignant diseases, the most frequent response was to withdraw (or taper) immune suppression (Figure 1). In addition, more than one-half of respondents chose more than one possible option, underscoring the complexities associated with managing such clinical situations. Caveats must certainly be applied, because in certain scenarios, such as the presence of active GVHD, withdrawing (or tapering) immune suppression might be inappropriate.

In the case of declining CD3 and CD33 donor chimerism in the setting of nonmalignant disorders, both panels also chose withdrawing immune suppression as the next immediate step in managing a downward trend in CD3 and CD33 chimerism. Again, more than one-half of the participants chose more than one option. Such decisions need to consider several factors, including but not limited to the patient's underlying disease indication for allo-HCT, whether the downtrend occurred in the context of minimal versus heavy pretransfusion, whether the decreases in chimerism and blood counts were observed during steady-state versus tapered immune suppression, and the intensity of the preparative regimen (MAC versus RIC). We acknowledge that optimal management of declining donor chimerism, particularly in patients with nonmalignant disorders, remains an area in which future research is definitely needed.

The main goal in developing these consensus definitions and recommendations is to harmonize allo-HCT clinical practice. These guidelines are not intended to replace clinical judgment, as there are several situations where decisions need to be individualized.

ACKNOWLEDGMENTS

Financial disclosure: Please refer to conflicts of interest statement which lists financial disclosures whenever applicable.

Conflict of interest statement: M.A.K-D. reports consultancy for Daiichi Sankyo and Pharmacyclics. L.M.B. has received support for a clinical trial conducted through the Fred Hutchinson Cancer Research Center by Medac, including supply of the study drug treosulfan; is a member of the data safety and monitoring boards (DSMB) for a clinical trial with Rocket Pharmaceuticals and another clinical trial with Jasper Therapeutics. N. M. has served as a consultant for Anthem and has received honoraria from Incyte and Nkarta, M.B. reports employment by Bristol Myers Squibb. J.J.B. reports consultancy for Race Oncology, Takeda, AvroBio, Bluerock, Omeros, and Advanced Clinical. S.C. serves on an advisory board for bluebird bio. Z.D. has received research support from Incyte and RegImmune-Corp and has served as a consultant for Syndax Pharmaceuticals. B.D. has received research support from Takeda, Janssen, Angiocrine, Poseida, and Celgene and serves on consultancy/advisory boards for Jazz Pharmaceuticals and Celgene. S.F. serves on speakers bureaus for TG Pharma, Sanofi, BMS, and Takeda and as a consultant for Genentech. U.G. serves as a consultant for Jazz, Incyte, Astellas, Mesoblast, and Gamida Cell. S. G. serves on consultancy/advisory boards for Amgen, Celgene, Janssen, Quintiles, Pfizer, CSL Behring, Sanofi, Adiene, Kite Pharma, Jazz Pharmaceuticals, and Actinuum. Y.I. serves as a consultant for Novartis, Meiji Seika, and Janssen Pharmaceutical. T.J. serves as a consultant for Targeted Oncology and on advisory boards for CareDx and Bristol Myers Squibb. H.L. serves on the speakers bureau for Sanofi. B.O. has received research funding from ASTEX and AROG Pharmaceuticals. M.A.P. has received honoraria from Abbvie, Bellicum, Celgene, Bristol-Myers Squibb, Incyte, Kite/Gilead, Merck, Novartis, Nektar Therapeutics, Omeros, and Takeda. He serves on DSMBs

for Cidara Therapeutics, Servier, and Medigene and on the scientific advisory boards of MolMed and NexImmune. He has received research support for clinical trials from Incyte, Kite/Gilead, and Miltenyi Biotec. He serves in a volunteer capacity as a member of the Board of Directors of Be The Match (National Marrow Donor Program), as well as on the CIBMTR Cellular Immunotherapy Data Resource Executive Committee. S.E.P. receives support for the conduct of sponsored trials from Atara Biotherapeutics, Mesoblast, and Jasper and is an inventor of IP licensed to Atara Biotherapeutics by Memorial Sloan Kettering Cancer Center (MSKCC) (assigned all rights to MSKCC and has no financial interest in Atara Biotherapeutics). I.P. serves on advisory boards for Kadmon, Incyte, and Syndex. M. L.R. serves on an advisory board for BioIntellect. C.R. serves as a consultant for Amgen, Bristol Myers Squibb, Takeda, and Sanofi. R.R. has received research funding from Crispr Therapeutics and serves on a scientific advisory board for Glycostem. A.S. serves as a consultant for Magenta, Incyte Pharmaceuticals, and CareDx and receives research support from Amgen, Kadmon, and OrcaBio. N.S. has received research funding from Celgene/Bristol Myers Squibb, Janssen, bluebird bio, Sutro Biopharma, Teneobio, Poseida, Nektar, and has served as an advisor for GSK, Amgen, Indapta Therapeutics, Sanofi, CareDx, Kite Pharma, Karyopharm, Oncopeptides, and CSL Behring. J.S. reports personal fees from Astellas, Jazz Pharmaceuticals, Abbvie, Daiichi Sankyo, Pfizer, and grants and personal fees from Novartis. M.R.V. reports advisory board participation for Jazz Pharmaceuticals and Novartis and consultancy with Fate Therapeutics and Terumo. J.E.W. serves as a clinical advisor to Magenta Therapeutics and Rocket Pharmaceuticals. M.H. reports receiving research support/funding from Takeda Pharmaceutical, Spectrum Pharmaceuticals, and Astellas Pharma; serving as a consultant for Janssen, Incyte, ADC Therapeutics, Celgene, Omeros, Verastem, and MorphoSys; and serving on the speakers bureau for Sanofi Genzyme, AstraZeneca, and Beigene. E.A., A. Kumar, M.A., T.N., R.M., A.S.A., Z.S.A., A.B., R.C., A. E.-J., E.F., B. Hamilton, S.K.H., B. Horn, D.A.J., L.J., A.S.K., A. Kansagra, A. Kassim, L.S.K., C.L.K., J.K-P., J.K., M.L.M., Z.M., M. Mielcarek, M. Mohty, A.N., E.N., T.S.O., M.A.P., G.R., P.J.S., S.S., J.T., P. V., B.N.S., and P.A.C. declare no conflicts of interest.

REFERENCES

- Jenq RR, van den Brink MRM. Allogeneic haematopoietic stem cell transplantation: individualized stem cell and immune therapy of cancer. *Nat Rev Cancer*. 2010;10:213–221.
- Gooley TA, Chien JW, Pergam SA, et al. Reduced mortality after allogeneic hematopoietic-cell transplantation. *N Engl J Med*. 2010;363:2091–2101.
- Gluckman E, Rocha V, Boyer-Chammard A, et al. Outcome of cord-blood transplantation from related and unrelated donors. Eurocord Transplant Group and the European Blood and Marrow Transplantation Group. *N Engl J Med*. 1997;337:373–381.
- Ballen KK, Gluckman E, Broxmeyer HE. Umbilical cord blood transplantation: the first 25 years and beyond. *Blood*. 2013;122:491–498.
- Luznik L, O'Donnell PV, Symons HJ, et al. HLA-haploidentical bone marrow transplantation for hematologic malignancies using nonmyeloablative conditioning and high-dose, posttransplantation cyclophosphamide. *Biol Blood Marrow Transplant*. 2008;14:641–650.
- Ciurea SO, Zhang MJ, Bacigalupo AA, et al. Haploidentical transplant with posttransplant cyclophosphamide vs matched unrelated donor transplant for acute myeloid leukemia. *Blood*. 2015;126:1033–1040.
- Kanate AS, Mussetti A, Kharfan-Dabaja MA, et al. Reduced-intensity transplantation for lymphomas using haploidentical related donors vs HLA-matched unrelated donors. *Blood*. 2016;127:938–947.
- Lee SJ, Klein J, Haagenson M, et al. High-resolution donor-recipient HLA matching contributes to the success of unrelated donor marrow transplantation. *Blood*. 2007;110:4576–4583.
- Anasetti C, Logan BR, Lee SJ, et al. Peripheral-blood stem cells versus bone marrow from unrelated donors. *N Engl J Med*. 2012;367:1487–1496.

10. Shpall EJ, Champlin R, Glaspy JA. Effect of CD34⁺ peripheral blood progenitor cell dose on hematopoietic recovery. *Biol Blood Marrow Transplant.* 1998;4:84–92.
11. Stewart WA, Pearce R, Kirkland KE, et al. The role of allogeneic SCT in primary myelofibrosis: a British Society for Blood and Marrow Transplantation study. *Bone Marrow Transplant.* 2010;45:1587–1593.
12. Kumar A, Reljic T, Hamadani M, Mohy M, Kharfan-Dabaja MA. Antithymocyte globulin for graft-versus-host disease prophylaxis: an updated systematic review and meta-analysis. *Bone Marrow Transplant.* 2019;54:1094–1106.
13. McSweeney PA, Storb R. Mixed chimerism: preclinical studies and clinical applications. *Biol Blood Marrow Transplant.* 1999;5:192–203.
14. Sharabi Y, Abraham VS, Sykes M, Sachs DH. Mixed allogeneic chimeras prepared by a non-myeloablative regimen: requirement for chimerism to maintain tolerance. *Bone Marrow Transplant.* 1992;9:191–197.
15. Antin JH, Childs R, Filipovich AH, et al. Establishment of complete and mixed donor chimerism after allogeneic lymphohematopoietic transplantation: recommendations from a workshop at the 2001 Tandem Meetings of the International Bone Marrow Transplant Registry and the American Society of Blood and Marrow Transplantation. *Biol Blood Marrow Transplant.* 2001;7:473–485.
16. Barrios M, Jiménez-Velasco A, Román-Gómez J, et al. Chimerism status is a useful predictor of relapse after allogeneic stem cell transplantation for acute leukemia. *Haematologica.* 2003;88:801–810.
17. Bader P, Beck J, Frey A, et al. Serial and quantitative analysis of mixed hematopoietic chimerism by PCR in patients with acute leukemias allows the prediction of relapse after allogeneic BMT. *Bone Marrow Transplant.* 1998;21:487–495.