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## Access to Hematopoietic-cell Transplantation in the United States

Navneet S. Majhail, MD, MS<sup>1,2</sup>, Nancy A. Omondi, MBA, MS<sup>3</sup>, Ellen Denzen, MS<sup>3</sup>, Elizabeth A. Murphy, EdD, RN<sup>3</sup>, and J Douglas Rizzo, MD, MS<sup>4,5</sup>

<sup>1</sup>Center for International Blood and Marrow Transplant Research, Minneapolis, MN

<sup>2</sup>University of Minnesota, Minneapolis, MN

<sup>3</sup>National Marrow Donor Program<sup>®</sup>, Minneapolis, MN

<sup>4</sup>Center for International Blood and Marrow Transplant Research, Milwaukee, WI

<sup>5</sup>Medical College of Wisconsin, Milwaukee, WI

### Abstract

Hematopoietic cell-transplantation (HCT) is a highly specialized and resource-intensive medical procedure that can be associated with disparities in access to transplantation. Barriers to access to HCT are multifactorial, complex and interrelated. Our current knowledge of specific barriers that prevent access to HCT is very limited. As the utilization of HCT increases, it is imperative that underserved populations receive the benefit of this life-saving procedure. We review the prevailing literature on access to HCT and describe research priorities for eliminating disparities in transplantation. Better understanding of these complex barriers will minimize inequities, inform health policy, guide development of interventions targeted to eliminate disparities and continue the expansion of HCT in the future.

### Keywords

Hematopoietic-cell transplantation; autologous; allogeneic; access; underserved populations

## INTRODUCTION

Hematopoietic-cell transplantation (HCT) is curative therapy for a variety of malignant and non-malignant hematologic disorders. The utilization of HCT has progressively increased over the last four decades since reports of first successful transplantations in 1968 and an estimated 50,000 transplants are performed worldwide every year, including 20,000 in the United States.<sup>1</sup> With emerging indications, improvements in technology and supportive care, and increasing availability of alternative graft sources and reduced intensity conditioning regimens, use of HCT can be expected to increase further in the future. However, HCT is a highly specialized, technologically sophisticated, resource-intensive and expensive procedure that can be associated with health-care associated disparities. These health care disparities have clinical, ethical and policy implications. We review the available literature on access to HCT and describe barriers that need to be addressed to ensure equitable access to HCT for all populations.

Address for correspondence: Navneet Majhail, MD, MS, Assistant Professor, Division of Hematology, Oncology and Transplantation, University of Minnesota, 420 Delaware St SE, MMC 480, Minneapolis, MN 55455, Phone: 612 624 0123, Fax: 612 625 6919, majha001@umn.edu.

## Access to Cancer Care

Access to health care has been defined as “the timely use of affordable personal health services to achieve the best possible health outcomes”.<sup>2,3</sup> Mandelblatt et al have very elegantly summarized the complexities of access to health care; according to them, “the process of gaining access to care represents dynamic interactions of diverse individuals in their social context interfacing with health care providers, who, in turn, are operating in a variety of changing and often constrained medical care structures and environments”.<sup>3</sup> Disparities exist in the health care of minority populations in the United States and minorities do not have the same access to health care and as a result do not receive the same quality of health care and have poorer overall health status than non-minorities.<sup>4-6</sup> The Institute of Medicine in its report, *Unequal Treatment: Confronting Racial and Ethnic Disparities in Healthcare*, further concluded that even when other healthcare access-related factors, such as ability to pay for care are the same, racial and ethnic minorities receive lower quality healthcare than Whites.<sup>5</sup> The report recommended a comprehensive, multi-level strategy to eliminate these disparities, including increasing awareness among providers, patients, payors, health plan purchasers and the society at large, enhancing training and education and conducting research on interventions.

Cancer care is also associated with disparities in detection, treatment and outcomes for specific high-risk populations. These high-risk populations include elderly patients, women, patients of Black or Hispanic race/ethnicity, the under- or un-insured, patients from the lower socioeconomic strata, patients with lower levels of health literacy and education, and patients with rural residence.<sup>3,7-11</sup> The origins of these inequities are multifactorial and complex. Patient barriers include demographics, language, acculturation, attitudes and family and cultural contexts.<sup>3</sup> In addition, health care providers play an important role in ensuring access to cancer care. Physician and provider specific barriers that have been reported in the literature include age or race biases, biases and beliefs about screening and treatment efficacy, deficient knowledge and training, lack of confidence, lack of culturally sensitive resources, lack of time, concerns about patient acceptance, cost concerns, and logistic or organizational barriers.<sup>3,12-15</sup> Finally, health care system barriers such as organizational and structural factors and reimbursement and financial forces can facilitate or hinder access to optimal cancer care.<sup>3</sup> Factors can also be closely interrelated; for instance, racial and ethnic minorities are more likely to be uninsured compared to Whites.<sup>16</sup>

## Access to Hematopoietic-cell Transplantation

HCT is most commonly performed for malignant hematologic disorders and barriers that prevent access to cancer care may also be relevant for HCT. However, additional barriers may also have a role since HCT is a high-cost and sophisticated medical procedure that involves complex interactions between patient, provider and health-care system factors (Figure 1).

The available literature on access to HCT is very limited (Table 2). Studies have generally had insufficient statistical power to detect differences among access indicators and/or have frequently utilized databases with limited applicability to understanding access issues, particularly their cause. Inpatient hospital discharge databases have been frequently utilized in these studies. However, such databases may not be truly appropriate to health disparities research as they may not capture the universe of patients with hematologic malignancies or who received transplants in a population cohort. Also, disease and procedure codes are used to identify patients from these datasets; medical codes lack precision and important prognostic factors such as disease stage and remission status which may affect decision making regarding use of HCT could not be considered in these analyses. Furthermore,

contemporaneous studies are lacking and the majority of studies addressed barriers in an era when present day transplantation techniques were not widely available.

Possible limitations in study design notwithstanding, previously conducted studies have increased our characterization of barriers that limit access to transplantation. For instance, current literature highlights substantial geographic variation in access to HCT. Mitchell et al, in a study that utilized hospital discharge data from four states (California, Massachusetts, Maryland and New York) for the years 1988 and 1991, showed state wise differences in access to HCT by insurance coverage and race.<sup>17</sup> Compared to patients with private insurance, Medicaid beneficiaries in California, New York and Maryland/Massachusetts were 78%, 64% and 61% as likely to receive a transplant for leukemia and 69%, 56% and 32% as likely to receive a transplant for lymphoma, respectively. Similarly, compared to Whites, Hispanics were significantly less likely to receive a transplant for lymphoma in New York but had similar rates of transplantation for lymphoma in California and for leukemia in all four states.

Specific disparities to access to HCT that have been identified in the literature include:

**Age**—Studies that have investigated age as a predictor of access to HCT indicate that younger patients are more likely to receive a transplant compared to older patients. Mitchell et al showed that each 10-year increase in age was associated with 10% to 18% (variation by state) lower odds of receiving HCT for leukemia or lymphoma.<sup>17</sup> In another study that used inpatient discharge data for the state of Texas from 1999, Hwang et al reported that elderly (age  $\geq 65$  years) patients had a significantly lower likelihood of receiving a transplant for leukemia with each year increase in age; however, no age effect was noted among pediatric (age  $< 18$  years) and adult (age 18–64 years) recipients.<sup>18</sup> In a study using Arizona hospital discharge data from 1997–2003, Cho has also reported that increasing age reduces the probability of receiving a transplant for leukemia; they did not detect any effect of age on the likelihood of transplantation for lymphoma.<sup>19</sup> These previous studies pre-date the advent of reduced-intensity and non-myeloablative preparative regimens which are associated with lower risks of morbidity and mortality and now allow transplantation as a viable treatment option for older patients. Additional factors may impact utilization of HCT in older patients. Older patients may decline or their providers may not recommend aggressive therapies such as HCT. Also, some differences in transplant utilization among older patients may be appropriate since older patients may have comorbidities and disease characteristics which may make them ineligible for transplantation; previous studies have not been able to sufficiently account for these important variables.

**Gender**—Mitchell et al and Cho found no impact of gender on the likelihood of transplantation for leukemia or lymphoma.<sup>17,19</sup> Hwang et al reported that elderly men were more likely to receive a transplant for leukemia than elderly women, but they found no effect of gender on pediatric and adult HCT recipients. In a study that specifically tried to address the issue of gender and access to HCT, Mehta et al used data for 1989–1999 from the International Bone Marrow Transplant Registry and Surveillance Epidemiology and End Results (SEER) database.<sup>20</sup> They concluded that there was no significant bias towards the use of HCT in males compared to females. However, in a more recent and large study that used data from the Center for International Blood and Marrow Transplant Research (CIBMTR) and SEER, Joshua et al showed that men were more likely to receive HCT than women and this difference was primarily seen in autologous HCT for lymphoma or myeloma, but not in allogeneic HCT.<sup>21</sup> The reasons for gender specific disparities, if any, are unclear and need to be explored in future studies.

**Race**—The role of race in access to HCT has to be interpreted with caution. Race is a complex social, cultural and political construct and not a biological concept and accordingly, the definition of race has changed and evolved over time. Self-reported race is most accurate, but race is frequently assigned by centers or providers for a number of databases. Among the earliest studies of access to HCT, Mitchell et al showed that Blacks were less likely than Whites to undergo a transplant for leukemia or lymphoma in each of the four states investigated.<sup>17</sup> Joshua et al have also shown that the likelihood of undergoing HCT for leukemia, lymphoma and multiple myeloma is significantly lower for Blacks compared to Whites and that these differences existed for autologous, matched sibling donor and unrelated donor HCT.<sup>21</sup> On the other hand, Hwang et al and Cho did not find any impact of race of transplantation rates.<sup>18,19</sup>

**Insurance Status**—HCT is a costly procedure,<sup>22,23</sup> and patients with no or limited health insurance coverage may have a lower likelihood of receiving HCT. Three previous studies have attempted to address the impact of insurance coverage on access to HCT. Mitchell et al showed that patients enrolled with Medicaid, self-paid (uninsured) patients and Health Maintenance Organization (HMO) enrollees with leukemia or lymphoma were significantly less likely to undergo HCT compared with patients with private insurance.<sup>17</sup> The authors suggested that the lower probability of getting a transplant among HMO enrollees could be related to coverage restrictions or delay in approval for costly medical procedures such as HCT. Cho also reported that patients with less generous insurance coverage were less likely to receive HCT for leukemia and lymphoma.<sup>19</sup> However, Hwang et al did not find any association between payor status (commercial insurance, HMO, Medicare, Medicaid, self-pay and other payor) and receipt of HCT for leukemia.<sup>18</sup> Their findings were specific to the state of Texas and authors commented that the lack of relationship between payor status and HCT use could be due to equitable access to HCT or lack of statistical power to identify significant associations. The interaction of insurance status with other sociodemographic factors, albeit complex, has not been explored. For example, children may have greater access to HCT compared to adults due to the presence of hospital, state or federal programs that may provide coverage for HCT.

**Other barriers**—Education status, estimated by Zip Code of residence, was not identified as a major factor associated with transplant access by Mitchell et al.<sup>17</sup> Cho examined the association between hospital characteristics and likelihood of transplantation for leukemia in Arizona.<sup>19</sup> Patients with leukemia and lymphoma admitted to a minor teaching hospitals (vs. major teaching hospitals) and small or medium sized hospitals (vs. large hospitals, >250 beds) were less likely to receive a transplant. Patients admitted to for-profit hospitals and government-owned hospitals had comparable probabilities of transplantation.

### Areas for Further Research

Research is needed to further characterize disparities in access to HCT, identify causes for any disparities deemed inappropriate and to investigate interventions to mitigate those barriers. However, health disparities research in HCT can be very challenging. Typically, a very large population cohort has to be assembled for studies of access to health-care. A reliable estimate of the ‘numerator’ (e.g., number of transplants for a disease) and ‘denominator’ (e.g., total number of patients with that disease for whom a transplant is appropriate) for a cohort over a given period of time is also needed. Finally, comprehensive information about the factors that may be associated with disparate access (e.g., race and ethnicity, education status, socioeconomic status, cultural attitudes, insurance/payment status) is required. Large administrative databases such as the SEER-Medicare dataset are frequently used to identify disparities in access to cancer care. Since these large databases cannot robustly collect information about access indicators, surrogate variables are used to

evaluate barriers that may impact access to treatment (e.g., Zip Code to assign socioeconomic status, education status and place of residence). The majority of federal and claims databases do not have robust information about hematologic malignancies and HCT and details of important prognostic factors (e.g. cytogenetic risk) that predict which patients should be considered for HCT are generally not available. However, good quality studies using administrative and claims databases may be possible in the near future due to enhanced data collection efforts by multiple groups. For example, SEER has collected data on MDS and chronic myeloproliferative disorders since 2001. Since 2007, all allogeneic transplants in the United States should be reported to the CIBMTR under the requirements of the Stem Cell Therapeutic and Research Act of 2005.

Database studies can be useful for identification of some aspects of health-care disparities. However, they are not optimal for evaluation of individual patient and provider level barriers or to identify the causes of disparate access. Additional health services research methodologies (e.g. patients and physician surveys, qualitative research methods such as focus groups) will be needed to better understand obstacles to universal access to HCT and must also account for inherent inequities in access to HCT due to biological and medical factors. For instance, ethnic and racial minorities have a lower probability of finding a suitable donor and have a higher prevalence of comorbidities that may make them ineligible for transplantation.<sup>24–26</sup> Once etiologies of disparate access have been characterized, studies evaluating targeted interventions to address barriers to access are also needed.

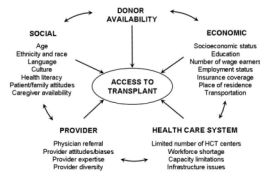
In order for underserved populations to obtain the benefit of a life-saving procedure such as HCT, it is imperative that the medical community work to reduce inappropriate disparities and ensure equitable access to transplantation. Our current knowledge about specific barriers that prohibit access to HCT is very limited. While waiting for better information, the medical community, including payors, policy makers and healthcare providers must use the current awareness of disparate access as a call to action to examine their own practices and work to eliminate inappropriate disparities. Better understanding of these complex barriers will minimize inequities, inform health policy, guide development of interventions targeted to eliminate disparities and continue the expansion of HCT in the future.

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**Figure 1.**  
Potential barriers to access to hematopoietic-cell transplantation

**Table 1**

Access to hematopoietic cell transplantation: summary of published studies

Reference	Access focus	Data sources	Study design	N	Population characteristics	Results
Mitchell et al (1997) <sup>17</sup>	Age Gender Race Education Insurance	Inpatient hospital discharge data for California, Maryland, Massachusetts and New York	ICD-9 codes used to identify inpatients with leukemia or lymphoma and recipients of auto or allo HCT in 1988 and 1991	<ul style="list-style-type: none"> <li>38,420 inpatients with leukemia or lymphoma</li> <li>1,655 HCT recipients</li> </ul>	<ul style="list-style-type: none"> <li>AML 13%, ALL 15%, CML 6%, NHL 45%</li> <li>Whites 72%, Blacks 9%</li> <li>Blue Cross 53%, Medicaid 18%, HMO 12%</li> </ul>	<ul style="list-style-type: none"> <li>Blacks and older patients less likely to receive HCT</li> <li>Patients with private insurance more likely to receive HCT</li> </ul>
Mehta et al (2003) <sup>20</sup>	Gender	SEER, IBMTR	SEER incidence rates and data from IBMTR used to estimate rates of allo HCT for AML, ALL and CML from 1989–1999*	<ul style="list-style-type: none"> <li>18,932 patients with AML, ALL or CML</li> <li>13,083 HCT recipients</li> </ul>	<ul style="list-style-type: none"> <li>AML 24%, ALL 22%, CML 54%</li> </ul>	<ul style="list-style-type: none"> <li>No gender differences in allo HCT utilization</li> </ul>
Hwang et al (2004) <sup>18</sup>	Age Gender Race Insurance Comorbidity	Texas inpatient hospital discharge data	ICD-9 codes used to identify inpatients with acute or chronic leukemia's and recipients of auto or allo HCT in 1999	<ul style="list-style-type: none"> <li>6,574 inpatients with leukemia</li> <li>1,604 HCT recipients</li> </ul>	<ul style="list-style-type: none"> <li>AML 27%, ALL 24%, CML 13%, CLL 31%</li> <li>Whites 70%, Blacks 8%</li> <li>Medicare/Medicaid 50%, commercial payer 30%</li> </ul>	<ul style="list-style-type: none"> <li>Elderly (&gt;65 years) women less likely to receive HCT</li> <li>No impact of payer status and ethnicity on HCT utilization</li> </ul>
Cho (2006) <sup>19 †</sup>	Age Gender Race Insurance Center factors Comorbidities	Arizona inpatient hospital discharge data	ICD-9 codes used to identify inpatients with leukemia or lymphoma and recipients of auto or allo HCT from 1997–2003	<ul style="list-style-type: none"> <li>6,435 inpatients with leukemia or lymphoma</li> <li>207 HCT recipients</li> </ul>	<ul style="list-style-type: none"> <li>AML 14%, ALL 17%, NHL 43%</li> <li>Private payer 35%, HMO 32%, Medicare/Medicaid 24%</li> </ul>	<ul style="list-style-type: none"> <li>Patients with private insurance more likely to receive HCT</li> <li>No impact of gender and race on HCT utilization</li> </ul>
Joshua et al (2007) <sup>21</sup>	Gender Race	SEER, US Census Bureau and CIBMTR	SEER incidence rates and data from CIBMTR used to estimate rates of auto and allo HCT for leukemia, lymphoma and myeloma from 1997–2002	<ul style="list-style-type: none"> <li>273,853 patients with leukemia, lymphoma or myeloma</li> <li>45,750 HCT recipients</li> </ul>	<ul style="list-style-type: none"> <li>AML 21%, ALL 9%, CML 11%, NHL 21%, MM 40%</li> <li>White 90%, Blacks 10%</li> </ul>	<ul style="list-style-type: none"> <li>Blacks less likely to receive auto or allo HCT</li> <li>Women less likely to receive auto HCT</li> </ul>

ICD – international classification of diseases; auto – autologous; allo – allogeneic; HCT – hematopoietic cell transplantation; International Classification of Diseases; SEER – Surveillance Epidemiology and End Results; IBMTR – International Bone Marrow Transplant Registry (now CIBMTR); CIBMTR – Center for International Blood and Marrow Transplant Research; AML – acute myeloid leukemia; ALL – acute lymphoblastic leukemia; CML – chronic myeloid leukemia; CLL – chronic lymphocytic leukemia; NHL – non-Hodgkin's lymphoma; MM – multiple myeloma; HMO – Health Maintenance Organization

\* HCT reported to IBMTR from 1989–1992 and SEER incidence estimates from 1992–1999 were used for this analysis



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